

NOVEL BETULIN DERIVATIVES, PREPARATION THEREOF AND USE THEREOF

[0001] This application claims the benefit of the filing date of U.S. Appl. No. 60/626,886, filed November 12, 2004 and U.S. Appl. No. 60/653,080, filed February 16, 2005, both of which are incorporated by reference herein in their entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] The present invention relates to novel synthetic derivatives of betulin and the use of such derivatives as pharmaceuticals.

Related Art

[0003] Retroviruses are small, single-stranded positive-sense RNA viruses. A retroviral particle comprises two identical single-stranded positive sense RNA molecules. Their genome contains, among other things, the sequence of the RNA-dependent DNA polymerase, also known as reverse transcriptase. Many molecules of reverse transcriptase are found in close association with the genomic RNA in the mature viral particles. Upon entering a cell, this reverse transcriptase produces a double-stranded DNA copy of the viral genome, which is then inserted into the chromatin of a host cell. Once inserted, the viral sequence is called a provirus. Retroviral integration is directly dependent upon viral proteins. Linear viral DNA termini (the LTRs) are the immediate precursors to the integrated proviral DNA. There is a characteristic duplication of short stretches of the host's DNA at the site of integration.

[0004] Progeny viral genomes and mRNAs are transcribed from the inserted proviral sequence by host cell RNA polymerase in response to transcriptional, regulatory signals in the terminal regions of the proviral sequence, the long terminal repeats, or LTRs. The host cell's protein production machinery is used to produce viral proteins, many of which are inactive until processed by virally encoded proteases. Typically, progeny viral particles bud from the cell surface in a non-lytic manner. Retroviral infection does not

- 2 -

necessarily interfere with the normal life cycle of an infected cell or organism. However, neither is it always benign with respect to the host organism. While most classes of DNA viruses can be implicated in tumorigenesis, retroviruses are the only taxonomic group of RNA viruses that are oncogenic. Various retroviruses, such as Human Immunodeficiency Virus (HIV), which is the etiological agent responsible for acquired immune deficiency syndrome (AIDS) in humans, are also responsible for several very unusual diseases of the immune system of higher animals.

[0005] Human Immunodeficiency Virus (HIV) is a member of the lentiviruses, a subfamily of retroviruses. HIV infects and invades cells of the immune system; it breaks down the body's immune system and renders the patient susceptible to opportunistic infections and neoplasms. The immune defect appears to be progressive and irreversible, with a high mortality rate that approaches 100% over several years.

[0006] HIV-1 is trophic and cytopathic for T4 lymphocytes, cells of the immune system which express the cell surface differentiation antigen CD4, also known as OKT4, T4 and leu3. The viral tropism is due to the interactions between the viral envelope glycoprotein, gp120, and the cell-surface CD4 molecules (Dalgleish *et al.*, *Nature* 312:763-767 (1984)). These interactions not only mediate the infection of susceptible cells by HIV, but are also responsible for the virus-induced fusion of infected and uninfected T cells. This cell fusion results in the formation of giant multinucleated syncytia, cell death, and progressive depletion of CD4 cells in HIV-infected patients. These events result in HIV-induced immunosuppression and its subsequent sequelae, opportunistic infections and neoplasms.

[0007] In addition to CD4+ T cells, the host range of HIV includes cells of the mononuclear phagocytic lineage (Dalgleish *et al.*, *supra*), including blood monocytes, tissue macrophages, Langerhans cells of the skin and dendritic reticulum cells within lymph nodes. HIV is also neurotropic, capable of infecting monocytes and macrophages in the central nervous system causing severe neurologic damage. Macrophage/monocytes are a major reservoir of HIV. They can interact and fuse with CD4-bearing T cells, causing T cell depletion and thus contributing to the pathogenesis of AIDS.

[0008] Considerable progress has been made in the development of drugs for HIV-1 therapy during the past few years. Therapeutic agents for HIV include, but are not limited

- 3 -

to, AZT, 3TC, ddC, d4T, ddI, tenofovir, abacavir, nevirapine, delavirdine, emtricitabine, efavirenz, saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, amprenavir, fosamprenavir, tipranavir, and atazanavir or any other antiretroviral drugs or antibodies in combination with each other, or associated with a biologically based therapeutic, such as, for example, gp41-derived peptides enfuvirtide (Fuzeon; Trimeris-Roche) and T-1249 (Trimeris), or soluble CD4, antibodies to CD4, and conjugates of CD4 or anti-CD4. Combinations of these drugs are particularly effective and can reduce levels of viral RNA to undetectable levels in the plasma and slow the development of viral resistance, with resulting improvements in patient health and life span.

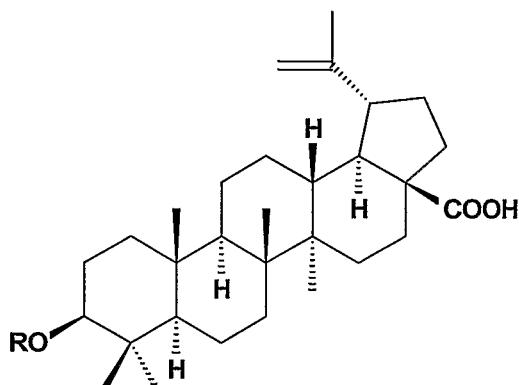
[0009] Despite these advances, there are still problems with the currently available drug regimens. Many of the drugs exhibit severe toxicities, have other side-effects (*e.g.*, fat redistribution) or require complicated dosing schedules that reduce compliance and thereby limit efficacy. Resistant strains of HIV often appear over extended periods of time even on combination therapy. The high cost of these drugs is also a limitation to their widespread use, especially outside of developed countries.

[0010] There is still a major need for the development of additional drugs to circumvent these issues. Ideally these would target different stages in the viral life cycle, adding to the armamentarium for combination therapy, and exhibit minimal toxicity, yet have lower manufacturing costs.

[0011] Previously, betulinic acid and platanic acid were isolated as anti-HIV principles from *Syzigium claviflorum*. Betulinic acid and platanic acid exhibited inhibitory activity against HIV-1 replication in H9 lymphocyte cells with EC₅₀ values of 1.4 μ M and 6.5 μ M, respectively, and T.I. values of 9.3 and 14, respectively. Hydrogenation of betulinic acid yielded dihydrobetulinic acid, which showed slightly more potent anti-HIV activity with an EC₅₀ value of 0.9 and a T.I. value of 14 (Fujioka, T., *et al.*, *J. Nat. Prod.* 57:243-247 (1994)).

[0012] Esterification of betulinic acid with certain substituted acyl groups, such as 3',3'-dimethylglutaryl and 3',3'-dimethylsuccinyl groups produced derivatives having enhanced activity (Kashiwada, Y., *et al.*, *J. Med. Chem.* 39:1016-1017 (1996)). Acylated betulinic acid and dihydrobetulinic acid derivatives that are potent anti-HIV agents are also described in U.S. Patent No. 5,679,828.

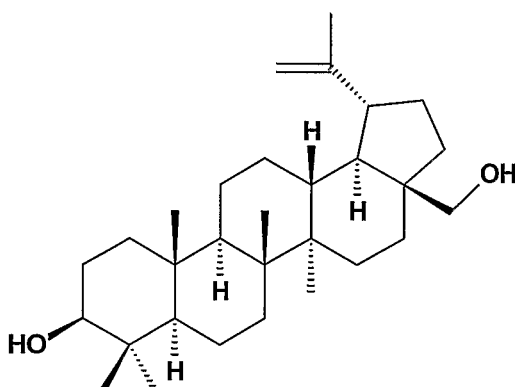
- 4 -



R = H (Betulinic acid)

[0013] U.S. Patent No. 5,468,888 discloses 28-amido derivatives of lupanes that are described as having a cytoprotecting effect for HIV-infected cells.

[0014] Japanese Patent Application No. JP 01 143,832 discloses that betulin and 3,28-diester thereof are useful in the anti-cancer field.



(Betulin)

[0015] Esterification of the 3 carbon of betulin with succinic acid produced a compound capable of inhibiting HIV-1 activity (Pokrovskii, A.G. *et al.*, *Gos. Nauchnyi Tsentri Virusol. Biotekhnol. "Vector"* 9:485-491 (2001)).

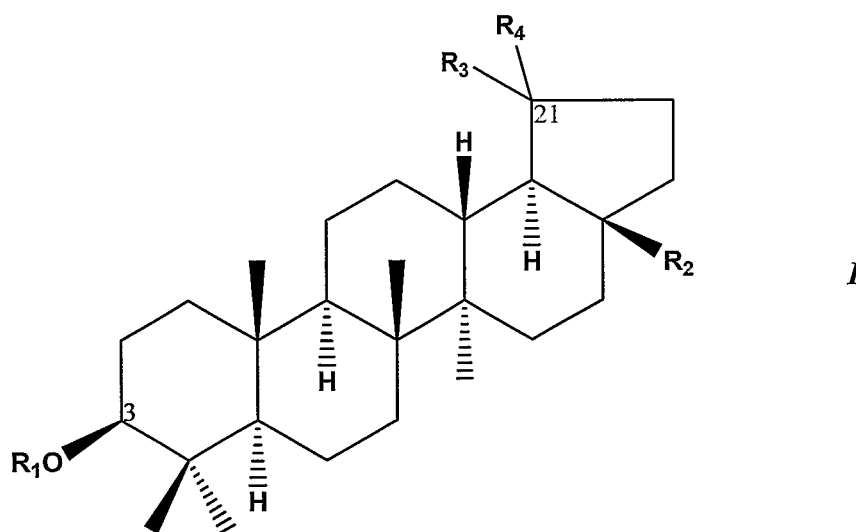
[0016] A need continues to exist for compounds which possess potent antiretroviral activity, especially anti-HIV activity, with improved biodistribution properties and different modes of action. Such compounds are urgently needed to add to existing anti-HIV therapies. There is also a need for safe and effective compounds that can be

- 5 -

topically applied to vaginal or other mucosa to prevent HIV infections between individuals.

SUMMARY OF THE INVENTION

[0017] The present invention is related to novel betulin derivative compounds having Formula *I*,



or a pharmaceutically acceptable salt or prodrug thereof, wherein the substituents are as defined herein.

[0018] Another aspect of the present invention is directed to pharmaceutical compositions, comprising one or more compounds of Formula *I*, and a pharmaceutically acceptable carrier or diluent. One or more additional pharmaceutically active compounds can also be included in these compositions.

[0019] The compounds of Formula *I* are useful as anti-retroviral agents. Therefore, the present invention provides methods for inhibiting a retroviral infection in cells or tissue of an animal, comprising administering an effective retroviral inhibiting amount of a compound of Formula *I*. Some embodiments are directed to a method for treating a patient suffering from a retroviral-related pathology, comprising administering to the subject a retroviral inhibiting effective amount of a pharmaceutical composition that includes a compound of Formula *I*. Also included is a method of treating HIV-infected cells, wherein the HIV infecting said cells does not respond to other HIV therapies.

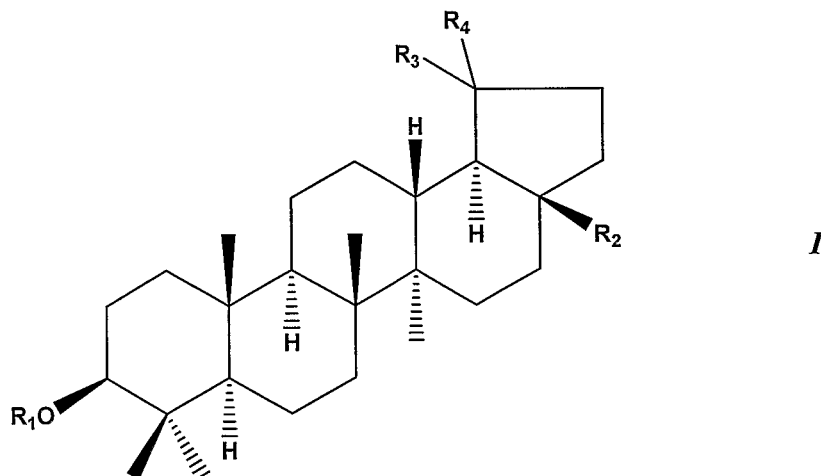
- 6 -

- [0020] The betulin derivatives of Formula *I* can be used in a combination therapy with one or more antiviral agents. Thus, the present invention provides a method of treating a patient suffering from a retroviral-related pathology, comprising administering to the patient a retroviral inhibiting effective amount of at least one compound of Formula *I* in combination with one or more antiviral agents. The present invention is also directed to a method for treating a subject infected with HIV-1 by administering at least one of the above-noted betulin derivatives, optionally in combination with any one or more of the known anti-AIDS therapeutics or an immunostimulant.
- [0021] The present invention also provides a method of preventing transmission of HIV infection between individuals. In particular, the present invention provides a method of preventing transmission of HIV infection from an HIV infected pregnant woman to a fetus, comprising administering to the woman and/or the fetus a retroviral inhibiting effective amount of one or more compounds of Formula *I* during pregnancy or immediately prior to, at, or subsequent to birth.
- [0022] Further, the present invention provides a method of preventing transmission of HIV infection during sexual intercourse, comprising applying a retroviral inhibiting effective amount of a topical composition including one or more compounds of Formula *I* to vaginal or other mucosa prior to sexual intercourse.
- [0023] Furthermore, the present invention is directed to a method for making compounds of Formula *I*.
- [0024] Additional embodiments and advantages of the invention will be set forth in part in the description as follows, and in part will be obvious from the description, or can be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.
- [0025] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

- 7 -

DETAILED DESCRIPTION

[0026] The present invention is directed to compounds having Formula *I*:

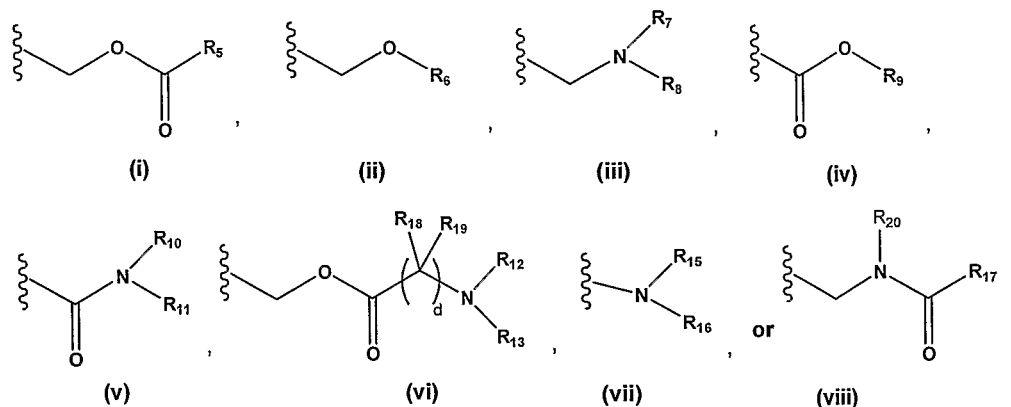


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

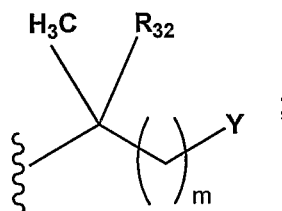
R_1 is C_3 - C_{20} alkanoyl, carboxyalkanoyl, carboxyalkenoyl, alkoxyalkanoyl, alkenyloxyalkanoyl, cyanoalkanoyl, hydroxyalkanoyl, aminocarbonylalkanoyl, hydroxyaminocarbonylalkanoyl, monoalkylaminocarbonylalkanoyl, dialkylaminocarbonylalkanoyl, heteroarylalkanoyl, heterocyclalkanoyl, heterocyclcarbonylalkanoyl, heteroarylaminocarbonylalkanoyl, heterocyclaminocarbonylalkanoyl, cyanoaminocarbonylalkanoyl, alkylsulfonylaminocarbonylalkanoyl, arylsulfonylaminocarbonylalkanoyl, sulfoaminocarbonylalkanoyl, phosphonoaminocarbonylalkanoyl, phosphono, sulfo, phosphonoalkanoyl, sulfoalkanoyl, alkylsulfonylalkanoyl, or alkylphosphonoalkanoyl;

R_2 is formyl, carboxyalkenyl, heterocycl, heteroaryl, $-CH_2SR_{14}$, CH_2SOR_{14} , $CH_2SO_2R_{14}$,

- 8 -



R_3 is hydrogen, hydroxyl, isopropenyl, isopropyl, 1'-hydroxyisopropyl, 1'-haloisopropyl, 1'-thioisopropyl, 1'-trifluoromethylisopropyl, 2'-hydroxyisopropyl, 2'-haloisopropyl, 2'-thioisopropyl, 2'-trifluoromethylisopropyl, 1'-hydroxyethyl, 1'-(alkoxy)ethyl, 1'-(alkoxyalkoxy)ethyl, 1'-(arylalkoxy)ethyl; 1'-(arylcabonyloxy)ethyl, acetyl, 1'-(hydroxyl)-1'-(hydroxyalkyl)ethyl, (2'-oxo)tetrahydrooxazolyl, 1',2'-epoxyisopropyl, 2'-haloisopropenyl, 2'-hydroxyisopropenyl, 2'-aminoisopropenyl, 2'-thioisopropenyl, 3'-haloisopropenyl, 3'-hydroxyisopropenyl, 3'-aminoisopropenyl, 3'-thioisopropenyl, 1'-alkoxyethyl, 1'-hydroxyiminoethyl, 1'-alkoxyiminoethyl, or



wherein Y is $-\text{SR}_{33}$ or $-\text{NR}_{33}\text{R}_{34}$;

R_{32} is hydrogen or hydroxy;

R_{33} and R_{34} are independently hydrogen, alkyl, alkanoyl, arylalkyl, heteroarylalkyl, arylsulfonyl or arylaminocarbonyl; or

R_{33} and R_{34} can be taken together with the nitrogen to which they are attached to form a heterocycle, wherein the heterocycle can optionally include one or more additional nitrogen, sulfur or oxygen atoms;

m is zero to three;

R_4 is hydrogen; or

R_3 and R_4 can be taken together to form oxo, alkylimino, alkoxyimino or benzyloxyimino;

R₅ is C₂-C₂₀ alkyl, alkenyl, alkynyl, carboxy(C₂-C₂₀)alkyl, amino, aminoalkyl, dialkylamino, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, cyanoalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, sulfo, phosphono, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, alkanoylaminoalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, heterocyclylcarbonylalkyl, cycloalkylcarbonylalkyl, heteroarylalkylaminocarbonylalkyl, arylalkylaminocarbonylalkyl, heterocyclylalkylaminocarbonylalkyl, carboxyalkylaminocarbonylalkyl, arylsulfonylaminocarbonylalkyl, alkylsulfonylaminocarbonylalkyl, arylphosphonoaminocarbonylalkyl, alkylphosphonoaminocarbonylalkyl, or hydroxyimino(amino)alkyl;

R₆ is hydrogen, phosphono, sulfo, alkyl, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, carboxyalkyl, alkoxyalkyl, cyanoalkyl; CH₂CONR₇R₈, trialkylsilyl, ethoxyethyl (OEE), or tetrahydropyranyl ether (OTHP);

R₇ and R₈ are independently hydrogen, alkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxyalkyl, alkoxyalkoxyalkyl, alkoxyalkylaminocarbonylalkyl, alkoxyalkylaminocarbonylalkyl, aminoalkoxyalkyl, alkylaminocarbonylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, arylaminocarbonylalkyl, cycloalkyl, alkylsulfonyl, arylsulfonyl, or heteroarylsulfonyl, heterocyclylsulfonyl, or R₇ and R₈ can together with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl group, wherein the heterocyclyl or heteroaryl can optionally include one or more additional nitrogen, sulfur or oxygen atoms;

R₉ is hydrogen, phosphono, sulfo, alkyl, alkenyl, trialkylsilyl, cycloalkyl, carboxyalkyl, alkoxyalkyl, cyanoalkyl, phosphonoalkyl, sulfoalkyl, alkylsulfonyl, alkylphosphono, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, or dialkoxyalkyl;

R₁₀ and R₁₁ are independently hydrogen, alkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, alkoxyalkoxyalkyl, alkoxyalkylaminocarbonylalkyl,

- 10 -

alkoxycarbonylalkyl, hydroxycarbonylalkyl, alkoxycarbonylaminoalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, arylcarbonylaminoalkyl, heterocyclylheterocyclylalkyl, heterocyclylarylalkyl, arylaminoalkyl, aminocycloalkyl, alkylsulfonyl, arylsulfonyl, alkylsulfonylaminoalkyl, arylsulfonylaminoalkyl, or cycloalkyl, or alkyl interrupted by one or more oxygen atoms, or R_{10} and R_{11} can together with the nitrogen atom to which they are attached form a heterocyclyl group, wherein the heterocyclyl can optionally include one or more additional nitrogen, sulfur or oxygen atoms;

R_{12} and R_{13} are independently hydrogen, alkyl, alkenyl, alkylamino, alkynyl, alkoxy, alkoxycarbonyl, alkoxyaminoalkyl, cycloalkyloxo, heterocyclylaminoalkyl, cycloalkyl, cyanoalkyl, cyano, sulfo, phosphono, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, alkoxyalkyl, heteroaryl, heteroarylalkyl, dialkylaminoalkyl, heterocyclylalkyl, or R_{12} and R_{13} can together with the nitrogen atom to which they are attached form a heterocyclyl group or a heteroaryl group, wherein the heterocyclyl or heteroaryl can optionally include one or more additional nitrogen, sulfur or oxygen atoms, or R_{12} and R_{13} can together with the nitrogen atom to which they are attached form an alkylazo group, and d is one to six;

R_{14} is hydrogen, alkyl, alkenyl, arylalkyl, carboxyalkyl, carboxyalkenyl, alkoxycarbonylalkyl, alkenyloxycarbonylalkyl, cyanoalkyl, hydroxyalkyl, carboxybenzyl, aminocarbonylalkyl;

R_{15} and R_{16} are independently hydrogen, alkyl, alkoxycarbonyl, alkoxyaminoalkyl, cyclo(oxo)alkyl, cycloalkylcarbonyl, heterocyclylaminoalkyl, cycloalkyl, cyanoalkyl, cyano, sulfo, phosphono, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, alkoxyalkyl, heterocyclylalkyl, or R_{15} and R_{16} can together with the nitrogen atom to which they are attached form a heterocyclyl group, wherein the heterocyclyl can optionally include one or more additional nitrogen, sulfur or oxygen atoms, or R_{15} and R_{16} can together with the nitrogen atom to which they are attached form an alkylazo;

R_{17} is hydrogen, alkyl, perhaloalkyl, alkoxy, alkenyl, carboxyalkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, alkoxycarbonyl, cyanoalkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, cycloalkyl,

- 11 -

cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, alkanoylaminoalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, heterocyclylcarbonylalkyl, cycloalkylcarbonylalkyl, heteroarylalkylaminocarbonylalkyl, arylalkylaminocarbonylalkyl, heterocyclylalkylaminocarbonylalkyl, carboxyalkylaminocarbonylalkyl, arylsulfonylaminoalkyl, alkylsulfonylaminoalkyl, or hydroxyimino(amino)alkyl;

R_{18} and R_{19} are independently hydrogen, methyl or ethyl, preferably hydrogen or methyl; and d is from one to six; and

R_{20} is hydrogen, C_1 - C_6 alkyl, or aryl;

wherein any alkyl, aryl, cycloalkyl, heterocyclyl, or heteroaryl group, or any substituent which includes any of these groups, is optionally substituted.

[0027] Preferred compounds of Formula *I* are defined as above, with the provisos that:

when R_1 is C_3 - C_{20} alkanoyl, carboxyalkanoyl or alkoxycarbonyl, and R_3 is isopropenyl, isopropyl, 2'-hydroxyisopropyl, 2'-haloisopropyl, or 2'-thioisopropyl, and R_2 is formula (i), formula (ii) or formula (iv), then R_5 cannot be C_2 - C_{20} alkyl or carboxy(C_2 - C_{20})alkyl, or R_6 cannot be hydrogen or carboxyalkyl, or R_9 cannot be hydrogen;

when R_1 is carboxyalkanoyl, and R_3 is isopropenyl, isopropyl, isobutyl, isobutenyl, or 2'-hydroxyisopropyl, and R_2 is formula (ii), formula (iv) or formula (v), then R_6 cannot be alkyl, R_9 cannot be alkyl or carboxyalkyl, and R_{10} and R_{11} cannot be carboxyalkyl;

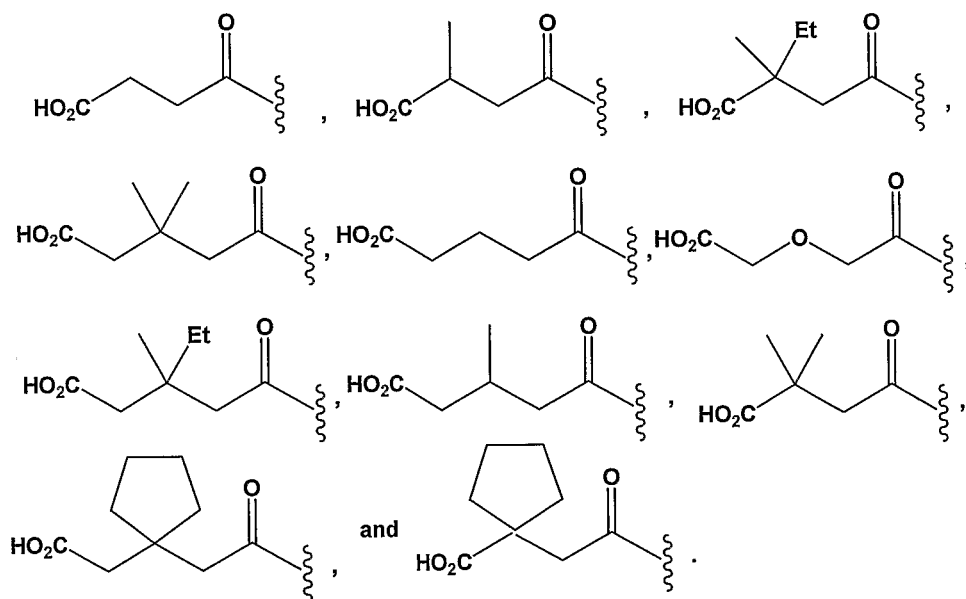
when R_1 is carboxyalkenoyl, R_2 is formula (ii), and R_3 is isopropenyl, then R_6 cannot be hydrogen; and

when R_1 is 3',3'-dimethylsuccinyl, R_2 is formula (iv), and R_9 is hydrogen, then R_3 cannot be 1'-hydroxyethyl, 1'-(oxo)ethyl or 1'-(alkoxy)ethyl.

[0028] In certain embodiments, R_1 is C_3 - C_{20} alkanoyl, carboxyalkanoyl, carboxyalkenoyl, alkoxycarbonylalkanoyl, alkenyloxycarbonylalkanoyl, cyanoalkanoyl, hydroxyalkanoyl, aminocarbonylalkanoyl, monoalkylaminocarbonylalkanoyl, dialkylaminocarbonylalkanoyl, heteroarylalkanoyl, heteroarylaminocarbonylalkanoyl, cyanoaminocarbonylalkanoyl, alkylsulfonylaminoalkyl, arylsulfonylaminoalkyl, tetrazolylalkanoyl, phosphonoalkyl, or sulfoalkyl. In

certain other embodiments, R_1 is C_3 - C_{20} alkanoyl, carboxyalkanoyl, carboxyalkenoyl, alkoxyalkanoyl, alkenyloxyalkanoyl, cyanoalkanoyl, hydroxyalkanoyl, aminocarbonylalkanoyl, alkylaminocarbonylalkanoyl, alkylsulfonylaminocarbonylalkanoyl, arylsulfonylaminocarbonylalkanoyl, or tetrazolylalkanoyl.

[0029] In other embodiments, R_1 can be carboxyalkanoyl, wherein the carboxyalkanoyl is succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl. Additional suitable carboxyalkanoyl include 2',2'-dimethylmalonyl, 2',3'-dihydroxysuccinyl, 2',2',3',3'-tetramethylsuccinyl, 3'-methylsuccinyl, or 2',2'-dimethylsuccinyl. In certain preferred embodiments, R_1 is a carboxyalkanoyl selected from the group consisting of:



[0030] In some embodiments, R_1 is alkenyloxyalkanoyl, wherein the alkenyloxyalkanoyl is C_1 - C_4 alkene ester of 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl. In some embodiments, a suitable C_1 - C_4 alkene ester is an allyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl.

[0031] In some embodiments, R_1 is alkoxyalkanoyl. Suitable alkoxyalkanoyl can include C_1 - C_4 alkyl esters of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl.

- 13 -

Preferably, the C₁-C₄ alkyl ester is a methyl, ethyl or propyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl.

[0032] Suitable R₁ substituents include alkanoyl. Preferably, the alkanoyl is *tert*-butylcarbonyl or isopropylcarbonyl. Suitable R₁ substituents include carboxyalkenoyl. Preferably, the carboxyalkenoyl is alk-2-enyloyl. Suitable R₁ substituents include cyanoalkanoyl. Preferably the cyanoalkanoyl is 4'-cyanopropanoyl or 4'-cyanobutanoyl. Suitable R₁ substituents include hydroxyalkanoyl. Preferably, the hydroxyalkanoyl is 3',3'-dimethyl-4'-hydroxybutanoyl. Suitable R₁ substituents include aminocarbonylalkanoyl. Preferably, the aminocarbonylalkanoyl is 4'-amino-3',3'-dimethylsuccinyl or 4'-aminosuccinyl. Suitable R₁ substituents include alkylsulfonylaminocarbonylalkanoyl. Preferably, the alkylsulfonylaminocarbonylalkanoyl is 4'-methylsulfonylamino-3',3'-dimethylsuccinyl. Suitable R₁ substituents include arylsulfonylaminocarbonylalkanoyl. Preferably, the arylsulfonylaminocarbonylalkanoyl is 4'-phenylsulfonylamino-3',3'-dimethylsuccinyl. Suitable R₁ substituents include tetrazolylalkanoyl. Preferably, the tetrazolylalkanoyl is C₂-C₆ tetrazolylalkanoyl. Suitable R₁ substituents include phosphonoalkyl. Preferably, the phosphonoalkyl is C₁-C₆ phosphonoalkyl. Suitable R₁ substituents include sulfoalkyl. Preferably, the sulfoalkyl is C₁-C₆ sulfoalkyl. Suitable R₁ substituents include heterocyclylcarbonylalkanoyl. Preferably, the heterocyclylcarbonylalkanoyl is 5'-morpholino-3',3'-dimethylglutaryl. Suitable R₁ substituents include hydroxyaminocarbonylalkanoyl.

[0033] In some other embodiments, R₁ can be C₃-C₂₀ alkanoyl, carboxyalkanoyl, carboxyalkenoyl, alkoxy carbonylalkanoyl, alkenyloxycarbonylalkanoyl, cyanoalkanoyl, hydroxyalkanoyl, aminocarbonylalkanoyl, hydroxyaminocarbonylalkanoyl, monoalkylaminocarbonylalkanoyl, dialkylaminocarbonylalkanoyl, heteroarylalkanoyl, heterocyclylalkanoyl, heterocyclylcarbonylalkanoyl, heteroarylaminocarbonylalkanoyl, heterocyclylaminocarbonylalkanoyl, cyanoaminocarbonylalkanoyl, alkylsulfonylaminocarbonylalkanoyl, arylsulfonylaminocarbonylalkanoyl, sulfoaminocarbonylalkanoyl, phosphonoaminocarbonylalkanoyl, tetrazolylalkanoyl, phosphono, sulfo, phosphonoalkanoyl, sulfoalkanoyl, alkylsulfonylalkanoyl, or alkylphosphonoalkanoyl.

- 14 -

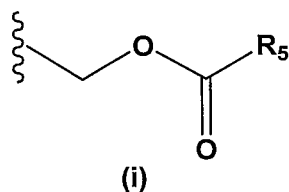
[0034] In some embodiments, R_2 is formyl, carboxyalkenyl, heterocyclyl, heteroaryl, - CH_2SR_{14} , CH_2SOR_{14} , or $CH_2SO_2R_{14}$.

[0035] In some other embodiments, R_{14} is hydrogen, alkyl, alkenyl, arylalkyl, carboxyalkyl, carboxyalkenyl, alkoxycarbonylalkyl, alkenyloxycarbonylalkyl, cyanoalkyl, hydroxyalkyl, carboxybenzyl, aminocarbonylalkyl.

[0036] In some embodiments, R_2 is heterocyclyl. Suitable heterocyclyl groups include, but are not limited to, oxazolyl, morpholinyl, piperidinyl, piperazinyl, pyranyl, azetidyl, dihydropyrrolyl, dihydrofuranyl, 1,3-oxazinyl, isoxazinyl, and oxathiazinyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2-oxathiolyl, 1,3-oxathiolyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dioxanyl, 1,3-dioxathianyl, and 1,3-dithianyl any of which can be optionally substituted.

[0037] In some embodiments, R_2 is heteroaryl. Suitable heteroaryl groups include, but are not limited to, tetrazolyl, pyridinyl, imidazolyl, isoxazolyl, furanyl, oxazolyl, thiazolyl, pyrrolyl, thienyl, pyrazolyl, triazolyl, oxazolyl, isothiazolyl, oxadiazolyl, oxatriazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl, any of which can be optionally substituted.

[0038] A group of compounds useful in the present invention are those wherein R_2 is

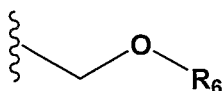


[0039] In some embodiments, R_5 is C_2 - C_{20} alkyl, alkenyl, alkynyl, carboxy(C_2 - C_{20})alkyl, amino, aminoalkyl, dialkylamino, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, cyanoalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, alkanoylaminoalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, heterocyclylcarbonylalkyl, cycloalkylcarbonylalkyl, heteroarylalkylaminocarbonylalkyl, arylalkylaminocarbonylalkyl, heterocyclylalkylaminocarbonylalkyl, carboxyalkylaminocarbonylalkyl, arylsulfonylaminocarbonylalkyl, alkylsulfonylaminocarbonylalkyl, or hydroxyimino(amino)alkyl. In some embodiments, R_5 is alkyl, preferably C_1 - C_6 alkyl. In some embodiments, R_5 is alkenyl, preferably

propen-2-yl, buten-2-yl, or penten-2-yl. In some embodiments, R_5 is C_2 - C_{10} carboxyalkyl, preferably 2'-carboxy-2',2'-dimethylethyl or 3'-carboxy-3',3'-dimethylpropyl. R_5 can also be heterocyclyl, heterocyclylalkyl, heterocycloalkanoyl, or heteroarylalkyl. Preferable heterocyclyls include tetrazolyl, pyridinyl, imidazolyl, isoxazolyl, morpholinyl, or furanyl. Preferable heterocycloalkyls include heterocyclyl(C_1 - C_6)alkyl, wherein the heterocyclyls are as previously defined.

[0040] In some embodiments, R_5 is C_2 - C_{20} alkyl, alkenyl, C_2 - C_{20} carboxyalkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, cyano, cyanoalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, sulfo, phosphono, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, alkanoylaminoalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, heterocyclylcarbonylalkyl, cycloalkylcarbonylalkyl, heteroarylalkylaminocarbonylalkyl, arylalkylaminocarbonylalkyl, heterocyclylalkylaminocarbonylalkyl, carboxyalkylaminocarbonylalkyl, arylsulfonylaminocarbonylalkyl, alkylsulfonylaminocarbonylalkyl, arylphosphonoaminocarbonylalkyl, alkylphosphonoaminocarbonylalkyl, or hydroxyimino(amino)alkyl.

[0041] A group of compounds useful in the present invention are those wherein R_2 is



(ii)

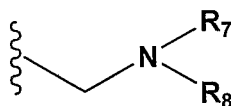
[0042] Suitable R_6 substituents include hydrogen, phosphono, sulfo. Suitable R_6 substituents also include alkyl, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, carboxyalkyl, alkoxycarbonylalkyl, cyanoalkyl; $\text{CH}_2\text{CONR}_7\text{R}_8$, trialkylsilyl, ethoxyethyl (OEE), or tetrahydropyranyl ether (OTHP). In some embodiments, R_6 can be one of the protecting groups listed above, or any other suitable protecting group known in the art, e.g., a suitable protecting group as described in *Protective Groups in Organic Synthesis*, 3rd ed. (eds. T.W. Greene and P.G.M. Wuts, John Wiley and Sons, Inc. (1999)), incorporated herein by reference. More preferred substituents include hydrogen, cycloalkyl, heterocyclyl, heteroaryl, carboxyalkyl, alkoxycarbonylalkyl, or cyanoalkyl; more

- 16 -

preferably cycloalkyl, heterocyclyl, heteroaryl, carboxyalkyl, alkoxycarbonylalkyl, or cyanoalkyl. In certain embodiments, R_6 is cycloalkyl or heterocycloalkyl. In other embodiments, R_6 is cyclopropyl, cyclopentyl, cyclohexyl, pyridinylmethyl or octacyclen-2-yl, preferably, pyridinylmethyl or octacyclen-2-yl. In other embodiments, R_6 is carboxyalkyl or R_6 is alkoxycarbonylalkyl or R_6 is cyanoalkyl.

[0043] In some embodiments, R_6 is hydrogen, phosphono, sulfo, alkyl, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, cycloalkyl, heterocyclyl, aryl, heteroaryl, carboxyalkyl, alkoxycarbonylalkyl, or cyanoalkyl.

[0044] A group of compounds useful in the present invention are compounds wherein R_2 is



(iii)

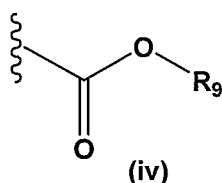
[0045] In some other embodiments, R_7 and R_8 are independently alkoxyalkylamine or hydrogen. In some embodiments, R_7 and R_8 are independently alkyl. Preferably, R_7 is methoxyethyl and R_8 is hydrogen, or R_7 is methoxyethyl and R_8 is methyl. In some other embodiments, R_7 and R_8 are alkylsulfonyl, arylsulfonyl, or heteroarylsulfonyl, heterocyclylsulfonyl. Alternatively, R_7 and R_8 together with the nitrogen atom to which they are attached can form a heterocyclyl group, wherein the heterocyclyl group can optionally include one or more additional nitrogen, sulfur or oxygen groups. Preferable heterocyclyl groups include, but are not limited to, pyrrolidinyl, morpholinyl, piperazinyl, piperidinyl, and thiomorpholinyl. In some embodiments, the heterocyclyl group is optionally substituted.

[0046] In some other embodiments, R_7 or R_8 are independently hydrogen, alkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxyalkyl, alkoxyalkoxyalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, arylcarbonylaminoalkyl, or cycloalkyl, or R_7 and R_8 can together with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl group, wherein

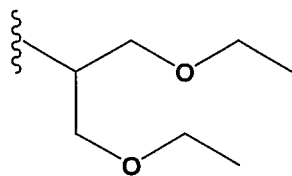
- 17 -

the heterocyclyl or heteroaryl can optionally include one or more additional nitrogen, sulfur or oxygen atoms.

[0047] A group of compounds useful in the present invention are compounds wherein R_2 is

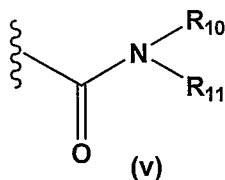


[0048] Suitable R_9 substituents include hydrogen, phosphono, sulfo, alkyl, alkenyl, trialkylsilyl, carboxyalkyl, alkoxycarbonyloxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, cyanoalkyl, phosphonoalkyl, sulfoalkyl, alkylsulfonyl, alkylphosphono, aryl, heteroaryl, heterocyclyl, or dialkoxyalkyl, preferably hydrogen, phosphono, sulfo, alkoxycarbonyloxyalkyl, cyanoalkyl, phosphonoalkyl, sulfoalkyl, alkylsulfonyl, aryl, heteroaryl, heterocyclyl, or dialkoxyalkyl, more preferably hydrogen, alkoxycarbonyloxyalkyl, cyanoalkyl, alkoxyalkyl, or dialkoxyalkyl. In some embodiments, R_9 is alkoxycarbonyloxyalkyl. Suitable alkoxycarbonyloxyalkyl include *tert*-butoxycarbonyloxymethyl and *tert*-butoxycarbonyloxymethyl(methyl). In some embodiments, R_9 is dialkylaminoalkyl, preferably dimethylaminoalkyl, more preferably dimethylaminoethyl. In some embodiments, R_9 is heterocyclyl, preferably tetrahydrofuranyl or tetrahydropyranyl, more preferably tetrahydrofuran-3-yl or tetrahydropyran-4-yl. In some embodiments, R_9 is phosphono or sulfo. In some embodiments, R_9 is dialkoxyalkyl, for example



[0049] In some other embodiments, R_9 is hydrogen, phosphono, sulfo, alkyl, alkylsilyl, cycloalkyl, carboxyalkyl, alkoxycarbonyloxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, cyanoalkyl, phosphonoalkyl, sulfoalkyl, alkylsulfonyl, alkylphosphono, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, or dialkoxyalkyl.

[0050] A group of compounds useful in the present invention can be wherein R₂ is



R₁₀ and R₁₁ can both be hydrogen. In some embodiments, R₁₀ and R₁₁ can be independently alkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, alkoxyalkoxyalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkoxyalkyl, alkoxycarbonylaminoalkyl, aminoalkoxyalkyl, alkoxycarbonylamino, alkoxycarbonylalkyl, heterocyclylheterocyclylalkyl, heterocyclylarylalkyl, arylaminoalkyl, aminocycloalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, arylcarbonylaminoalkyl, alkylsulfonyl, arylsulfonyl, alkylsulfonylaminoalkyl, arylsulfonylaminoalkyl, or cycloalkyl. In some embodiments, R₁₀ and R₁₁ can be independently alkyl interrupted by one or more oxygen atoms. Alternatively, R₁₀ and R₁₁ can be independently alkyl, aminoalkyl, aminoalkoxyalkyl, alkoxyalkyl, cycloalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, alkylcarbonylaminoalkyl, alkoxyalkoxyalkyl, or dialkylaminoalkyl. Preferably, R₁₀ and R₁₁ are alkyl or aminoalkyl. In other embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is heterocyclyl, aryl, arylalkyl, arylcarbonylaminoalkyl, or heterocycloalkyl. In other embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is alkoxycarbonylamino, alkoxycarbonylalkyl, cyanoalkyl, alkylsulfonyl. In some embodiments, R₁₀ and R₁₁ are taken together to form a heterocyclyl group, wherein the heterocyclyl group can optionally include one or more additional nitrogen, sulfur or oxygen atoms. Preferred heterocyclyl groups include, but are not limited to, morpholinyl, piperidinyl, pyrrolidinyl, thiomorpholinyl, and piperazinyl. In some embodiments, R₁₀ is phenylsulfonyl and R₁₁ is hydrogen. In some embodiments, both R₁₀ and R₁₁ are alkoxyalkyl, preferably both R₁₀ and R₁₁ are methoxyethyl.

[0051] In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is alkyl, wherein the alkyl group is selected from methyl, 2-hydroxyethyl, 2-hydroxy-2-

methylpropyl, propyl, ethyl, isopropyl, (R)-2-[2,3-dihydroxypropyl], (S)-2-[2,3-dihydroxypropyl], (S)-2-[1-hydroxy-4-methylpentyl], (R)-2-[1-hydroxy-4-methylpentyl], or (S)-1-carboxy-3-methylbutyl. In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is aminoalkyl, wherein the aminoalkyl is 2-(1-amino-2-methylpropyl). In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is alkoxyalkyl, wherein the alkoxyalkyl group is 2-methoxyethyl or 2-hydroxyethoxyethyl. In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is alkoxycarbonylaminoalkyl, wherein the alkoxycarbonylaminoalkyl group is 2-(*tert*-butoxycarbonylamino)ethyl. In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is dialkylaminoalkyl, wherein the dialkylaminoalkyl group is 2-*N,N*-dimethylaminoethyl, 2-*N,N*-dimethylaminopropyl, (1R, 3R)-3-*N,N*-dimethylaminocyclopentyl, or (1S, 3S)-3-*N,N*-dimethylaminocyclopentyl.

[0052] In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is cycloalkyl, heterocyclyl, aryl, arylalkyl, arylcarbonylaminoalkyl, arylsulfonyl, heterocyclylheterocyclylalkyl, heterocyclylarylalkyl, arylaminoalkyl, aminocycloalkyl, or heterocycloalkyl. In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is cycloalkyl, wherein the cycloalkyl group is cyclopropyl. In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is heterocyclyl, wherein the heterocyclyl group is selected from (S)-1-[(*tert*-butoxycarbonyl)pyrrolidinyl], (R)-1-[(*tert*-butoxycarbonyl)pyrrolidinyl], (S)-3-pyrrolidinyl, (R)-3-pyrrolidinyl, (S)-3-(1-methylpyrrolidinyl), (R)-3-(1-methylpyrrolidinyl), (S)-3-(1-acetylpyrrolidinyl), (R)-3-(1-acetylpyrrolidinyl), (S)-3-(1-methylsulfonylpyrrolidinyl), (R)-3-(1-methylsulfonylpyrrolidinyl), 4-(1-(*tert*-butoxycarbonyl)piperidinyl), 4-piperidinyl, 4-(1-methylpiperidinyl), or 4-[1-(1-hydroxyethyl)piperidinyl].

[0053] In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is aryl, wherein the aryl group is 4-fluorophenyl, 2-(1,3,4-thiadiazolyl)methyl, or 2,3-dichlorobenzyl, 4-azido-2,3,5,6-tetrafluorobenzyl. In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is arylalkyl, wherein the arylalkyl group is selected from 4-fluorobenzyl, 3-fluorobenzyl, 2-fluorobenzyl, 4-chlorobenzyl, 3-chlorobenzyl, 2-chlorobenzyl, 4-methylbenzyl, 3-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 3-methoxybenzyl, 2-methoxybenzyl, 4-*N,N*-dimethylaminobenzyl, 4-

trifluoromethylbenzyl, 4-carboxybenzyl, 3,4-dichlorobenzyl, 2,4-dichlorobenzyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-benzyl, 3-trifluoromethylbenzyl, 4-*tert*-butylbenzyl, 4-aminobenzyl, 4-acetamidobenzyl, (R)-1-phenylethyl, (S)-1-phenylethyl, (R)-2-hydroxy-1-phenylethyl, (S)-2-hydroxy-1-phenylethyl, or 2-phenylethyl.

[0054] In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is heterocycloalkyl, wherein the heterocycloalkyl group is selected from 4-(1-methylimidazolyl)methyl, 3-(5-methylisoxazolyl)methyl, 3-(4-morpholinyl)propyl, 3-(1-imidazolyl)propyl, 2-(4-methylmorpholinyl)methyl, 2-morpholinylmethyl, or 2-(4-*tert*-butoxycarbonyl morpholinyl)methyl. In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is heterocyclarylalkyl, wherein the heterocyclarylalkyl group is selected from 4-(4-morpholinyl)benzyl or 4-(4-methylpiperazinyl)benzyl. In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is heterocyclheterocyclalkyl, wherein the heterocyclheterocyclalkyl group is 3-[6-(4-morpholinyl)pyridinyl]methyl. In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is arylaminoalkyl, wherein the arylaminoalkyl is 2-[(4-azido-2,3,5,6-tetrafluorobenzoyl)amino]ethyl. In some embodiments, R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is aminocycloalkyl, wherein the aminocycloalkyl is (1R, 3R)-3-aminocyclopentyl, (1S, 3S)-3-aminocyclopentyl, (1r, 4r)-4-aminocyclohexyl, or (1s, 4s)-4-aminocyclohexyl.

[0055] In some embodiments, one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is dialkylaminocycloalkyl, wherein the dialkylaminocycloalkyl is (1r, 4r)-4-*N,N*-dimethylaminocyclohexyl or (1s, 4s)-4-*N,N*-dimethylaminocyclohexyl.

In some embodiments, R₁₀ and R₁₁ are taken together to form one of 4-(*tert*-butoxycarbonyl)piperazinyl, morpholinyl, piperidinyl, piperazinyl,

4-(4-morpholinylcarbonyl)piperazinyl, 4-methylpiperazinyl,
4-ethylpiperazinyl, 4-isopropylpiperazinyl,
4-(cyclopropylmethyl)piperazinyl, 4-benzylpiperazinyl,
4-[3-(5-methylisoxazolyl)methyl]piperazinyl,
4-(4-pyridinylmethyl)piperazinyl, 4-acetyl piperazinyl,

4-(isopropylaminocarbonyl)piperazinyl,
 4-(methylsulfonyl)piperazinyl, 4-cyclopropylpiperazinyl,
 4-(2-methoxyethylaminocarbonyl)piperazinyl,
 4-(2-hydroxyethyl)piperazinyl, 4-(2-methoxyethyl)piperazinyl,
 4-(3-dimethylaminopropyl)piperazinyl, 4-(aminocarbonyl)piperazinyl, 4-
 (aminosulfonyl)piperazinyl, 3-oxopiperazinyl,
 4-methyl-3-oxopiperazinyl, 4-(hydroxyethyl)-3-oxopiperazinyl,
 4-(2-hydroxybenzoyl)piperazinyl,
 4-[3-(1,2,4-oxadiazolyl)methyl]piperazinyl,
 4-[4-(dimethylaminosulfonyl)benzyl]piperazinyl,
 4-[1-(1,2,3,4-tetrahydronaphthyl)]piperazinyl,
 4-[4-(acetamidobenzyl)]piperazinyl,
 (1S, 4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptanyl,
 (1R, 4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptanyl,
 (1S, 4S)-2,5-diazabicyclo[2.2.1]heptanyl,
 (1R, 4R)-2,5-diazabicyclo[2.2.1]heptanyl,
 (1S, 4S)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl,
 (1R, 4R)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl,
 4-(4-azido-2,3,5,6-tetrafluorobenzyl)piperazinyl, pyrrolidinyl,
 (R,S)-3-hydroxypyrrolidinyl, (R)- 3-hydroxypyrrolidinyl,
 (S)- 3-hydroxypyrrolidinyl,
 (R)-3-(*tert*-butoxycarbonylamino)pyrrolidinyl,
 (S)-3-(*tert*-butoxycarbonylamino)pyrrolidinyl,
 (R)- 3-aminopyrrolidinyl, (S)- 3-aminopyrrolidinyl,
 (R)- 2-(hydroxymethyl)pyrrolidinyl,
 (S)- 2-(hydroxymethyl)pyrrolidinyl,
 (S)- 2-(hydroxymethyl)pyrrolidinyl,
 (S)- 2-(hydroxymethyl)pyrrolidinyl,
 (S)- 2-(hydroxymethyl)pyrrolidinyl,
 (R)- 3-*N*-methylaminopyrrolidinyl, (S)- 3-*N*-methylaminopyrrolidinyl,
 (R)- 3-*N,N*-dimethylaminopyrrolidinyl,

- 22 -

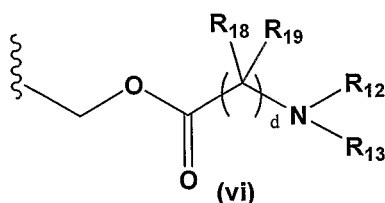
(S)- 3-*N,N*-dimethylaminopyrrolidinyl,
 (R)- 3-*N,N*-diethylaminopyrrolidinyl,
 (S)- 3-*N,N*-diethylaminopyrrolidinyl, (R)- 3-*N*-ethylaminopyrrolidinyl,
 (S)- 3-*N*-ethylaminopyrrolidinyl, (R)- 3-(4-morpholinyl)pyrrolidinyl,
 (S)- 3-(4-morpholinyl)pyrrolidinyl, (R)- 3-(1-pyrrolidinyl)pyrrolidinyl,
 (S)- 3-(1-pyrrolidinyl)pyrrolidinyl, 4-aminopiperidinyl,
 4-oxopiperidinyl, 4-hydroxypiperidinyl, 4-*N,N*-diaminopiperidinyl,
 4-(4-morpholinyl)piperidinyl, 4-acetamidopiperidinyl,
 4-(methylsulfonamide)piperidinyl, (R)- 3-acetamidopyrrolidinyl,
 (S)- 3-acetamidopyrrolidinyl,
 (R)- 3-(cyclopropanecarboxamido)pyrrolidinyl,
 (S)- 3-(cyclopropanecarboxamido)pyrrolidinyl,
 (R)- 3-(2-hydroxyacetamido)pyrrolidinyl,
 (S)- 3-(2-hydroxyacetamido)pyrrolidinyl,
 (R)- 3-(methylsulfonamido)pyrrolidinyl,
 (S)- 3-(methylsulfonamido)pyrrolidinyl,
 (R)- 2-(aminomethyl)pyrrolidinyl, (S)- 2-(aminomethyl)pyrrolidinyl,
 (R)- 2-(*N,N*-dimethylaminomethyl)pyrrolidinyl,
 (S)- 2-(*N,N*-dimethylaminomethyl)pyrrolidinyl,
 (R)- 2-(acetamidomethyl)pyrrolidinyl,
 (S)- 2-(acetamidomethyl)pyrrolidinyl,
 (R)- 2-(methylsulfonamidomethyl)pyrrolidinyl,
 (S)- 2-(methylsulfonamidomethyl)pyrrolidinyl,
 (R)- 2-(*N,N*-diethylaminomethyl)pyrrolidinyl,
 (S)- 2-(*N,N*-diethylaminomethyl)pyrrolidinyl,
 (R)- 2-(4-morpholinylmethyl)pyrrolidinyl,
 (S)- 2-(4-morpholinylmethyl)pyrrolidinyl,
 2,6-dimethylmorpholinyl, 1,4-oxazepanyl, thiomorpholinyl,
 thiomorpholinyl 1-oxide, or thiomorpholinyl 1,1-dioxide.

[0056] In some other embodiments, R₁₀ and R₁₁ are independently hydrogen, hydroxy, cyano, alkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyl,

- 23 -

carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, alkoxyalkoxyalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, arylcarbonylaminoalkyl, arylsulfonyl, or cycloalkyl, or alkyl interrupted by one or more oxygen atoms, or R_{10} and R_{11} can together with the nitrogen atom to which they are attached form a heterocyclyl group, wherein the heterocyclyl can optionally include one or more additional nitrogen, sulfur or oxygen atoms.

[0057] A group of compounds useful in the present invention are those compounds wherein R_2 is



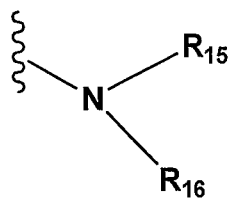
[0058] In some embodiments, one of R_{12} and R_{13} are hydrogen and one of R_{12} and R_{13} is alkylamino, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, cycloalkyl, cycloalkyloxy, heteroaryl, heteroarylalkyl, dialkylaminoalkyl, or cyanoalkyl. R_{12} and R_{13} can be hydrogen. In some embodiments, one or both of R_{12} and R_{13} can be cyano, sulfo, phosphono, sulfoalkyl, phosphonoalkyl, or alkylsulfonyl. Alternatively, R_{12} and R_{13} can together with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl, wherein the heterocyclyl or heteroaryl group can optionally include one or more additional nitrogen, sulfur or oxygen atoms. In some embodiments R_{18} and R_{19} can be independently hydrogen or C_1 - C_6 alkyl. In some embodiments, R_{18} and R_{19} can both be hydrogen. In some embodiments, R_{18} and R_{19} can both be methyl. In some embodiments, d can be one to six, preferably one to four, most preferably one to two. In some embodiments, d is one.

[0059] In some other embodiments, R_{12} and R_{13} are independently hydrogen, alkyl, alkoxycarbonyl, alkoxyaminoalkyl, cycloalkyloxy, heterocyclylaminoalkyl, cycloalkyl, cyanoalkyl, cyano, sulfo, phosphono, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, alkoxyalkyl, heterocyclylalkyl, or R_{12} and R_{13} can together with the nitrogen atom to which they are attached form a heterocyclyl group, wherein the heterocyclyl can optionally include one or more additional nitrogen, sulfur or oxygen

- 24 -

atoms, or R_{12} and R_{13} can together with the nitrogen atom to which they are attached form an alkylazo group, and b is one to six.

[0060] A group of compounds useful in the present invention are those compounds wherein R_2 is



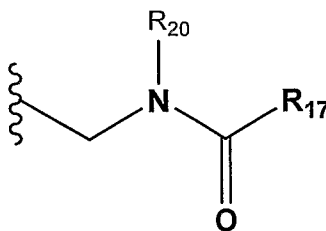
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[0061] R_{15} and R_{16} are independently hydrogen, alkyl, alkoxycarbonyl, alkoxyaminoalkyl, cyclo(oxo)alkyl, cycloalkylcarbonyl, heterocyclylaminoalkyl, cycloalkyl, cyanoalkyl, alkoxyalkyl, or heterocyclylalkyl. In some embodiments, R_{15} and R_{16} are independently cyano, sulfo, phosphono, sulfoalkyl, phosphonoalkyl, or alkylsulfonyl. In some embodiments, R_{15} and R_{16} can together with the nitrogen atom to which they are attached form a heterocyclyl group, wherein the heterocyclyl can optionally include one or more additional nitrogen, sulfur or oxygen atoms. In some embodiments, R_{15} and R_{16} together with the nitrogen atom to which they are attached form an alkylazo group.

[0062] In some embodiments, R_{15} and R_{16} are independently hydrogen, alkyl, alkoxycarbonyl, alkoxyaminoalkyl, cycloalkyloxy, heterocyclylaminoalkyl, cycloalkyl, cyanoalkyl, cyano, sulfo, phosphono, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, alkoxyalkyl, heterocyclylalkyl, or R_{15} and R_{16} can together with the nitrogen atom to which they are attached form a heterocyclyl group, wherein the heterocyclyl can optionally include one or more additional nitrogen, sulfur or oxygen atoms, or R_{15} and R_{16} can together with the nitrogen atom to which they are attached form an alkylazo group.

[0063] A group of compounds useful in the present invention are compounds wherein R_2

- 25 -



(viii)

[0064] R_{17} is hydrogen, alkyl, perhaloalkyl, alkoxy, alkenyl, carboxyalkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, alkoxycarbonyl, cyanoalkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl, alkanoylaminoalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, heterocyclalkyl, cycloalkylcarbonylalkyl, heteroarylalkylaminocarbonylalkyl, arylalkylaminocarbonylalkyl, heterocyclalkylaminocarbonylalkyl, carboxyalkylaminocarbonylalkyl, arylsulfonylaminocarbonylalkyl, alkylsulfonylaminocarbonylalkyl, or hydroxyimino(amino)alkyl, preferably alkenyl, carboxyalkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, cyanoalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl, alkanoylaminoalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, heterocyclalkyl, or cycloalkylcarbonylalkyl. In some embodiments, R_{17} is hydrogen. In some embodiments, R_{17} is alkenyl, carboxyalkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, cyanoalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl, alkanoylaminoalkyl, aminocarbonylalkyl, or alkylaminocarbonylalkyl.

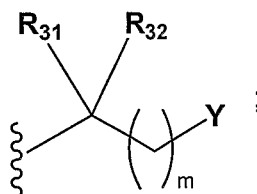
[0065] In some embodiments, R_{17} is hydrogen, alkyl, alkenyl, carboxyalkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, alkoxycarbonyl, cyanoalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl, alkanoylaminoalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, heterocyclalkyl, cycloalkylcarbonylalkyl, heteroarylalkylaminocarbonylalkyl,

- 26 -

arylalkylaminocarbonylalkyl, heterocyclalkylaminocarbonylalkyl,
 carboxyalkylaminocarbonylalkyl, arylsulfonylaminocarbonylalkyl,
 alkylsulfonylaminocarbonylalkyl, or hydroxyimino(amino)alkyl.

[0066] In some embodiments, R_{20} is hydrogen, C_1 - C_6 alkyl, or aryl. In some embodiments, R_{20} is methyl or ethyl. In some embodiments, R_{20} is phenyl.

[0067] In some embodiments, R_3 can include hydroxyl, isopropenyl, isopropyl, 1'-hydroxyisopropyl, 1'-haloisopropyl, 1'-thioisopropyl, 1'-trifluoromethylisopropyl, 2'-hydroxyisopropyl, 2'-haloisopropyl, 2'-thioisopropyl, 2'-trifluoromethylisopropyl, 1'-hydroxyethyl, 1'-(alkoxy)ethyl, 1'-(alkoxyalkoxy)ethyl, 1'-(arylalkoxy)ethyl; 1'-(arylcarbonyloxy)ethyl, 1'-(oxo)ethyl, 1'-(hydroxyl)-1'-(hydroxyalkyl)ethyl, 1'-(oxo)oxazolidinyl, 1',2'-epoxyisopropyl, 2'-haloisopropenyl, 2'-hydroxyisopropenyl, 2'-aminoisopropenyl, 2'-thioisopropenyl, 3'-haloisopropenyl, 3'-hydroxyisopropenyl, 3'-aminoisopropenyl, 3'-thioisopropenyl, 1'-alkoxyethyl, 1'-hydroximoyl, 1'-alkoxyimoyl, or



wherein Y is $-SR_{33}$ or $-NR_{33}R_{34}$;

R_{31} is methyl;

R_{32} is hydrogen or hydroxyl;

R_{33} and R_{34} are independently hydrogen, alkyl, alkanoyl, arylalkyl, heteroarylalkyl, arylsulfonyl or arylaminocarbonyl; or

R_{33} and R_{34} can be taken together with the nitrogen to which they are attached to form a heterocycle, wherein the heterocycle can optionally include one or more additional nitrogen, sulfur or oxygen atoms;

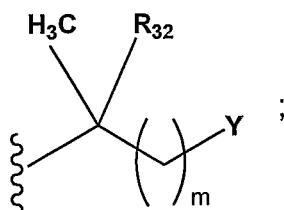
m is zero to three;

R_4 is hydrogen; or

R_3 and R_4 can be taken together to form oxo, alkylimino, alkoxyimino or benzyloxyimino.

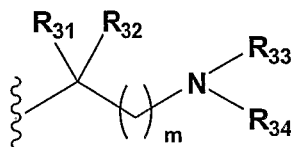
- 27 -

[0068] R_3 useful groups include, but are not limited to, hydrogen, hydroxyl, isopropenyl, 1'-hydroxyethyl, 1'-(alkoxy)ethyl, 1'-(alkoxyalkoxy)ethyl, 1'-(arylalkoxy)ethyl; 1'-(arylcabonyloxy)ethyl, acetyl, 1'-(hydroxyl)-1'-(hydroxyalkyl)ethyl, (2'-oxo)tetrahydrooxazolyl, 2'-haloisopropenyl, 2'-hydroxyisopropenyl, 2'-aminoisopropenyl, 2'-thioisopropenyl, 3'-haloisopropenyl, 3'-hydroxyisopropenyl, 3'-aminoisopropenyl, 3'-thioisopropenyl, 1'-alkoxyethyl, 1'-hydroxyiminoethyl, or 1'-alkoxyiminoethyl. In some embodiments, R_3 can include, but is not limited to hydroxyl, isopropenyl, 1'-hydroxyethyl, 1'-(alkoxy)ethyl, 1'-(alkoxyalkoxy)ethyl, 1'-(arylalkoxy)ethyl; 1'-(arylcabonyloxy)ethyl, acetyl, 1'-(hydroxyl)-1'-(hydroxyalkyl)ethyl, or (2'-oxo)tetrahydrooxazolyl. In some embodiments, R_3 includes, but is not limited to, 1'-alkoxyethyl, 1'-hydroxyiminoethyl, or 1'-alkoxyiminoethyl. In some embodiments, R_3 includes, but is not limited to 3'-haloisopropenyl, 3'-hydroxyisopropenyl, 3'-aminoisopropenyl, or 3'-thioisopropenyl. In some embodiments, R_3 is 1'-methoxyiminoethyl. In some embodiments, R_4 is hydrogen, and R_3 is



wherein Y is $-SR_{33}$ or $-NR_{33}R_{34}$, R_{31} is hydrogen, R_{32} is methyl, R_{33} and R_{34} are independently hydrogen, alkyl, alkanoyl, arylalkyl, heteroarylalkyl, arylsulfonyl or arylaminocarbonyl. In some embodiments, R_{31} is hydrogen, R_{32} is methyl, and R_{33} and R_{34} are taken together with the nitrogen to which they are attached to form heterocyclyl, wherein the heterocyclyl can optionally include one or more additional nitrogen, sulfur or oxygen atoms. The value of m can be zero to three.

[0069] In some embodiments, R_4 is hydrogen, and R_3 is



wherein R_{31} is hydrogen, R_{32} is methyl, R_{33} and R_{34} are independently hydrogen, alkyl, alkanoyl, arylalkyl, heteroarylalkyl, arylsulfonyl or arylaminocarbonyl. In some

embodiments, R₃₁ is hydrogen, R₃₂ is methyl, and R₃₃ and R₃₄ can be taken together with the nitrogen to which they are attached to form heterocyclyl, wherein the heterocyclyl can optionally include one or more additional nitrogen, sulfur or oxygen atoms. The value of m can be zero to three.

[0070] Preferred compounds include those in which R₂ is (i), and R₃ is isopropenyl; wherein R₂ is (ii), and R₃ is isopropenyl; wherein R₂ is (iii), and R₃ is isopropenyl; wherein R₂ is (iv), and R₃ is isopropenyl; or wherein R₂ is (v), and R₃ is isopropenyl. Most preferred compounds include those in which R₂ is (v) and R₃ is isopropenyl. Additional preferred compounds include those in which R₂ is (i), and R₃ is isopropyl; wherein R₂ is (ii), and R₃ is isopropyl; wherein R₂ is (iii), and R₃ is isopropyl; wherein R₂ is (iv), and R₃ is isopropyl; or wherein R₂ is (v), and R₃ is isopropyl. Most preferred compounds include those in which R₂ is (v) and R₃ is isopropyl.

[0071] Preferred compounds include compounds wherein R₁ is succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl or an allyl or alkyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl; R₂ is heteroaryl; and R₃ is isopropenyl. More preferred compounds can include compounds wherein R₁ is succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl, 3',3'-dimethylglutaryl, or an allyl or alkyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl, or 3',3'-dimethylglutaryl; R₂ is dihydrooxazolyl; and R₃ is isopropenyl.

[0072] Preferred compounds include compounds wherein R₁ is succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl, 3',3'-dimethylglutaryl, or an allyl or alkyl ester or arylalkyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl, or 3',3'-dimethylglutaryl; R₂ is (i), (ii) or (iv); and R₃ is isopropenyl. Preferred compounds include compounds wherein R₁ is succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl, 3',3'-dimethylglutaryl, or an allyl or alkyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl, or 3',3'-dimethylglutaryl; R₂ is (iii), (v) or (vi); and R₃ is isopropenyl. Preferred compounds include compounds wherein R₁ is succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl, 3',3'-dimethylglutaryl, or an allyl or alkyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-

methylsuccinyl, 3',3'-dimethylsuccinyl, or 3',3'-dimethylglutaryl; R₂ is (v) and R₃ is isopropenyl.

[0073] Additional preferred compounds include those wherein R₂ is (i), and R₅ is a heteroarylalkyl; wherein R₂ is (ii), and R₆ is a heteroaryl; wherein R₂ is (iv), and R₉ is cyanoalkyl; wherein R₂ is (iii), and R₇ and R₈ taken together with the nitrogen to which they are attached to form a heterocycloalkyl or heteroaryl; wherein R₂ is (v), and R₁₀ and R₁₁ taken together with the nitrogen to which they are attached to form a heterocycloalkyl or heteroaryl; wherein R₂ is (vi), and R₁₂ and R₁₃ taken together with the nitrogen to which they are attached to form a heterocycloalkyl or heteroaryl.

[0074] One preferred subgenus of compounds are those having Formula *I*, or a pharmaceutically acceptable salt thereof, wherein R₁ is 3',3'-dimethylglutaryl or 3',3'-dimethylsuccinyl; R₂ is formula (v); R₃ isopropenyl, or isopropyl; R₁₀ is hydrogen, C₁₋₄alkyl, preferably methyl, or C₁₋₄alkoxy(C₁₋₄)alkyl, preferably methoxyethyl; and R₁₁ is hydrogen, C₁₋₆ alkyl, amino, C₃₋₇ cycloalkyl, C₆₋₁₀aryl, C₆₋₁₀aryl(C₁₋₄)alkyl, C₁₋₄alkylsulfonyl, phenylsulfonyl, piperidinyl, or pyrrolidinyl, any of which is optionally substituted by 1-5, preferably 1-3 groups independently selected from halo, trifluoromethyl, hydroxy, carboxy, amino, azido, C₁₋₄ alkoxy, monoalkylamino, dialkylamino, morpholinyl, cyano, acetyl, acetamido, pyridinyl, furanyl, thienyl, methylimidazolyl, methylisoxazolyl, methylpiperazinyl, methylmorpholinyl, *tert*-butoxycarbonyl, *tert*-butoxy-2-oxoethyl, and 4- *tert*-butoxycarbonylmorpholinyl, and wherein the C₆₋₁₀aryl, C₆₋₁₀aryl(C₁₋₄)alkyl, phenylsulfonyl, piperidinyl, and pyrrolidinyl can be also substituted by C₁₋₄alkyl, C₁₋₄hydroxyalkyl or C₁₋₄alkoxy(C₁₋₄)alkyl.

[0075] Preferred compounds wherein R₂ is (i) include, but are not limited to, those found in Table 1:

TABLE 1

#	R ₁	R ₃	R ₅
1	3',3'-dimethylsuccinyl	isopropenyl	dimethylamino
2	3',3'-dimethylglutaryl	isopropenyl	dimethylamino
3	3',3'-dimethylsuccinyl	isopropenyl	1-piperidinylmethyl
4	3',3'-dimethylglutaryl	isopropenyl	1-piperidinylmethyl
5	3',3'-dimethylsuccinyl	isopropenyl	5-tetrazolylmethyl
6	3',3'-dimethylglutaryl	isopropenyl	5-tetrazolylmethyl
7	3',3'-dimethylsuccinyl	isopropenyl	3-(5-methylisoxazolyl)methyl
8	3',3'-dimethylglutaryl	isopropenyl	3-(5-methylisoxazolyl)methyl
9	3',3'-dimethylsuccinyl	isopropenyl	2-(acetamido)ethyl
10	3',3'-dimethylglutaryl	isopropenyl	2-(acetamido)ethyl
11	3',3'-dimethylsuccinyl	isopropenyl	2-(dimethylaminocarbonyl)ethyl
12	3',3'-dimethylglutaryl	isopropenyl	2-(dimethylaminocarbonyl)ethyl
13	3',3'-dimethylsuccinyl	isopropyl	dimethylamino
14	3',3'-dimethylglutaryl	isopropyl	dimethylamino
15	3',3'-dimethylsuccinyl	isopropyl	1-piperidinylmethyl
16	3',3'-dimethylglutaryl	isopropyl	1-piperidinylmethyl
17	3',3'-dimethylsuccinyl	isopropyl	5-tetrazolylmethyl
18	3',3'-dimethylglutaryl	isopropyl	5-tetrazolylmethyl
19	3',3'-dimethylsuccinyl	isopropyl	3-(5-methylisoxazolyl)methyl
20	3',3'-dimethylglutaryl	isopropyl	3-(5-methylisoxazolyl)methyl
21	3',3'-dimethylsuccinyl	isopropyl	2-(acetamido)ethyl
22	3',3'-dimethylglutaryl	isopropyl	2-(acetamido)ethyl
23	3',3'-dimethylsuccinyl	isopropyl	2-(dimethylaminocarbonyl)ethyl
24	3',3'-dimethylglutaryl	isopropyl	2-(dimethylaminocarbonyl)ethyl

[0076] Preferred compounds wherein R₂ is (ii) include, but are not limited to, those found in Table 2:

TABLE 2

#	R ₁	R ₃	R ₆
25	3',3'-dimethylsuccinyl	isopropenyl	2-pyridinylmethyl
26	3',3'-dimethylglutaryl	isopropenyl	2-pyridinylmethyl
27	3',3'-dimethylsuccinyl	isopropenyl	<i>tert</i> -butoxycarbonylmethyl
28	3',3'-dimethylglutaryl	isopropenyl	<i>tert</i> -butoxycarbonylmethyl
29	3',3'-dimethylsuccinyl	isopropenyl	2-cyanoethyl
30	3',3'-dimethylglutaryl	isopropenyl	2-cyanoethyl
31	3',3'-dimethylsuccinyl	isopropenyl	cycloocten-1-yl
32	3',3'-dimethylglutaryl	isopropenyl	cycloocten-1-yl
33	3',3'-dimethylsuccinyl	isopropyl	2-pyridinylmethyl
34	3',3'-dimethylglutaryl	isopropyl	2-pyridinylmethyl
35	3',3'-dimethylsuccinyl	isopropyl	<i>tert</i> -butoxycarbonylmethyl
36	3',3'-dimethylglutaryl	isopropyl	<i>tert</i> -butoxycarbonylmethyl
37	3',3'-dimethylsuccinyl	isopropyl	2-cyanoethyl
38	3',3'-dimethylglutaryl	isopropyl	2-cyanoethyl
39	3',3'-dimethylsuccinyl	isopropyl	cycloocten-1-yl
40	3',3'-dimethylglutaryl	isopropyl	cycloocten-1-yl

[0077] Preferred compounds wherein R₂ is (iii) include, but are not limited to, those found in Table 3:

TABLE 3

#	R ₁	R ₃	R ₇	R ₈
41	3',3'-dimethylsuccinyl	isopropenyl	hydrogen	2-methoxyethyl
42	3',3'-dimethylglutaryl	isopropenyl	hydrogen	2-methoxyethyl
43	3',3'-dimethylsuccinyl	isopropenyl	methyl	methoxymethyl
44	3',3'-dimethylglutaryl	isopropenyl	methyl	methoxymethyl
45	3',3'-dimethylsuccinyl	isopropyl	hydrogen	2-methoxyethyl
46	3',3'-dimethylglutaryl	isopropyl	hydrogen	2-methoxyethyl
47	3',3'-dimethylsuccinyl	isopropyl	methyl	methoxymethyl
48	3',3'-dimethylglutaryl	isopropyl	methyl	methoxymethyl
49	3',3'-dimethylglutaryl	isopropenyl	hydrogen	hydrogen
50	3',3'-dimethylglutaryl	isopropyl	hydrogen	hydrogen
51	3',3'-dimethylsuccinyl	isopropenyl	hydrogen	hydrogen
52	3',3'-dimethylsuccinyl	isopropyl	hydrogen	hydrogen
53	3',3'-dimethylglutaryl	isopropenyl	methyl	hydrogen
54	3',3'-dimethylglutaryl	isopropyl	methyl	hydrogen
55	3',3'-dimethylsuccinyl	isopropenyl	methyl	hydrogen
56	3',3'-dimethylsuccinyl	isopropyl	methyl	hydrogen
57	3',3'-dimethylglutaryl	isopropenyl	methyl	methyl
58	3',3'-dimethylglutaryl	isopropyl	methyl	methyl

59	3',3'-dimethylsuccinyl	isopropenyl	methyl	methyl
60	3',3'-dimethylsuccinyl	isopropyl	methyl	methyl
61	3',3'-dimethylglutaryl	isopropenyl	ethyl	hydrogen
62	3',3'-dimethylglutaryl	isopropyl	ethyl	hydrogen
63	3',3'-dimethylsuccinyl	isopropenyl	ethyl	hydrogen
64	3',3'-dimethylsuccinyl	isopropyl	ethyl	hydrogen
65	3',3'-dimethylglutaryl	isopropenyl	ethyl	ethyl
66	3',3'-dimethylglutaryl	isopropyl	ethyl	ethyl
67	3',3'-dimethylsuccinyl	isopropenyl	ethyl	ethyl
68	3',3'-dimethylsuccinyl	isopropyl	ethyl	ethyl
69	3',3'-dimethylglutaryl	isopropenyl	ethyl	methyl
70	3',3'-dimethylglutaryl	isopropyl	ethyl	methyl
71	3',3'-dimethylsuccinyl	isopropenyl	ethyl	methyl
72	3',3'-dimethylsuccinyl	isopropyl	ethyl	methyl
73	3',3'-dimethylglutaryl	isopropenyl	propyl	methyl
74	3',3'-dimethylglutaryl	isopropyl	propyl	methyl
75	3',3'-dimethylsuccinyl	isopropenyl	propyl	methyl
76	3',3'-dimethylsuccinyl	isopropyl	propyl	methyl
77	3',3'-dimethylglutaryl	isopropenyl	propyl	propyl
78	3',3'-dimethylglutaryl	isopropyl	propyl	propyl
79	3',3'-dimethylsuccinyl	isopropenyl	propyl	propyl
80	3',3'-dimethylsuccinyl	isopropyl	propyl	propyl
81	3',3'-dimethylglutaryl	isopropenyl	cyclopropyl	methyl
82	3',3'-dimethylglutaryl	isopropyl	cyclopropyl	methyl
83	3',3'-dimethylsuccinyl	isopropenyl	cyclopropyl	methyl
84	3',3'-dimethylsuccinyl	isopropyl	cyclopropyl	methyl
85	3',3'-dimethylglutaryl	isopropenyl	cyclopropylmet hyl	methyl
86	3',3'-dimethylglutaryl	isopropyl	cyclopropylmet hyl	methyl
87	3',3'-dimethylsuccinyl	isopropenyl	cyclopropylmet hyl	methyl
88	3',3'-dimethylsuccinyl	isopropyl	cyclopropylmet hyl	methyl
89	3',3'-dimethylglutaryl	isopropenyl	hydroxyethyl	methyl
90	3',3'-dimethylglutaryl	isopropyl	hydroxyethyl	methyl
91	3',3'-dimethylsuccinyl	isopropenyl	hydroxyethyl	methyl
92	3',3'-dimethylsuccinyl	isopropyl	hydroxyethyl	methyl
93	3',3'-dimethylglutaryl	isopropenyl	methylsulfonyl	hydrogen
94	3',3'-dimethylglutaryl	isopropyl	methylsulfonyl	hydrogen
95	3',3'-dimethylsuccinyl	isopropenyl	methylsulfonyl	hydrogen
96	3',3'-dimethylsuccinyl	isopropyl	methylsulfonyl	hydrogen
97	3',3'-dimethylglutaryl	isopropenyl	methylsulfonyl	methyl
98	3',3'-dimethylglutaryl	isopropyl	methylsulfonyl	methyl
99	3',3'-dimethylsuccinyl	isopropenyl	methylsulfonyl	methyl

100	3',3'-dimethylsuccinyl	isopropyl	methylsulfonyl	methyl
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[0078] Preferred compounds wherein R₂ is (iii) and R₇ and R₈ are taken together to form a heterocycle include, but are not limited to, those found in Table 4:

TABLE 4

#	R ₁	R ₃	R ₇ and R ₈ taken with the nitrogen to which they are attached
101	3',3'-dimethylsuccinyl	isopropenyl	pyrrolidinyl
102	3',3'-dimethylglutaryl	isopropenyl	pyrrolidinyl
103	3',3'-dimethylsuccinyl	isopropenyl	morpholinyl
104	3',3'-dimethylglutaryl	isopropenyl	morpholinyl
105	3',3'-dimethylsuccinyl	isopropenyl	piperazinyl
106	3',3'-dimethylglutaryl	isopropenyl	piperazinyl
107	3',3'-dimethylsuccinyl	isopropyl	pyrrolidinyl
108	3',3'-dimethylglutaryl	isopropyl	pyrrolidinyl
109	3',3'-dimethylsuccinyl	isopropyl	morpholinyl
110	3',3'-dimethylglutaryl	isopropyl	morpholinyl
111	3',3'-dimethylsuccinyl	isopropyl	piperazinyl
112	3',3'-dimethylglutaryl	isopropyl	piperazinyl
113	3',3'-dimethylglutaryl	isopropenyl	4-methylpiperazinyl
114	3',3'-dimethylglutaryl	isopropyl	4-methylpiperazinyl
115	3',3'-dimethylsuccinyl	isopropenyl	4-methylpiperazinyl
116	3',3'-dimethylsuccinyl	isopropyl	4-methylpiperazinyl
117	3',3'-dimethylglutaryl	isopropenyl	4-ethylpiperazinyl
118	3',3'-dimethylglutaryl	isopropyl	4-ethylpiperazinyl
119	3',3'-dimethylsuccinyl	isopropenyl	4-ethylpiperazinyl
120	3',3'-dimethylsuccinyl	isopropyl	4-ethylpiperazinyl
121	3',3'-dimethylglutaryl	isopropenyl	4-cyclopropylpiperazinyl
122	3',3'-dimethylglutaryl	isopropyl	4-cyclopropylpiperazinyl
123	3',3'-dimethylsuccinyl	isopropenyl	4-cyclopropylpiperazinyl
124	3',3'-dimethylsuccinyl	isopropyl	4-cyclopropylpiperazinyl
125	3',3'-dimethylglutaryl	isopropenyl	4-(cyclopropylmethyl)piperazinyl
126	3',3'-dimethylglutaryl	isopropyl	4-(cyclopropylmethyl)piperazinyl
127	3',3'-dimethylsuccinyl	isopropenyl	4-(cyclopropylmethyl)piperazinyl
128	3',3'-dimethylsuccinyl	isopropyl	4-(cyclopropylmethyl)piperazinyl
129	3',3'-dimethylglutaryl	isopropenyl	4-acetylpiperazinyl
130	3',3'-dimethylglutaryl	isopropyl	4-acetylpiperazinyl
131	3',3'-dimethylsuccinyl	isopropenyl	4-acetylpiperazinyl
132	3',3'-dimethylsuccinyl	isopropyl	4-acetylpiperazinyl
133	3',3'-dimethylglutaryl	isopropenyl	4-(methylsulfonyl)piperazinyl
134	3',3'-dimethylglutaryl	isopropyl	4-(methylsulfonyl)piperazinyl

135	3',3'-dimethylsuccinyl	isopropenyl	4-(methylsulfonyl)piperazinyl
136	3',3'-dimethylsuccinyl	isopropyl	4-(methylsulfonyl)piperazinyl
137	3',3'-dimethylglutaryl	isopropenyl	4-(hydroxyethyl)piperazinyl
138	3',3'-dimethylglutaryl	isopropyl	4-(hydroxyethyl)piperazinyl
139	3',3'-dimethylsuccinyl	isopropenyl	4-(hydroxyethyl)piperazinyl
140	3',3'-dimethylsuccinyl	isopropyl	4-(hydroxyethyl)piperazinyl
141	3',3'-dimethylglutaryl	isopropenyl	4-(methoxyethyl)piperazinyl
142	3',3'-dimethylglutaryl	isopropyl	4-(methoxyethyl)piperazinyl
143	3',3'-dimethylsuccinyl	isopropenyl	4-(methoxyethyl)piperazinyl
144	3',3'-dimethylsuccinyl	isopropyl	4-(methoxyethyl)piperazinyl
145	3',3'-dimethylglutaryl	isopropenyl	4-isopropylpiperazinyl
146	3',3'-dimethylglutaryl	isopropyl	4-isopropylpiperazinyl
147	3',3'-dimethylsuccinyl	isopropenyl	4-isopropylpiperazinyl
148	3',3'-dimethylsuccinyl	isopropyl	4-isopropylpiperazinyl
149	3',3'-dimethylglutaryl	isopropenyl	3-aminopyrrolidinyl
150	3',3'-dimethylglutaryl	isopropyl	3-aminopyrrolidinyl
151	3',3'-dimethylsuccinyl	isopropenyl	3-aminopyrrolidinyl
152	3',3'-dimethylsuccinyl	isopropyl	3-aminopyrrolidinyl
153	3',3'-dimethylglutaryl	isopropenyl	3- <i>N,N</i> -dimethylaminopyrrolidinyl
154	3',3'-dimethylglutaryl	isopropyl	3- <i>N,N</i> -dimethylaminopyrrolidinyl
155	3',3'-dimethylsuccinyl	isopropenyl	3- <i>N,N</i> -dimethylaminopyrrolidinyl
156	3',3'-dimethylsuccinyl	isopropyl	3- <i>N,N</i> -dimethylaminopyrrolidinyl
157	3',3'-dimethylglutaryl	isopropenyl	3-hydroxypyrrolidinyl
158	3',3'-dimethylglutaryl	isopropyl	3-hydroxypyrrolidinyl
159	3',3'-dimethylsuccinyl	isopropenyl	3-hydroxypyrrolidinyl
160	3',3'-dimethylsuccinyl	isopropyl	3-hydroxypyrrolidinyl
161	3',3'-dimethylglutaryl	isopropenyl	3-acetamidopyrrolidinyl
162	3',3'-dimethylglutaryl	isopropyl	3-acetamidopyrrolidinyl
163	3',3'-dimethylsuccinyl	isopropenyl	3-acetamidopyrrolidinyl
164	3',3'-dimethylsuccinyl	isopropyl	3-acetamidopyrrolidinyl
165	3',3'-dimethylglutaryl	isopropenyl	3-(methylsulfonamido)pyrrolidinyl
166	3',3'-dimethylglutaryl	isopropyl	3-(methylsulfonamido)pyrrolidinyl
167	3',3'-dimethylsuccinyl	isopropenyl	3-(methylsulfonamido)pyrrolidinyl
168	3',3'-dimethylsuccinyl	isopropyl	3-(methylsulfonamido)pyrrolidinyl
169	3',3'-dimethylglutaryl	isopropenyl	4-benzylpiperazinyl
170	3',3'-dimethylglutaryl	isopropyl	4-benzylpiperazinyl
171	3',3'-dimethylsuccinyl	isopropenyl	4-benzylpiperazinyl
172	3',3'-dimethylsuccinyl	isopropyl	4-benzylpiperazinyl
173	3',3'-dimethylglutaryl	isopropenyl	thiomorpholinyl
174	3',3'-dimethylglutaryl	isopropyl	thiomorpholinyl
175	3',3'-dimethylsuccinyl	isopropenyl	thiomorpholinyl
176	3',3'-dimethylsuccinyl	isopropyl	thiomorpholinyl
177	3',3'-dimethylglutaryl	isopropenyl	thiomorpholinyl 1-oxide
178	3',3'-dimethylglutaryl	isopropyl	thiomorpholinyl 1-oxide

179	3',3'-dimethylsuccinyl	isopropenyl	thiomorpholinyl 1-oxide
180	3',3'-dimethylsuccinyl	isopropyl	thiomorpholinyl 1-oxide
181	3',3'-dimethylglutaryl	isopropenyl	thiomorpholinyl 1,1-dioxide
182	3',3'-dimethylglutaryl	isopropyl	thiomorpholinyl 1,1-dioxide
183	3',3'-dimethylsuccinyl	isopropenyl	thiomorpholinyl 1,1-dioxide
184	3',3'-dimethylsuccinyl	isopropyl	thiomorpholinyl 1,1-dioxide
185	3',3'-dimethylglutaryl	isopropenyl	4-aminopiperidinyl
186	3',3'-dimethylglutaryl	isopropyl	4-aminopiperidinyl
187	3',3'-dimethylsuccinyl	isopropenyl	4-aminopiperidinyl
188	3',3'-dimethylsuccinyl	isopropyl	4-aminopiperidinyl
189	3',3'-dimethylglutaryl	isopropenyl	4- <i>N,N</i> -dimethylaminopiperidinyl
190	3',3'-dimethylglutaryl	isopropyl	4- <i>N,N</i> -dimethylaminopiperidinyl
191	3',3'-dimethylsuccinyl	isopropenyl	4- <i>N,N</i> -dimethylaminopiperidinyl
192	3',3'-dimethylsuccinyl	isopropyl	4- <i>N,N</i> -dimethylaminopiperidinyl
193	3',3'-dimethylglutaryl	isopropenyl	4-acetamidopiperidinyl
194	3',3'-dimethylglutaryl	isopropyl	4-acetamidopiperidinyl
195	3',3'-dimethylsuccinyl	isopropenyl	4-acetamidopiperidinyl
196	3',3'-dimethylsuccinyl	isopropyl	4-acetamidopiperidinyl
197	3',3'-dimethylglutaryl	isopropenyl	4-(methylsulfonamido)piperidinyl
198	3',3'-dimethylglutaryl	isopropyl	4-(methylsulfonamido)piperidinyl
199	3',3'-dimethylsuccinyl	isopropenyl	4-(methylsulfonamido)piperidinyl
200	3',3'-dimethylsuccinyl	isopropyl	4-(methylsulfonamido)piperidinyl

[0079] Preferred compounds wherein R₂ is (iv) include, but are not limited to, those found in Table 5:

TABLE 5

#	R ₁	R ₃	R ₉
201	3',3'-dimethylsuccinyl	isopropenyl	<i>tert</i> -butoxycarbonyloxymethyl
202	3',3'-dimethylglutaryl	isopropenyl	<i>tert</i> -butoxycarbonyloxymethyl
203	3',3'-dimethylsuccinyl	isopropenyl	(1'-ethoxycarbonyloxy) (1'-methyl)methyl
204	3',3'-dimethylglutaryl	isopropenyl	(1'-ethoxycarbonyloxy) (1'-methyl)methyl
205	3',3'-dimethylsuccinyl	isopropenyl	2-cyanoethyl
206	3',3'-dimethylglutaryl	isopropenyl	2-cyanoethyl
207	3',3'-dimethylsuccinyl	isopropenyl	(1'-ethoxymethyl)ethoxyethyl
208	3',3'-dimethylglutaryl	isopropenyl	(1'-ethoxymethyl)ethoxyethyl

209	3',3'-dimethylsuccinyl	isopropyl	<i>tert</i> -butoxycarbonyloxymethyl
210	3',3'-dimethylglutaryl	isopropyl	<i>tert</i> -butoxycarbonyloxymethyl
211	3',3'-dimethylsuccinyl	isopropyl	ethoxycarbonyloxy(1'methyl)methyl
212	3',3'-dimethylglutaryl	isopropyl	ethoxycarbonyloxy(1'methyl)methyl
213	3',3'-dimethylsuccinyl	isopropyl	2-cyanoethyl
214	3',3'-dimethylglutaryl	isopropyl	2-cyanoethyl
215	3',3'-dimethylsuccinyl	isopropyl	(1'-ethoxymethyl)ethoxyethyl
216	3',3'-dimethylglutaryl	isopropyl	(1'-ethoxymethyl)ethoxyethyl
217	3',3'-dimethylsuccinyl	isopropenyl	2-dimethylaminoethyl
218	3',3'-dimethylglutaryl	isopropenyl	2-dimethylaminoethyl
219	3',3'-dimethylsuccinyl	isopropyl	2-dimethylaminoethyl
220	3',3'-dimethylglutaryl	isopropyl	2-dimethylaminoethyl
221	3',3'-dimethylsuccinyl	isopropenyl	2-methoxyethyl
222	3',3'-dimethylsuccinyl	isopropyl	2-methoxyethyl
223	3',3'-dimethylglutaryl	isopropenyl	2-methoxyethyl
224	3',3'-dimethylglutaryl	isopropyl	2-methoxyethyl
225	3',3'-dimethylsuccinyl	isopropenyl	3-[1-(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]
226	3',3'-dimethylsuccinyl	isopropyl	3-[1-(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]
227	3',3'-dimethylglutaryl	isopropenyl	3-[1-(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]
228	3',3'-dimethylglutaryl	isopropyl	3-[1-(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]
229	3',3'-dimethylsuccinyl	isopropenyl	3-tetrahydrofuranyl
230	3',3'-dimethylsuccinyl	isopropyl	3-tetrahydrofuranyl
231	3',3'-dimethylglutaryl	isopropenyl	3-tetrahydrofuranyl
232	3',3'-dimethylglutaryl	isopropyl	3-tetrahydrofuranyl
233	3',3'-dimethylsuccinyl	isopropenyl	ethyl
234	3',3'-dimethylsuccinyl	isopropyl	ethyl
235	3',3'-dimethylglutaryl	isopropenyl	ethyl
236	3',3'-dimethylglutaryl	isopropyl	ethyl
237	3',3'-dimethylsuccinyl	isopropenyl	isopropyl
238	3',3'-dimethylsuccinyl	isopropyl	isopropyl
239	3',3'-dimethylglutaryl	isopropenyl	isopropyl
240	3',3'-dimethylglutaryl	isopropyl	isopropyl
241	3',3'-dimethylsuccinyl	isopropenyl	<i>tert</i> -butyl
242	3',3'-dimethylsuccinyl	isopropyl	<i>tert</i> -butyl
243	3',3'-dimethylglutaryl	isopropenyl	<i>tert</i> -butyl
244	3',3'-dimethylglutaryl	isopropyl	<i>tert</i> -butyl

[0080] Preferred compounds wherein R₂ is (v) can include, but are not limited to, those found in Table 6:

TABLE 6

#	R ₁	R ₃	R ₁₁	R ₁₀
245	3',3'-dimethylsuccinyl	isopropenyl	propyl	hydrogen
246	3',3'-dimethylglutaryl	isopropenyl	propyl	hydrogen
247	3',3'-dimethylsuccinyl	isopropenyl	2-methoxyethyl	hydrogen
248	3',3'-dimethylglutaryl	isopropenyl	2-methoxyethyl	hydrogen
249	3',3'-dimethylsuccinyl	isopropenyl	2-(<i>tert</i> -butoxycarbonylamino)ethyl	hydrogen
250	3',3'-dimethylglutaryl	isopropenyl	2-(<i>tert</i> -butoxycarbonylamino)ethyl	hydrogen
251	3',3'-dimethylsuccinyl	isopropenyl	hydrogen	hydrogen
252	3',3'-dimethylglutaryl	isopropenyl	hydrogen	hydrogen
253	3',3'-dimethylsuccinyl	isopropenyl	ethyl	hydrogen
254	3',3'-dimethylglutaryl	isopropenyl	ethyl	hydrogen
255	3',3'-dimethylsuccinyl	isopropenyl	cyclopropyl	hydrogen
256	3',3'-dimethylglutaryl	isopropenyl	cyclopropyl	hydrogen
257	3',3'-dimethylsuccinyl	isopropenyl	isopropyl	hydrogen
258	3',3'-dimethylglutaryl	isopropenyl	isopropyl	hydrogen
259	3',3'-dimethylsuccinyl	isopropenyl	2-(4-morpholinyl)ethyl	hydrogen
260	3',3'-dimethylglutaryl	isopropenyl	2-(4-morpholinyl)ethyl	hydrogen
261	3',3'-dimethylsuccinyl	isopropenyl	4-fluorophenyl	hydrogen
262	3',3'-dimethylglutaryl	isopropenyl	4-fluorophenyl	hydrogen
263	3',3'-dimethylsuccinyl	isopropenyl	4-fluorobenzyl	hydrogen
264	3',3'-dimethylglutaryl	isopropenyl	4-fluorobenzyl	hydrogen
265	3',3'-dimethylsuccinyl	isopropenyl	2-aminoethyl	hydrogen
266	3',3'-dimethylglutaryl	isopropenyl	2-aminoethyl	hydrogen
267	3',3'-dimethylsuccinyl	isopropyl	propyl	hydrogen
268	3',3'-dimethylglutaryl	isopropyl	propyl	hydrogen
269	3',3'-dimethylsuccinyl	isopropyl	2-methoxyethyl	hydrogen
270	3',3'-dimethylglutaryl	isopropyl	2-methoxyethyl	hydrogen
271	3',3'-dimethylsuccinyl	isopropyl	2-(<i>tert</i> -butoxycarbonylamino)ethyl	hydrogen
272	3',3'-dimethylglutaryl	isopropyl	2-(<i>tert</i> -butoxycarbonylamino)ethyl	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
273	3',3'-dimethylsuccinyl	isopropyl	hydrogen	hydrogen
274	3',3'-dimethylglutaryl	isopropyl	hydrogen	hydrogen
275	3',3'-dimethylsuccinyl	isopropyl	ethyl	hydrogen
276	3',3'-dimethylglutaryl	isopropyl	ethyl	hydrogen
277	3',3'-dimethylsuccinyl	isopropyl	cyclopropyl	hydrogen
278	3',3'-dimethylglutaryl	isopropyl	cyclopropyl	hydrogen
279	3',3'-dimethylsuccinyl	isopropyl	isopropyl	hydrogen
280	3',3'-dimethylglutaryl	isopropyl	isopropyl	hydrogen
281	3',3'-dimethylsuccinyl	isopropyl	2-(4-morpholinyl)ethyl	hydrogen
282	3',3'-dimethylglutaryl	isopropyl	2-(4-morpholinyl)ethyl	hydrogen
283	3',3'-dimethylsuccinyl	isopropyl	4-fluorophenyl	hydrogen
284	3',3'-dimethylglutaryl	isopropyl	4-fluorophenyl	hydrogen
285	3',3'-dimethylsuccinyl	isopropyl	4-fluorobenzyl	hydrogen
286	3',3'-dimethylglutaryl	isopropyl	4-fluorobenzyl	hydrogen
287	3',3'-dimethylsuccinyl	isopropyl	2-aminoethyl	hydrogen
288	3',3'-dimethylglutaryl	isopropyl	2-aminoethyl	hydrogen
289	3',3'-dimethylsuccinyl	isopropenyl	<i>tert</i> -butoxycarbonylamino	hydrogen
290	3',3'-dimethylsuccinyl	isopropyl	<i>tert</i> -butoxycarbonylamino	hydrogen
291	3',3'-dimethylglutaryl	isopropenyl	<i>tert</i> -butoxycarbonylamino	hydrogen
292	3',3'-dimethylglutaryl	isopropyl	<i>tert</i> -butoxycarbonylamino	hydrogen
293	3',3'-dimethylglutaryl	isopropenyl	methyl	hydrogen
294	3',3'-dimethylglutaryl	isopropyl	methyl	hydrogen
295	3',3'-dimethylsuccinyl	isopropenyl	methyl	hydrogen
296	3',3'-dimethylsuccinyl	isopropyl	methyl	hydrogen
297	3',3'-dimethylglutaryl	isopropenyl	2-hydroxyethyl	hydrogen
298	3',3'-dimethylglutaryl	isopropyl	2-hydroxyethyl	hydrogen
299	3',3'-dimethylsuccinyl	isopropenyl	2-hydroxyethyl	hydrogen
300	3',3'-dimethylsuccinyl	isopropyl	2-hydroxyethyl	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
301	3',3'-dimethylglutaryl	isopropenyl	2-hydroxy-2-methylpropyl	hydrogen
302	3',3'-dimethylglutaryl	isopropyl	2-hydroxy-2-methylpropyl	hydrogen
303	3',3'-dimethylsuccinyl	isopropenyl	2-hydroxy-2-methylpropyl	hydrogen
304	3',3'-dimethylsuccinyl	isopropyl	2-hydroxy-2-methylpropyl	hydrogen
305	4'-(methylsulfonylamino)-4'oxo-3',3'-dimethylbutanoyl	isopropenyl	phenylsulfonyl	hydrogen
306	4'-(methylsulfonylamino)-4'oxo-3',3'-dimethylbutanoyl	isopropyl	phenylsulfonyl	hydrogen
307	5'-(methylsulfonylamino)-5'oxo-3',3'-dimethylpentanoyl	isopropenyl	phenylsulfonyl	hydrogen
308	5'-(methylsulfonylamino)-5'oxo-3',3'-dimethylpentanoyl	isopropyl	phenylsulfonyl	hydrogen
309	4'-(phenylsulfonylamino)-4'oxo-3',3'-dimethylbutanoyl	isopropenyl	phenylsulfonyl	hydrogen
310	4'-(phenylsulfonylamino)-4'oxo-3',3'-dimethylbutanoyl	isopropyl	phenylsulfonyl	hydrogen
311	4'-(methylsulfonylamino)-4'oxo-3',3'-dimethylbutanoyl	isopropenyl	methylsulfonyl	hydrogen
312	4'-(methylsulfonylamino)-4'oxo-3',3'-dimethylbutanoyl	isopropyl	methylsulfonyl	hydrogen
313	3',3'-dimethylsuccinyl	isopropenyl	phenylsulfonyl	hydrogen
314	3',3'-dimethylsuccinyl	isopropyl	phenylsulfonyl	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
315	3',3'-dimethylglutaryl	isopropenyl	phenylsulfonyl	hydrogen
316	3',3'-dimethylglutaryl	isopropyl	phenylsulfonyl	hydrogen
317	3',3'-dimethylsuccinyl	isopropenyl	methylsulfonyl	hydrogen
318	3',3'-dimethylsuccinyl	isopropyl	methylsulfonyl	hydrogen
319	3',3'-dimethylglutaryl	isopropenyl	methylsulfonyl	hydrogen
320	3',3'-dimethylglutaryl	isopropyl	methylsulfonyl	hydrogen
321	3',3'-dimethylglutaryl	isopropenyl	2-hydroxyethoxyethyl	hydrogen
322	3',3'-dimethylglutaryl	isopropyl	2-hydroxyethoxyethyl	hydrogen
323	3',3'-dimethylsuccinyl	isopropenyl	2-hydroxyethoxyethyl	hydrogen
324	3',3'-dimethylsuccinyl	isopropyl	2-hydroxyethoxyethyl	hydrogen
325	3',3'-dimethylglutaryl	isopropenyl	(R,S)-2-[2,3-dihydroxypropyl]	hydrogen
326	3',3'-dimethylglutaryl	isopropyl	(R,S)-2-[2,3-dihydroxypropyl]	hydrogen
327	3',3'-dimethylsuccinyl	isopropenyl	(R,S)-2-[2,3-dihydroxypropyl]	hydrogen
328	3',3'-dimethylsuccinyl	isopropyl	(R,S)-2-[2,3-dihydroxypropyl]	hydrogen
329	3',3'-dimethylglutaryl	isopropenyl	(S)-2-[2,3-dihydroxypropyl]	hydrogen
330	3',3'-dimethylglutaryl	isopropyl	(S)-2-[2,3-dihydroxypropyl]	hydrogen
331	3',3'-dimethylsuccinyl	isopropenyl	(S)-2-[2,3-dihydroxypropyl]	hydrogen
332	3',3'-dimethylsuccinyl	isopropyl	(S)-2-[2,3-dihydroxypropyl]	hydrogen
333	3',3'-dimethylglutaryl	isopropenyl	(R)-[2,3-dihydroxypropyl]	hydrogen
334	3',3'-dimethylglutaryl	isopropyl	(R)-[2,3-dihydroxypropyl]	hydrogen
335	3',3'-dimethylsuccinyl	isopropenyl	(R)-[2,3-dihydroxypropyl]	hydrogen
336	3',3'-dimethylsuccinyl	isopropyl	(R)-[2,3-dihydroxypropyl]	hydrogen
337	3',3'-dimethylglutaryl	isopropenyl	(S)-2-[(1-hydroxy-4-methylpentyl)]	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
338	3',3'-dimethylglutaryl	isopropyl	(S)-2-[(1-hydroxy-4-methylpentyl)]	hydrogen
339	3',3'-dimethylsuccinyl	isopropenyl	(S)-2-[(1-hydroxy-4-methylpentyl)]	hydrogen
340	3',3'-dimethylsuccinyl	isopropyl	(S)-2-[(1-hydroxy-4-methylpentyl)]	hydrogen
341	3',3'-dimethylglutaryl	isopropenyl	(R)-2-[(1-hydroxy-4-methylpentyl)]	hydrogen
342	3',3'-dimethylglutaryl	isopropyl	(R)-2-[(1-hydroxy-4-methylpentyl)]	hydrogen
343	3',3'-dimethylsuccinyl	isopropenyl	(R)-2-[(1-hydroxy-4-methylpentyl)]	hydrogen
344	3',3'-dimethylsuccinyl	isopropyl	(R)-2-[(1-hydroxy-4-methylpentyl)]	hydrogen
345	3',3'-dimethylglutaryl	isopropenyl	2-methoxyethyl	methyl
346	3',3'-dimethylglutaryl	isopropyl	2-methoxyethyl	methyl
347	3',3'-dimethylsuccinyl	isopropenyl	2-methoxyethyl	methyl
348	3',3'-dimethylsuccinyl	isopropyl	2-methoxyethyl	methyl
349	3',3'-dimethylglutaryl	isopropenyl	2-methoxyethyl	2-methoxyethyl
350	3',3'-dimethylglutaryl	isopropyl	2-methoxyethyl	2-methoxyethyl
351	3',3'-dimethylsuccinyl	isopropenyl	2-methoxyethyl	2-methoxyethyl
352	3',3'-dimethylsuccinyl	isopropyl	2-methoxyethyl	2-methoxyethyl
353	3',3'-dimethylglutaryl	isopropenyl	2- <i>tert</i> -butoxy-2-oxoethyl	hydrogen
354	3',3'-dimethylglutaryl	isopropyl	2- <i>tert</i> -butoxy-2-oxoethyl	hydrogen
355	3',3'-dimethylsuccinyl	isopropenyl	2- <i>tert</i> -butoxy-2-oxoethyl	hydrogen
356	3',3'-dimethylsuccinyl	isopropyl	2- <i>tert</i> -butoxy-2-oxoethyl	hydrogen
357	3',3'-dimethylglutaryl	isopropenyl	(S)-1-carboxy-3-methylbutyl	hydrogen
358	3',3'-dimethylglutaryl	isopropyl	(S)-1-carboxy-3-methylbutyl	hydrogen
359	3',3'-dimethylsuccinyl	isopropenyl	(S)-1-carboxy-3-	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
			methylbutyl	
360	3',3'-dimethylsuccinyl	isopropyl	(S)-1-carboxy-3-methylbutyl	hydrogen
361	3',3'-dimethylglutaryl	isopropenyl	2-cyanoethyl	hydrogen
362	3',3'-dimethylglutaryl	isopropyl	2-cyanoethyl	hydrogen
363	3',3'-dimethylsuccinyl	isopropenyl	2-cyanoethyl	hydrogen
364	3',3'-dimethylsuccinyl	isopropyl	2-cyanoethyl	hydrogen
365	3',3'-dimethylglutaryl	isopropenyl	2-acetamidoethyl	hydrogen
366	3',3'-dimethylglutaryl	isopropyl	2-acetamidoethyl	hydrogen
367	3',3'-dimethylsuccinyl	isopropenyl	2-acetamidoethyl	hydrogen
368	3',3'-dimethylsuccinyl	isopropyl	2-acetamidoethyl	hydrogen
369	3',3'-dimethylglutaryl	isopropenyl	(S)-1-[(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]	hydrogen
370	3',3'-dimethylglutaryl	isopropyl	(S)-1-[(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]	hydrogen
371	3',3'-dimethylsuccinyl	isopropenyl	(S)-1-[(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]	hydrogen
372	3',3'-dimethylsuccinyl	isopropyl	(S)-1-[(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]	hydrogen
373	3',3'-dimethylglutaryl	isopropenyl	(R)-1-[(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]	hydrogen
374	3',3'-dimethylglutaryl	isopropyl	(R)-1-[(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]	hydrogen
375	3',3'-dimethylsuccinyl	isopropenyl	(R)-1-[(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]	hydrogen
376	3',3'-dimethylsuccinyl	isopropyl	(R)-1-[(<i>tert</i> -butoxycarbonyl)pyrrolidinyl]	hydrogen
377	3',3'-dimethylglutaryl	isopropenyl	(S)-3-pyrrolidinyl	hydrogen
378	3',3'-dimethylglutaryl	isopropyl	(S)-3-pyrrolidinyl	hydrogen
379	3',3'-dimethylsuccinyl	isopropenyl	(S)-3-pyrrolidinyl	hydrogen
380	3',3'-dimethylsuccinyl	isopropyl	(S)-3-pyrrolidinyl	hydrogen
381	3',3'-dimethylglutaryl	isopropenyl	(R)-3-pyrrolidinyl	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
382	3',3'-dimethylglutaryl	isopropyl	(R)-3-pyrrolidinyl	hydrogen
383	3',3'-dimethylsuccinyl	isopropenyl	(R)-3-pyrrolidinyl	hydrogen
384	3',3'-dimethylsuccinyl	isopropyl	(R)-3-pyrrolidinyl	hydrogen
385	3',3'-dimethylglutaryl	isopropenyl	(S)-3-(1-methylpyrrolidinyl)	hydrogen
386	3',3'-dimethylglutaryl	isopropyl	(S)-3-(1-methylpyrrolidinyl)	hydrogen
387	3',3'-dimethylsuccinyl	isopropenyl	(S)-3-(1-methylpyrrolidinyl)	hydrogen
388	3',3'-dimethylsuccinyl	isopropyl	(S)-3-(1-methylpyrrolidinyl)	hydrogen
389	3',3'-dimethylglutaryl	isopropenyl	(R)-3-(1-methylpyrrolidinyl)	hydrogen
390	3',3'-dimethylglutaryl	isopropyl	(R)-3-(1-methylpyrrolidinyl)	hydrogen
391	3',3'-dimethylsuccinyl	isopropenyl	(R)-3-(1-methylpyrrolidinyl)	hydrogen
392	3',3'-dimethylsuccinyl	isopropyl	(R)-3-(1-methylpyrrolidinyl)	hydrogen
393	3',3'-dimethylglutaryl	isopropenyl	(S)-3-(1-acetylpyrrolidinyl)	hydrogen
394	3',3'-dimethylglutaryl	isopropyl	(S)-3-(1-acetylpyrrolidinyl)	hydrogen
395	3',3'-dimethylsuccinyl	isopropenyl	(S)-3-(1-acetylpyrrolidinyl)	hydrogen
396	3',3'-dimethylsuccinyl	isopropyl	(S)-3-(1-acetylpyrrolidinyl)	hydrogen
397	3',3'-dimethylglutaryl	isopropenyl	(R)-3-(1-acetylpyrrolidinyl)	hydrogen
398	3',3'-dimethylglutaryl	isopropyl	(R)-3-(1-acetylpyrrolidinyl)	hydrogen
399	3',3'-dimethylsuccinyl	isopropenyl	(R)-3-(1-acetylpyrrolidinyl)	hydrogen
400	3',3'-dimethylsuccinyl	isopropyl	(R)-3-(1-acetylpyrrolidinyl)	hydrogen
401	3',3'-dimethylglutaryl	isopropenyl	(S)-3-(1-methylsulfonylpyrrolidinyl)	hydrogen
402	3',3'-dimethylglutaryl	isopropyl	(S)-3-(1-methylsulfonylpyrrolidinyl)	hydrogen
403	3',3'-dimethylsuccinyl	isopropenyl	(S)-3-(1-methylsulfonylpyrrolidinyl)	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
			dinyl)	
404	3',3'-dimethylsuccinyl	isopropyl	(S)-3-(1-methylsulfonylpyrroli dinyl)	hydrogen
405	3',3'-dimethylglutaryl	isopropenyl	(R)-3-(1-methylsulfonylpyrroli dinyl)	hydrogen
406	3',3'-dimethylglutaryl	isopropenyl	(R)-3-(1-methylsulfonylpyrroli dinyl)	hydrogen
407	3',3'-dimethylglutaryl	isopropenyl	(R)-3-(1-methylsulfonylpyrroli dinyl)	hydrogen
408	3',3'-dimethylglutaryl	isopropenyl	(R)-3-(1-methylsulfonylpyrroli dinyl)	hydrogen
409	3',3'-dimethylglutaryl	isopropenyl	4-(1-(<i>tert</i> - butoxycarbonyl)piperi dinyl	hydrogen
410	3',3'-dimethylsuccinyl	isopropenyl	4-(1-(<i>tert</i> - butoxycarbonyl)piperi dinyl	hydrogen
411	3',3'-dimethylglutaryl	isopropyl	4-(1-(<i>tert</i> - butoxycarbonyl)piperi dinyl	hydrogen
412	3',3'-dimethylsuccinyl	isopropyl	4-(1-(<i>tert</i> - butoxycarbonyl)piperi dinyl	hydrogen
413	3',3'-dimethylglutaryl	isopropenyl	4-piperidinyl	hydrogen
414	3',3'-dimethylsuccinyl	isopropenyl	4-piperidinyl	hydrogen
415	3',3'-dimethylglutaryl	isopropyl	4-piperidinyl	hydrogen
416	3',3'-dimethylsuccinyl	isopropyl	4-piperidinyl	hydrogen
417	3',3'-dimethylglutaryl	isopropenyl	4-(1-methylpiperidinyl)	hydrogen
418	3',3'-dimethylglutaryl	isopropyl	4-(1-methylpiperidinyl)	hydrogen
419	3',3'-dimethylsuccinyl	isopropenyl	4-(1-methylpiperidinyl)	hydrogen
420	3',3'-dimethylsuccinyl	isopropyl	4-(1-methylpiperidinyl)	hydrogen
421	3',3'-dimethylglutaryl	isopropenyl	4-[1-(1-hydroxyethyl)piperidi nyl	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
422	3',3'-dimethylglutaryl	isopropyl	4-[1-(1-hydroxyethyl)piperidinyl	hydrogen
423	3',3'-dimethylsuccinyl	isopropenyl	4-[1-(1-hydroxyethyl)piperidinyl	hydrogen
424	3',3'-dimethylsuccinyl	isopropyl	4-[1-(1-hydroxyethyl)piperidinyl	hydrogen
425	3',3'-dimethylglutaryl	isopropenyl	4-[1-(1-methoxyethyl)piperidinyl	hydrogen
426	3',3'-dimethylglutaryl	isopropyl	4-[1-(1-methoxyethyl)piperidinyl	hydrogen
427	3',3'-dimethylsuccinyl	isopropenyl	4-[1-(1-methoxyethyl)piperidinyl	hydrogen
428	3',3'-dimethylsuccinyl	isopropyl	4-[1-(1-methoxyethyl)piperidinyl	hydrogen
429	3',3'-dimethylglutaryl	isopropenyl	3-fluorobenzyl	hydrogen
430	3',3'-dimethylglutaryl	isopropyl	3-fluorobenzyl	hydrogen
431	3',3'-dimethylsuccinyl	isopropenyl	3-fluorobenzyl	hydrogen
432	3',3'-dimethylsuccinyl	isopropyl	3-fluorobenzyl	hydrogen
433	3',3'-dimethylglutaryl	isopropenyl	2-fluorobenzyl	hydrogen
434	3',3'-dimethylglutaryl	isopropyl	2-fluorobenzyl	hydrogen
435	3',3'-dimethylsuccinyl	isopropenyl	2-fluorobenzyl	hydrogen
436	3',3'-dimethylsuccinyl	isopropyl	2-fluorobenzyl	hydrogen
437	3',3'-dimethylglutaryl	isopropenyl	4-chlorobenzyl	hydrogen
438	3',3'-dimethylglutaryl	isopropyl	4-chlorobenzyl	hydrogen
439	3',3'-dimethylsuccinyl	isopropenyl	4-chlorobenzyl	hydrogen
440	3',3'-dimethylsuccinyl	isopropyl	4-chlorobenzyl	hydrogen
441	3',3'-dimethylglutaryl	isopropenyl	3-chlorobenzyl	hydrogen
442	3',3'-dimethylglutaryl	isopropyl	3-chlorobenzyl	hydrogen
443	3',3'-dimethylsuccinyl	isopropenyl	3-chlorobenzyl	hydrogen
444	3',3'-dimethylsuccinyl	isopropyl	3-chlorobenzyl	hydrogen
445	3',3'-dimethylglutaryl	isopropenyl	2-chlorobenzyl	hydrogen
446	3',3'-dimethylglutaryl	isopropyl	2-chlorobenzyl	hydrogen

- 46 -

#	R ₁	R ₃	R ₁₁	R ₁₀
447	3',3'-dimethylsuccinyl	isopropenyl	2-chlorobenzyl	hydrogen
448	3',3'-dimethylsuccinyl	isopropyl	2-chlorobenzyl	hydrogen
449	3',3'-dimethylglutaryl	isopropenyl	4-methylbenzyl	Hydrogen
450	3',3'-dimethylglutaryl	isopropyl	4-methylbenzyl	hydrogen
451	3',3'-dimethylsuccinyl	isopropenyl	4-methylbenzyl	hydrogen
452	3',3'-dimethylsuccinyl	isopropyl	4-methylbenzyl	hydrogen
453	3',3'-dimethylglutaryl	isopropenyl	3-methylbenzyl	hydrogen
454	3',3'-dimethylglutaryl	isopropyl	3-methylbenzyl	hydrogen
455	3',3'-dimethylsuccinyl	isopropenyl	3-methylbenzyl	hydrogen
456	3',3'-dimethylsuccinyl	isopropyl	3-methylbenzyl	hydrogen
457	3',3'-dimethylglutaryl	isopropenyl	2-methylbenzyl	hydrogen
458	3',3'-dimethylglutaryl	isopropyl	2-methylbenzyl	hydrogen
459	3',3'-dimethylsuccinyl	isopropenyl	2-methylbenzyl	hydrogen
460	3',3'-dimethylsuccinyl	isopropyl	2-methylbenzyl	hydrogen
461	3',3'-dimethylglutaryl	isopropenyl	4-methoxybenzyl	hydrogen
462	3',3'-dimethylglutaryl	isopropyl	4-methoxybenzyl	hydrogen
463	3',3'-dimethylsuccinyl	isopropenyl	4-methoxybenzyl	hydrogen
464	3',3'-dimethylsuccinyl	isopropyl	4-methoxybenzyl	hydrogen
465	3',3'-dimethylglutaryl	isopropenyl	3-methoxybenzyl	hydrogen
466	3',3'-dimethylglutaryl	isopropyl	3-methoxybenzyl	hydrogen
467	3',3'-dimethylsuccinyl	isopropenyl	3-methoxybenzyl	hydrogen
468	3',3'-dimethylsuccinyl	isopropyl	3-methoxybenzyl	hydrogen
469	3',3'-dimethylglutaryl	isopropenyl	2-methoxybenzyl	hydrogen
470	3',3'-dimethylglutaryl	isopropyl	2-methoxybenzyl	hydrogen
471	3',3'-dimethylsuccinyl	isopropenyl	2-methoxybenzyl	hydrogen
472	3',3'-dimethylsuccinyl	isopropyl	2-methoxybenzyl	hydrogen
473	3',3'-dimethylglutaryl	isopropenyl	4- <i>N,N</i> -dimethylaminobenzyl	hydrogen
474	3',3'-dimethylglutaryl	isopropyl	4- <i>N,N</i> -dimethylaminobenzyl	hydrogen
475	3',3'-dimethylsuccinyl	isopropenyl	4- <i>N,N</i> -dimethylaminobenzyl	hydrogen
476	3',3'-dimethylsuccinyl	isopropyl	4- <i>N,N</i> -dimethylaminobenzyl	hydrogen
477	3',3'-dimethylglutaryl	isopropenyl	4-trifluoromethylbenzyl	hydrogen

- 47 -

#	R ₁	R ₃	R ₁₁	R ₁₀
478	3',3'-dimethylglutaryl	isopropyl	4-trifluoromethylbenzyl	hydrogen
479	3',3'-dimethylsuccinyl	isopropenyl	4-trifluoromethylbenzyl	hydrogen
480	3',3'-dimethylsuccinyl	isopropyl	4-trifluoromethylbenzyl	hydrogen
481	3',3'-dimethylglutaryl	isopropenyl	4-carboxybenzyl	hydrogen
482	3',3'-dimethylglutaryl	isopropyl	4-carboxybenzyl	hydrogen
483	3',3'-dimethylsuccinyl	isopropenyl	4-carboxybenzyl	hydrogen
484	3',3'-dimethylsuccinyl	isopropyl	4-carboxybenzyl	hydrogen
485	3',3'-dimethylglutaryl	isopropenyl	3,4-dichlorobenzyl	hydrogen
486	3',3'-dimethylglutaryl	isopropyl	3,4-dichlorobenzyl	hydrogen
487	3',3'-dimethylsuccinyl	isopropenyl	3,4-dichlorobenzyl	hydrogen
488	3',3'-dimethylsuccinyl	isopropyl	3,4-dichlorobenzyl	hydrogen
489	3',3'-dimethylglutaryl	isopropenyl	2,4-dichlorobenzyl	hydrogen
490	3',3'-dimethylglutaryl	isopropyl	2,4-dichlorobenzyl	hydrogen
491	3',3'-dimethylsuccinyl	isopropenyl	2,4-dichlorobenzyl	hydrogen
492	3',3'-dimethylsuccinyl	isopropyl	2,4-dichlorobenzyl	hydrogen
493	3',3'-dimethylglutaryl	isopropenyl	2-pyridinylmethyl	hydrogen
494	3',3'-dimethylglutaryl	isopropyl	2-pyridinylmethyl	hydrogen
495	3',3'-dimethylsuccinyl	isopropenyl	2-pyridinylmethyl	hydrogen
496	3',3'-dimethylsuccinyl	isopropyl	2-pyridinylmethyl	hydrogen
497	3',3'-dimethylglutaryl	isopropenyl	3-pyridinylmethyl	hydrogen
498	3',3'-dimethylglutaryl	isopropyl	3-pyridinylmethyl	hydrogen
499	3',3'-dimethylsuccinyl	isopropenyl	3-pyridinylmethyl	hydrogen
500	3',3'-dimethylsuccinyl	isopropyl	3-pyridinylmethyl	hydrogen
501	3',3'-dimethylglutaryl	isopropenyl	4-pyridinylmethyl	hydrogen
502	3',3'-dimethylglutaryl	isopropyl	4-pyridinylmethyl	hydrogen
503	3',3'-dimethylsuccinyl	isopropenyl	4-pyridinylmethyl	hydrogen
504	3',3'-dimethylsuccinyl	isopropyl	4-pyridinylmethyl	hydrogen
505	3',3'-dimethylglutaryl	isopropenyl	2-furanylmethyl	hydrogen
506	3',3'-dimethylglutaryl	isopropyl	2-furanylmethyl	hydrogen
507	3',3'-dimethylsuccinyl	isopropenyl	2-furanylmethyl	hydrogen
508	3',3'-dimethylsuccinyl	isopropyl	2-furanylmethyl	hydrogen
509	3',3'-dimethylglutaryl	isopropenyl	2-thienylmethyl	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
510	3',3'-dimethylglutaryl	isopropyl	2-thienylmethyl	hydrogen
511	3',3'-dimethylsuccinyl	isopropenyl	2-thienylmethyl	hydrogen
512	3',3'-dimethylsuccinyl	isopropyl	2-thienylmethyl	hydrogen
513	3',3'-dimethylglutaryl	isopropenyl	2-benzyl	hydrogen
514	3',3'-dimethylglutaryl	isopropyl	2-benzyl	hydrogen
515	3',3'-dimethylsuccinyl	isopropenyl	2-benzyl	hydrogen
516	3',3'-dimethylsuccinyl	isopropyl	2-benzyl	hydrogen
517	3',3'-dimethylglutaryl	isopropenyl	3-trifluoromethylbenzyl	hydrogen
518	3',3'-dimethylglutaryl	isopropyl	3-trifluoromethylbenzyl	hydrogen
519	3',3'-dimethylsuccinyl	isopropenyl	3-trifluoromethylbenzyl	hydrogen
520	3',3'-dimethylsuccinyl	isopropyl	3-trifluoromethylbenzyl	hydrogen
521	3',3'-dimethylglutaryl	isopropenyl	2-(1,3,4-thiadiazolyl)methyl	hydrogen
522	3',3'-dimethylglutaryl	isopropyl	2-(1,3,4-thiadiazolyl)methyl	hydrogen
523	3',3'-dimethylsuccinyl	isopropenyl	2-(1,3,4-thiadiazolyl)methyl	hydrogen
524	3',3'-dimethylsuccinyl	isopropyl	2-(1,3,4-thiadiazolyl)methyl	hydrogen
525	3',3'-dimethylglutaryl	isopropenyl	4-cyanomethyl	hydrogen
526	3',3'-dimethylglutaryl	isopropyl	4-cyanomethyl	hydrogen
527	3',3'-dimethylsuccinyl	isopropenyl	4-cyanomethyl	hydrogen
528	3',3'-dimethylsuccinyl	isopropyl	4-cyanomethyl	hydrogen
529	3',3'-dimethylglutaryl	isopropenyl	4- <i>tert</i> -butylbenzyl	hydrogen
530	3',3'-dimethylglutaryl	isopropyl	4- <i>tert</i> -butylbenzyl	hydrogen
531	3',3'-dimethylsuccinyl	isopropenyl	4- <i>tert</i> -butylbenzyl	hydrogen
532	3',3'-dimethylsuccinyl	isopropyl	4- <i>tert</i> -butylbenzyl	hydrogen
533	3',3'-dimethylglutaryl	isopropenyl	4-aminobenzyl	hydrogen
534	3',3'-dimethylglutaryl	isopropyl	4-aminobenzyl	hydrogen
535	3',3'-dimethylsuccinyl	isopropenyl	4-aminobenzyl	hydrogen
536	3',3'-dimethylsuccinyl	isopropyl	4-aminobenzyl	hydrogen
537	3',3'-dimethylglutaryl	isopropenyl	4-acetamidobenzyl	hydrogen
538	3',3'-dimethylglutaryl	isopropyl	4-acetamidobenzyl	hydrogen
539	3',3'-dimethylsuccinyl	isopropenyl	4-acetamidobenzyl	hydrogen

- 49 -

#	R ₁	R ₃	R ₁₁	R ₁₀
540	3',3'-dimethylsuccinyl	isopropyl	4-acetamidobenzyl	hydrogen
541	3',3'-dimethylglutaryl	isopropenyl	1-(1,2,3,4-tetrahydronaphthyl)	hydrogen
542	3',3'-dimethylglutaryl	isopropyl	1-(1,2,3,4-tetrahydronaphthyl)	hydrogen
543	3',3'-dimethylsuccinyl	isopropenyl	1-(1,2,3,4-tetrahydronaphthyl)	hydrogen
544	3',3'-dimethylsuccinyl	isopropyl	1-(1,2,3,4-tetrahydronaphthyl)	hydrogen
545	3',3'-dimethylglutaryl	isopropenyl	(R)-1-phenylethyl	hydrogen
546	3',3'-dimethylglutaryl	isopropyl	(R)-1-phenylethyl	hydrogen
547	3',3'-dimethylsuccinyl	isopropenyl	(R)-1-phenylethyl	hydrogen
548	3',3'-dimethylsuccinyl	isopropyl	(R)-1-phenylethyl	hydrogen
549	3',3'-dimethylglutaryl	isopropenyl	(S)-1-phenylethyl	hydrogen
560	3',3'-dimethylglutaryl	isopropyl	(S)-1-phenylethyl	hydrogen
561	3',3'-dimethylsuccinyl	isopropenyl	(S)-1-phenylethyl	hydrogen
562	3',3'-dimethylsuccinyl	isopropyl	(S)-1-phenylethyl	hydrogen
563	3',3'-dimethylglutaryl	isopropenyl	4-(1-methylimidazolyl)methyl	hydrogen
564	3',3'-dimethylglutaryl	isopropyl	4-(1-methylimidazolyl)methyl	hydrogen
565	3',3'-dimethylsuccinyl	isopropenyl	4-(1-methylimidazolyl)methyl	hydrogen
566	3',3'-dimethylsuccinyl	isopropyl	4-(1-methylimidazolyl)methyl	hydrogen
567	3',3'-dimethylglutaryl	isopropenyl	3-(5-methylisoxazolyl)methyl	hydrogen
568	3',3'-dimethylglutaryl	isopropyl	3-(5-methylisoxazolyl)methyl	hydrogen
569	3',3'-dimethylsuccinyl	isopropenyl	3-(5-methylisoxazolyl)methyl	hydrogen
570	3',3'-dimethylsuccinyl	isopropyl	3-(5-methylisoxazolyl)methyl	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
571	3',3'-dimethylglutaryl	isopropenyl	2,3-dichlorobenzyl	hydrogen
572	3',3'-dimethylglutaryl	isopropyl	2,3-dichlorobenzyl	hydrogen
573	3',3'-dimethylsuccinyl	isopropenyl	2,3-dichlorobenzyl	hydrogen
574	3',3'-dimethylsuccinyl	isopropyl	2,3-dichlorobenzyl	hydrogen
575	3',3'-dimethylglutaryl	isopropenyl	4-(4-morpholinyl)benzyl	hydrogen
576	3',3'-dimethylglutaryl	isopropyl	4-(4-morpholinyl)benzyl	hydrogen
577	3',3'-dimethylsuccinyl	isopropenyl	4-(4-morpholinyl)benzyl	hydrogen
578	3',3'-dimethylsuccinyl	isopropyl	4-(4-morpholinyl)benzyl	hydrogen
579	3',3'-dimethylglutaryl	isopropenyl	4-(4-methylpiperazinyl)benzyl	hydrogen
580	3',3'-dimethylglutaryl	isopropyl	4-(4-methylpiperazinyl)benzyl	hydrogen
581	3',3'-dimethylsuccinyl	isopropenyl	4-(4-methylpiperazinyl)benzyl	hydrogen
582	3',3'-dimethylsuccinyl	isopropyl	4-(4-methylpiperazinyl)benzyl	hydrogen
583	3',3'-dimethylglutaryl	isopropenyl	3-[6-(4-morpholinyl)pyridinyl]methyl	hydrogen
584	3',3'-dimethylglutaryl	isopropyl	3-[6-(4-morpholinyl)pyridinyl]methyl	hydrogen
585	3',3'-dimethylsuccinyl	isopropenyl	3-[6-(4-morpholinyl)pyridinyl]methyl	hydrogen
586	3',3'-dimethylsuccinyl	isopropyl	3-[6-(4-morpholinyl)pyridinyl]methyl	hydrogen
587	3',3'-dimethylglutaryl	isopropenyl	4-azido-2,3,5,6-tetrafluorobenzyl	hydrogen
588	3',3'-dimethylglutaryl	isopropyl	4-azido-2,3,5,6-tetrafluorobenzyl	hydrogen
589	3',3'-dimethylsuccinyl	isopropenyl	4-azido-2,3,5,6-tetrafluorobenzyl	hydrogen
590	3',3'-dimethylsuccinyl	isopropyl	4-azido-2,3,5,6-	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
			tetrafluorobenzyl	
591	3',3'-dimethylglutaryl	isopropenyl	2-[(4-azido-2,3,5,6-tetrafluorobenzoyl)amino]ethyl	hydrogen
592	3',3'-dimethylglutaryl	isopropyl	2-[(4-azido-2,3,5,6-tetrafluorobenzoyl)amino]ethyl	hydrogen
593	3',3'-dimethylsuccinyl	isopropenyl	2-[(4-azido-2,3,5,6-tetrafluorobenzoyl)amino]ethyl	hydrogen
594	3',3'-dimethylsuccinyl	isopropyl	2-[(4-azido-2,3,5,6-tetrafluorobenzoyl)amino]ethyl	hydrogen
595	3',3'-dimethylglutaryl	isopropenyl	(R)-2-hydroxy-1-phenylethyl	hydrogen
596	3',3'-dimethylglutaryl	isopropyl	(R)-2-hydroxy-1-phenylethyl	hydrogen
597	3',3'-dimethylsuccinyl	isopropenyl	(R)-2-hydroxy-1-phenylethyl	hydrogen
598	3',3'-dimethylsuccinyl	isopropyl	(R)-2-hydroxy-1-phenylethyl	hydrogen
599	3',3'-dimethylglutaryl	isopropenyl	(S)-2-hydroxy-1-phenylethyl	hydrogen
600	3',3'-dimethylglutaryl	isopropyl	(S)-2-hydroxy-1-phenylethyl	hydrogen
601	3',3'-dimethylsuccinyl	isopropenyl	(S)-2-hydroxy-1-phenylethyl	hydrogen
602	3',3'-dimethylsuccinyl	isopropyl	(S)-2-hydroxy-1-phenylethyl	hydrogen
603	3',3'-dimethylglutaryl	isopropenyl	2-phenylethyl	hydrogen
604	3',3'-dimethylglutaryl	isopropyl	2-phenylethyl	hydrogen
605	3',3'-dimethylsuccinyl	isopropenyl	2-phenylethyl	hydrogen
606	3',3'-dimethylsuccinyl	isopropyl	2-phenylethyl	hydrogen
607	3',3'-dimethylglutaryl	isopropenyl	2- <i>N,N</i> -dimethylaminoethyl	hydrogen
608	3',3'-dimethylglutaryl	isopropyl	2- <i>N,N</i> -dimethylaminoethyl	hydrogen
609	3',3'-dimethylsuccinyl	isopropenyl	2- <i>N,N</i> -dimethylaminoethyl	hydrogen
610	3',3'-dimethylsuccinyl	isopropyl	2- <i>N,N</i> -dimethylaminoethyl	hydrogen
611	3',3'-dimethylglutaryl	isopropenyl	2-(1-amino-2-methylpropyl)	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
612	3',3'-dimethylglutaryl	isopropyl	2-(1-amino-2-methylpropyl)	hydrogen
613	3',3'-dimethylsuccinyl	isopropenyl	2-(1-amino-2-methylpropyl)	hydrogen
614	3',3'-dimethylsuccinyl	isopropyl	2-(1-amino-2-methylpropyl)	hydrogen
615	3',3'-dimethylglutaryl	isopropenyl	2- <i>N,N</i> -dimethylaminopropyl	hydrogen
616	3',3'-dimethylglutaryl	isopropyl	2- <i>N,N</i> -dimethylaminopropyl	hydrogen
617	3',3'-dimethylsuccinyl	isopropenyl	2- <i>N,N</i> -dimethylaminopropyl	hydrogen
618	3',3'-dimethylsuccinyl	isopropyl	2- <i>N,N</i> -dimethylaminopropyl	hydrogen
619	3',3'-dimethylglutaryl	isopropenyl	3-(4-morpholinyl)propyl	hydrogen
620	3',3'-dimethylglutaryl	isopropyl	3-(4-morpholinyl)propyl	hydrogen
621	3',3'-dimethylsuccinyl	isopropenyl	3-(4-morpholinyl)propyl	hydrogen
622	3',3'-dimethylsuccinyl	isopropyl	3-(4-morpholinyl)propyl	hydrogen
623	3',3'-dimethylglutaryl	isopropenyl	3-(1-imidazolyl)propyl	hydrogen
624	3',3'-dimethylglutaryl	isopropyl	3-(1-imidazolyl)propyl	hydrogen
625	3',3'-dimethylsuccinyl	isopropenyl	3-(1-imidazolyl)propyl	hydrogen
626	3',3'-dimethylsuccinyl	isopropyl	3-(1-imidazolyl)propyl	hydrogen
627	3',3'-dimethylglutaryl	isopropenyl	2-(4-methylmorpholinyl)methyl	methyl
628	3',3'-dimethylglutaryl	isopropyl	2-(4-methylmorpholinyl)methyl	methyl
629	3',3'-dimethylsuccinyl	isopropenyl	2-(4-methylmorpholinyl)methyl	methyl
630	3',3'-dimethylsuccinyl	isopropyl	2-(4-methylmorpholinyl)methyl	methyl
631	3',3'-dimethylglutaryl	isopropenyl	2-morpholinylmethyl	methyl
632	3',3'-dimethylglutaryl	isopropyl	2-morpholinylmethyl	methyl

#	R ₁	R ₃	R ₁₁	R ₁₀
633	3',3'-dimethylsuccinyl	isopropenyl	2-morpholinylmethyl	methyl
634	3',3'-dimethylsuccinyl	isopropyl	2-morpholinylmethyl	methyl
635	3',3'-dimethylglutaryl	isopropenyl	2-(4- <i>tert</i> -butoxycarbonyl morpholinyl)methyl	methyl
636	3',3'-dimethylglutaryl	isopropyl	2-(4- <i>tert</i> -butoxycarbonyl morpholinyl)methyl	methyl
637	3',3'-dimethylsuccinyl	isopropenyl	2-(4- <i>tert</i> -butoxycarbonyl morpholinyl)methyl	methyl
638	3',3'-dimethylsuccinyl	isopropyl	2-(4- <i>tert</i> -butoxycarbonyl morpholinyl)methyl	methyl
639	3',3'-dimethylglutaryl	isopropenyl	(1R, 3R)-3- <i>N,N</i> -dimethylaminocyclopentyl	hydrogen
640	3',3'-dimethylglutaryl	isopropyl	(1R, 3R)-3- <i>N,N</i> -dimethylaminocyclopentyl	hydrogen
641	3',3'-dimethylsuccinyl	isopropenyl	(1R, 3R)-3- <i>N,N</i> -dimethylaminocyclopentyl	hydrogen
642	3',3'-dimethylsuccinyl	isopropyl	(1R, 3R)-3- <i>N,N</i> -dimethylaminocyclopentyl	hydrogen
643	3',3'-dimethylglutaryl	isopropenyl	(1S, 3S)-3- <i>N,N</i> -dimethylaminocyclopentyl	hydrogen
644	3',3'-dimethylglutaryl	isopropyl	(1S, 3S)-3- <i>N,N</i> -dimethylaminocyclopentyl	hydrogen
645	3',3'-dimethylsuccinyl	isopropenyl	(1S, 3S)-3- <i>N,N</i> -dimethylaminocyclopentyl	hydrogen
646	3',3'-dimethylsuccinyl	isopropyl	(1S, 3S)-3- <i>N,N</i> -dimethylaminocyclopentyl	hydrogen
647	3',3'-dimethylglutaryl	isopropenyl	(1R, 3R)-3-aminocyclopentyl	hydrogen
648	3',3'-dimethylglutaryl	isopropyl	(1R, 3R)-3-aminocyclopentyl	hydrogen
649	3',3'-dimethylsuccinyl	isopropenyl	(1R, 3R)-3-aminocyclopentyl	hydrogen

- 54 -

#	R ₁	R ₃	R ₁₁	R ₁₀
650	3',3'-dimethylsuccinyl	isopropyl	(1R, 3R)-3-aminocyclopentyl	hydrogen
651	3',3'-dimethylglutaryl	isopropenyl	(1S, 3S)-3-aminocyclopentyl	hydrogen
652	3',3'-dimethylglutaryl	isopropyl	(1S, 3S)-3-aminocyclopentyl	hydrogen
653	3',3'-dimethylsuccinyl	isopropenyl	(1S, 3S)-3-aminocyclopentyl	hydrogen
654	3',3'-dimethylsuccinyl	isopropyl	(1S, 3S)-3-aminocyclopentyl	hydrogen
655	3',3'-dimethylglutaryl	isopropenyl	(1r, 4r)-4- <i>N,N</i> -dimethylaminocyclohexyl	hydrogen
656	3',3'-dimethylglutaryl	isopropyl	(1r, 4r)-4- <i>N,N</i> -dimethylaminocyclohexyl	hydrogen
657	3',3'-dimethylsuccinyl	isopropenyl	(1r, 4r)-4- <i>N,N</i> -dimethylaminocyclohexyl	hydrogen
658	3',3'-dimethylsuccinyl	isopropyl	(1r, 4r)-4- <i>N,N</i> -dimethylaminocyclohexyl	hydrogen
659	3',3'-dimethylglutaryl	isopropenyl	(1s, 4s)-4- <i>N,N</i> -dimethylaminocyclohexyl	hydrogen
660	3',3'-dimethylglutaryl	isopropyl	(1s, 4s)-4- <i>N,N</i> -dimethylaminocyclohexyl	hydrogen
661	3',3'-dimethylsuccinyl	isopropenyl	(1s, 4s)-4- <i>N,N</i> -dimethylaminocyclohexyl	hydrogen
662	3',3'-dimethylsuccinyl	isopropyl	(1s, 4s)-4- <i>N,N</i> -dimethylaminocyclohexyl	hydrogen
663	3',3'-dimethylglutaryl	isopropenyl	(1r, 4r)-4-aminocyclohexyl	hydrogen
664	3',3'-dimethylglutaryl	isopropyl	(1r, 4r)-4-aminocyclohexyl	hydrogen
665	3',3'-dimethylsuccinyl	isopropenyl	(1r, 4r)-4-aminocyclohexyl	hydrogen
666	3',3'-dimethylsuccinyl	isopropyl	(1r, 4r)-4-aminocyclohexyl	hydrogen
667	3',3'-dimethylglutaryl	isopropenyl	(1s, 4s)-4-aminocyclohexyl	hydrogen

#	R ₁	R ₃	R ₁₁	R ₁₀
668	3',3'-dimethylglutaryl	isopropyl	(1s, 4s)-4-aminocyclohexyl	hydrogen
669	3',3'-dimethylsuccinyl	isopropenyl	(1s, 4s)-4-aminocyclohexyl	hydrogen
670	3',3'-dimethylsuccinyl	isopropyl	(1s, 4s)-4-aminocyclohexyl	hydrogen

[0081] Preferred compounds wherein R₂ is (v) and R₁₀ and R₁₁ are taken together with the nitrogen to which they are attached to form a heterocycle or heteroaryl include, but are not limited to, those found in Table 7:

TABLE 7

#	R ₁	R ₃	R ₁₀ and R ₁₁ taken with the nitrogen to which they are attached
671	3',3'-dimethylsuccinyl	isopropenyl	4-(<i>tert</i> -butoxycarbonyl)piperazinyl
672	3',3'-dimethylglutaryl	isopropenyl	4-(<i>tert</i> -butoxycarbonyl)piperazinyl
673	3',3'-dimethylsuccinyl	isopropenyl	morpholinyl
674	3',3'-dimethylglutaryl	isopropenyl	morpholinyl
675	3',3'-dimethylsuccinyl	isopropenyl	piperidinyl
676	3',3'-dimethylglutaryl	isopropenyl	piperidinyl
677	3',3'-dimethylsuccinyl	isopropenyl	piperazinyl
678	3',3'-dimethylglutaryl	isopropenyl	piperazinyl
679	3',3'-dimethylsuccinyl	isopropyl	4-(<i>tert</i> -butoxycarbonyl)piperazinyl
680	3',3'-dimethylglutaryl	isopropyl	4-(<i>tert</i> -butoxycarbonyl)piperazinyl
681	3',3'-dimethylsuccinyl	isopropyl	morpholinyl
682	3',3'-dimethylglutaryl	isopropyl	morpholinyl
683	3',3'-dimethylsuccinyl	isopropyl	piperidinyl
684	3',3'-dimethylglutaryl	isopropyl	piperidinyl
685	3',3'-dimethylsuccinyl	isopropyl	piperazinyl
686	3',3'-dimethylglutaryl	isopropyl	piperazinyl
687	3',3'-dimethyl-4-(4-morpholinyl)-4-oxobutanoyl	isopropenyl	4-(4-morpholinylcarbonyl)piperazinyl
688	3',3'-dimethyl-4-(4-morpholinyl)-4-oxobutanoyl	isopropyl	4-(4-morpholinylcarbonyl)piperazinyl
689	3',3'-dimethylglutaryl	isopropenyl	4-methylpiperazinyl
690	3',3'-dimethylglutaryl	isopropyl	4-methylpiperazinyl
691	3',3'-dimethylsuccinyl	isopropenyl	4-methylpiperazinyl
692	3',3'-dimethylsuccinyl	isopropyl	4-methylpiperazinyl
693	3',3'-dimethylglutaryl	isopropenyl	4-ethylpiperazinyl

694	3',3'-dimethylglutaryl	isopropyl	4-ethylpiperazinyl
695	3',3'-dimethylsuccinyl	isopropenyl	4-ethylpiperazinyl
696	3',3'-dimethylsuccinyl	isopropyl	4-ethylpiperazinyl
697	3',3'-dimethylglutaryl	isopropenyl	4-isopropylpiperazinyl
698	3',3'-dimethylglutaryl	isopropyl	4-isopropylpiperazinyl
699	3',3'-dimethylsuccinyl	isopropenyl	4-isopropylpiperazinyl
700	3',3'-dimethylsuccinyl	isopropyl	4-isopropylpiperazinyl
701	3',3'-dimethylglutaryl	isopropenyl	4-(cyclopropylmethyl)piperazinyl
702	3',3'-dimethylglutaryl	isopropyl	4-(cyclopropylmethyl)piperazinyl
703	3',3'-dimethylsuccinyl	isopropenyl	4-(cyclopropylmethyl)piperazinyl
704	3',3'-dimethylsuccinyl	isopropyl	4-(cyclopropylmethyl)piperazinyl
705	3',3'-dimethylglutaryl	isopropenyl	4-benzylpiperazinyl
706	3',3'-dimethylglutaryl	isopropyl	4-benzylpiperazinyl
707	3',3'-dimethylsuccinyl	isopropenyl	4-benzylpiperazinyl
708	3',3'-dimethylsuccinyl	isopropyl	4-benzylpiperazinyl
709	3',3'-dimethylglutaryl	isopropenyl	4-[3-(5-methylisoxazolyl)methyl]piperazinyl
710	3',3'-dimethylglutaryl	isopropyl	4-[3-(5-methylisoxazolyl)methyl]piperazinyl
711	3',3'-dimethylsuccinyl	isopropenyl	4-[3-(5-methylisoxazolyl)methyl]piperazinyl
712	3',3'-dimethylsuccinyl	isopropyl	4-[3-(5-methylisoxazolyl)methyl]piperazinyl
713	3',3'-dimethylglutaryl	isopropenyl	4-(4-pyridinylmethyl)piperazinyl
714	3',3'-dimethylglutaryl	isopropyl	4-(4-pyridinylmethyl)piperazinyl
715	3',3'-dimethylsuccinyl	isopropenyl	4-(4-pyridinylmethyl)piperazinyl
716	3',3'-dimethylsuccinyl	isopropyl	4-(4-pyridinylmethyl)piperazinyl
717	3',3'-dimethylglutaryl	isopropenyl	4-acetyl piperazinyl
718	3',3'-dimethylglutaryl	isopropyl	4-acetyl piperazinyl
719	3',3'-dimethylsuccinyl	isopropenyl	4-acetyl piperazinyl
720	3',3'-dimethylsuccinyl	isopropyl	4-acetyl piperazinyl

721	3',3'-dimethylglutaryl	isopropenyl	4-(isopropylaminocarbonyl)piperazinyl
722	3',3'-dimethylglutaryl	isopropyl	4-(isopropylaminocarbonyl)piperazinyl
723	3',3'-dimethylsuccinyl	isopropenyl	4-(isopropylaminocarbonyl)piperazinyl
724	3',3'-dimethylsuccinyl	isopropyl	4-(isopropylaminocarbonyl)piperazinyl
725	3',3'-dimethylglutaryl	isopropenyl	4-(methylsulfonyl)piperazinyl
726	3',3'-dimethylglutaryl	isopropyl	4-(methylsulfonyl)piperazinyl
727	3',3'-dimethylsuccinyl	isopropenyl	4-(methylsulfonyl)piperazinyl
728	3',3'-dimethylsuccinyl	isopropyl	4-(methylsulfonyl)piperazinyl
729	3',3'-dimethylglutaryl	isopropenyl	4-cyclopropylpiperazinyl
730	3',3'-dimethylglutaryl	isopropyl	4-cyclopropylpiperazinyl
731	3',3'-dimethylsuccinyl	isopropenyl	4-cyclopropylpiperazinyl
732	3',3'-dimethylsuccinyl	isopropyl	4-cyclopropylpiperazinyl
733	3',3'-dimethylglutaryl	isopropenyl	4-(2-methoxyethylaminocarbonyl)piperazinyl
734	3',3'-dimethylglutaryl	isopropyl	4-(2-methoxyethylaminocarbonyl)piperazinyl
735	3',3'-dimethylsuccinyl	isopropenyl	4-(2-methoxyethylaminocarbonyl)piperazinyl
736	3',3'-dimethylsuccinyl	isopropyl	4-(2-methoxyethylaminocarbonyl)piperazinyl
737	3',3'-dimethylglutaryl	isopropenyl	4-(2-hydroxyethyl)piperazinyl
738	3',3'-dimethylglutaryl	isopropyl	4-(2-hydroxyethyl)piperazinyl
739	3',3'-dimethylsuccinyl	isopropenyl	4-(2-hydroxyethyl)piperazinyl
740	3',3'-dimethylsuccinyl	isopropyl	4-(2-hydroxyethyl)piperazinyl
741	3',3'-dimethylglutaryl	isopropenyl	4-(2-methoxyethyl)piperazinyl
742	3',3'-dimethylglutaryl	isopropyl	4-(2-methoxyethyl)piperazinyl
743	3',3'-dimethylsuccinyl	isopropenyl	4-(2-methoxyethyl)piperazinyl

744	3',3'-dimethylsuccinyl	isopropyl	4-(2-methoxyethyl)piperazinyl
745	3',3'-dimethylglutaryl	isopropenyl	4-(3-dimethylaminopropyl)piperazinyl
746	3',3'-dimethylglutaryl	isopropyl	4-(3-dimethylaminopropyl)piperazinyl
747	3',3'-dimethylsuccinyl	isopropenyl	4-(3-dimethylaminopropyl)piperazinyl
748	3',3'-dimethylsuccinyl	isopropyl	4-(3-dimethylaminopropyl)piperazinyl
749	3',3'-dimethylglutaryl	isopropenyl	4-(aminocarbonyl)piperazinyl
750	3',3'-dimethylglutaryl	isopropyl	4-(aminocarbonyl)piperazinyl
751	3',3'-dimethylsuccinyl	isopropenyl	4-(aminocarbonyl)piperazinyl
752	3',3'-dimethylsuccinyl	isopropyl	4-(aminocarbonyl)piperazinyl
753	3',3'-dimethylglutaryl	isopropenyl	4-(aminosulfonyl)piperazinyl
754	3',3'-dimethylglutaryl	isopropyl	4-(aminosulfonyl)piperazinyl
755	3',3'-dimethylsuccinyl	isopropenyl	4-(aminosulfonyl)piperazinyl
756	3',3'-dimethylsuccinyl	isopropyl	4-(aminosulfonyl)piperazinyl
757	3',3'-dimethylglutaryl	isopropenyl	3-oxopiperazinyl
758	3',3'-dimethylglutaryl	isopropyl	3-oxopiperazinyl
759	3',3'-dimethylsuccinyl	isopropenyl	3-oxopiperazinyl
760	3',3'-dimethylsuccinyl	isopropyl	3-oxopiperazinyl
761	3',3'-dimethylglutaryl	isopropenyl	4-methyl-3-oxopiperazinyl
762	3',3'-dimethylglutaryl	isopropyl	4-methyl-3-oxopiperazinyl
763	3',3'-dimethylsuccinyl	isopropenyl	4-methyl-3-oxopiperazinyl
764	3',3'-dimethylsuccinyl	isopropyl	4-methyl-3-oxopiperazinyl
765	3',3'-dimethylglutaryl	isopropenyl	4-(hydroxyethyl)-3-oxopiperazinyl
766	3',3'-dimethylglutaryl	isopropyl	4-(hydroxyethyl)-3-oxopiperazinyl
767	3',3'-dimethylsuccinyl	isopropenyl	4-(hydroxyethyl)-3-oxopiperazinyl
768	3',3'-dimethylsuccinyl	isopropyl	4-(hydroxyethyl)-3-oxopiperazinyl
769	3',3'-dimethylglutaryl	isopropenyl	4-(2-hydroxybenzoyl)piperazinyl
770	3',3'-dimethylglutaryl	isopropyl	4-(2-hydroxybenzoyl)piperazinyl
771	3',3'-dimethylsuccinyl	isopropenyl	4-(2-hydroxybenzoyl)piperazinyl
772	3',3'-dimethylsuccinyl	isopropyl	4-(2-hydroxybenzoyl)piperazinyl
773	3',3'-dimethylglutaryl	isopropenyl	4-[3-(1,2,4-oxadiazolyl)methyl]piperazinyl
774	3',3'-dimethylglutaryl	isopropyl	4-[3-(1,2,4-oxadiazolyl)methyl]piperazinyl

775	3',3'-dimethylsuccinyl	isopropenyl	4-[3-(1,2,4-oxadiazolyl)methyl]piperazinyl
776	3',3'-dimethylsuccinyl	isopropyl	4-[3-(1,2,4-oxadiazolyl)methyl]piperazinyl
777	3',3'-dimethylglutaryl	isopropenyl	4-[4-(dimethylaminosulfonyl)benzyl]piperazinyl
778	3',3'-dimethylglutaryl	isopropyl	4-[4-(dimethylaminosulfonyl)benzyl]piperazinyl
779	3',3'-dimethylsuccinyl	isopropenyl	4-[4-(dimethylaminosulfonyl)benzyl]piperazinyl
780	3',3'-dimethylsuccinyl	isopropyl	4-[4-(dimethylaminosulfonyl)benzyl]piperazinyl
781	3',3'-dimethylglutaryl	isopropenyl	4-[1-(1,2,3,4-tetrahydronaphthyl)]piperazinyl
782	3',3'-dimethylglutaryl	isopropyl	4-[1-(1,2,3,4-tetrahydronaphthyl)]piperazinyl
783	3',3'-dimethylsuccinyl	isopropenyl	4-[1-(1,2,3,4-tetrahydronaphthyl)]piperazinyl
784	3',3'-dimethylsuccinyl	isopropyl	4-[1-(1,2,3,4-tetrahydronaphthyl)]piperazinyl
785	3',3'-dimethylglutaryl	isopropenyl	4-[4-(acetamidobenzyl)]piperazinyl
786	3',3'-dimethylglutaryl	isopropyl	4-[4-(acetamidobenzyl)]piperazinyl
787	3',3'-dimethylsuccinyl	isopropenyl	4-[4-(acetamidobenzyl)]piperazinyl
788	3',3'-dimethylsuccinyl	isopropyl	4-[4-(acetamidobenzyl)]piperazinyl
789	3',3'-dimethylglutaryl	isopropenyl	(1S, 4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptanyl
790	3',3'-dimethylglutaryl	isopropyl	(1S, 4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptanyl
791	3',3'-dimethylsuccinyl	isopropenyl	(1S, 4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptanyl
792	3',3'-dimethylsuccinyl	isopropyl	(1S, 4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptanyl
793	3',3'-dimethylglutaryl	isopropenyl	(1R, 4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptanyl
794	3',3'-dimethylglutaryl	isopropyl	(1R, 4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptanyl
795	3',3'-dimethylsuccinyl	isopropenyl	(1R, 4R)-5-methyl-2,5-

			diazabicyclo[2.2.1]heptanyl
796	3',3'-dimethylsuccinyl	isopropyl	(1R, 4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptanyl
797	3',3'-dimethylglutaryl	isopropenyl	(1S, 4S)-2,5-diazabicyclo[2.2.1]heptanyl
798	3',3'-dimethylglutaryl	isopropyl	(1S, 4S)-2,5-diazabicyclo[2.2.1]heptanyl
799	3',3'-dimethylsuccinyl	isopropenyl	(1S, 4S)-2,5-diazabicyclo[2.2.1]heptanyl
800	3',3'-dimethylsuccinyl	isopropyl	(1S, 4S)-2,5-diazabicyclo[2.2.1]heptanyl
801	3',3'-dimethylglutaryl	isopropenyl	(1R, 4R)-2,5-diazabicyclo[2.2.1]heptanyl
802	3',3'-dimethylglutaryl	isopropyl	(1R, 4R)-2,5-diazabicyclo[2.2.1]heptanyl
803	3',3'-dimethylsuccinyl	isopropenyl	(1R, 4R)-2,5-diazabicyclo[2.2.1]heptanyl
804	3',3'-dimethylsuccinyl	isopropyl	(1R, 4R)-2,5-diazabicyclo[2.2.1]heptanyl
805	3',3'-dimethylglutaryl	isopropenyl	(1S, 4S)-5-(<i>tert</i> -butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl
806	3',3'-dimethylglutaryl	isopropyl	(1S, 4S)-5-(<i>tert</i> -butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl
807	3',3'-dimethylsuccinyl	isopropenyl	(1S, 4S)-5-(<i>tert</i> -butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl
808	3',3'-dimethylsuccinyl	isopropyl	(1S, 4S)-5-(<i>tert</i> -butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl
809	3',3'-dimethylglutaryl	isopropenyl	(1R, 4R)-5-(<i>tert</i> -butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl
810	3',3'-dimethylglutaryl	isopropyl	(1R, 4R)-5-(<i>tert</i> -butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl
811	3',3'-dimethylsuccinyl	isopropenyl	(1R, 4R)-5-(<i>tert</i> -butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl
812	3',3'-dimethylsuccinyl	isopropyl	(1R, 4R)-5-(<i>tert</i> -butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl
813	3',3'-dimethylglutaryl	isopropenyl	4-(4-azido-2,3,5,6-tetrafluorobenzyl)piperazinyl
814	3',3'-dimethylglutaryl	isopropyl	4-(4-azido-2,3,5,6-tetrafluorobenzyl)piperazinyl
815	3',3'-dimethylsuccinyl	isopropenyl	4-(4-azido-2,3,5,6-tetrafluorobenzyl)piperazinyl
816	3',3'-dimethylsuccinyl	isopropyl	4-(4-azido-2,3,5,6-tetrafluorobenzyl)piperazinyl
817	3',3'-dimethylglutaryl	isopropenyl	pyrrolidinyl

818	3',3'-dimethylglutaryl	isopropyl	pyrrolidinyl
819	3',3'-dimethylsuccinyl	isopropenyl	pyrrolidinyl
820	3',3'-dimethylsuccinyl	isopropyl	pyrrolidinyl
821	3',3'-dimethylglutaryl	isopropenyl	(R,S)-3-hydroxypyrrolidinyl
822	3',3'-dimethylglutaryl	isopropyl	(R,S)-3-hydroxypyrrolidinyl
823	3',3'-dimethylsuccinyl	isopropenyl	(R,S)-3-hydroxypyrrolidinyl
824	3',3'-dimethylsuccinyl	isopropyl	(R,S)-3-hydroxypyrrolidinyl
825	3',3'-dimethylglutaryl	isopropenyl	(R)- 3-hydroxypyrrolidinyl
826	3',3'-dimethylglutaryl	isopropyl	(R)- 3-hydroxypyrrolidinyl
827	3',3'-dimethylsuccinyl	isopropenyl	(R)- 3-hydroxypyrrolidinyl
828	3',3'-dimethylsuccinyl	isopropyl	(R)- 3-hydroxypyrrolidinyl
829	3',3'-dimethylglutaryl	isopropenyl	(S)- 3-hydroxypyrrolidinyl
830	3',3'-dimethylglutaryl	isopropyl	(S)- 3-hydroxypyrrolidinyl
831	3',3'-dimethylsuccinyl	isopropenyl	(S)- 3-hydroxypyrrolidinyl
832	3',3'-dimethylsuccinyl	isopropyl	(S)- 3-hydroxypyrrolidinyl
833	3',3'-dimethylglutaryl	isopropenyl	(R)-3-(<i>tert</i> -butoxycarbonylamino)pyrrolidinyl
834	3',3'-dimethylglutaryl	isopropyl	(R)-3-(<i>tert</i> -butoxycarbonylamino)pyrrolidinyl
835	3',3'-dimethylsuccinyl	isopropenyl	(R)-3-(<i>tert</i> -butoxycarbonylamino)pyrrolidinyl
836	3',3'-dimethylsuccinyl	isopropyl	(R)-3-(<i>tert</i> -butoxycarbonylamino)pyrrolidinyl
837	3',3'-dimethylglutaryl	isopropenyl	(S)-3-(<i>tert</i> -butoxycarbonylamino)pyrrolidinyl
838	3',3'-dimethylglutaryl	isopropyl	(S)-3-(<i>tert</i> -butoxycarbonylamino)pyrrolidinyl
839	3',3'-dimethylsuccinyl	isopropenyl	(S)-3-(<i>tert</i> -butoxycarbonylamino)pyrrolidinyl
840	3',3'-dimethylsuccinyl	isopropyl	(S)-3-(<i>tert</i> -butoxycarbonylamino)pyrrolidinyl
841	3',3'-dimethylglutaryl	isopropenyl	(R)- 3-aminopyrrolidinyl
842	3',3'-dimethylglutaryl	isopropyl	(R)- 3-aminopyrrolidinyl
843	3',3'-dimethylsuccinyl	isopropenyl	(R)- 3-aminopyrrolidinyl
844	3',3'-dimethylsuccinyl	isopropyl	(R)- 3-aminopyrrolidinyl
845	3',3'-dimethylglutaryl	isopropenyl	(S)- 3-aminopyrrolidinyl
846	3',3'-dimethylglutaryl	isopropyl	(S)- 3-aminopyrrolidinyl
847	3',3'-dimethylsuccinyl	isopropenyl	(S)- 3-aminopyrrolidinyl
848	3',3'-dimethylsuccinyl	isopropyl	(S)- 3-aminopyrrolidinyl

849	3',3'-dimethylglutaryl	isopropenyl	(R)- 2-(hydroxymethyl)pyrrolidinyl
850	3',3'-dimethylglutaryl	isopropyl	(R)- 2-(hydroxymethyl)pyrrolidinyl
851	3',3'-dimethylsuccinyl	isopropenyl	(R)- 2-(hydroxymethyl)pyrrolidinyl
852	3',3'-dimethylsuccinyl	isopropyl	(R)- 2-(hydroxymethyl)pyrrolidinyl
853	3',3'-dimethylglutaryl	isopropenyl	(S)- 2-(hydroxymethyl)pyrrolidinyl
854	3',3'-dimethylglutaryl	isopropyl	(S)- 2-(hydroxymethyl)pyrrolidinyl
855	3',3'-dimethylsuccinyl	isopropenyl	(S)- 2-(hydroxymethyl)pyrrolidinyl
856	3',3'-dimethylsuccinyl	isopropyl	(S)- 2-(hydroxymethyl)pyrrolidinyl
857	3',3'-dimethylglutaryl	isopropenyl	(R)- 3-N-methylaminopyrrolidinyl
858	3',3'-dimethylglutaryl	isopropyl	(R)- 3-N-methylaminopyrrolidinyl
859	3',3'-dimethylsuccinyl	isopropenyl	(R)- 3-N-methylaminopyrrolidinyl
860	3',3'-dimethylsuccinyl	isopropyl	(R)- 3-N-methylaminopyrrolidinyl
861	3',3'-dimethylglutaryl	isopropenyl	(S)- 3-N-methylaminopyrrolidinyl
862	3',3'-dimethylglutaryl	isopropyl	(S)- 3-N-methylaminopyrrolidinyl
863	3',3'-dimethylsuccinyl	isopropenyl	(S)- 3-N-methylaminopyrrolidinyl
864	3',3'-dimethylsuccinyl	isopropyl	(S)- 3-N-methylaminopyrrolidinyl
865	3',3'-dimethylglutaryl	isopropenyl	(R)- 3-N,N-dimethylaminopyrrolidinyl
866	3',3'-dimethylglutaryl	isopropyl	(R)- 3-N,N-dimethylaminopyrrolidinyl
867	3',3'-dimethylsuccinyl	isopropenyl	(R)- 3-N,N-dimethylaminopyrrolidinyl
868	3',3'-dimethylsuccinyl	isopropyl	(R)- 3-N,N-dimethylaminopyrrolidinyl
869	3',3'-dimethylglutaryl	isopropenyl	(S)- 3-N,N-dimethylaminopyrrolidinyl
870	3',3'-dimethylglutaryl	isopropyl	(S)- 3-N,N-dimethylaminopyrrolidinyl
871	3',3'-dimethylsuccinyl	isopropenyl	(S)- 3-N,N-dimethylaminopyrrolidinyl
872	3',3'-dimethylsuccinyl	isopropyl	(S)- 3-N,N-dimethylaminopyrrolidinyl
873	3',3'-dimethylglutaryl	isopropenyl	(R)- 3-N,N-diethylaminopyrrolidinyl
874	3',3'-dimethylglutaryl	isopropyl	(R)- 3-N,N-

			diethylaminopyrrolidinyl
875	3',3'-dimethylsuccinyl	isopropenyl	(R)- 3- <i>N,N</i> -diethylaminopyrrolidinyl
876	3',3'-dimethylsuccinyl	isopropyl	(R)- 3- <i>N,N</i> -diethylaminopyrrolidinyl
877	3',3'-dimethylglutaryl	isopropenyl	(S)- 3- <i>N,N</i> -diethylaminopyrrolidinyl
878	3',3'-dimethylglutaryl	isopropyl	(S)- 3- <i>N,N</i> -diethylaminopyrrolidinyl
879	3',3'-dimethylsuccinyl	isopropenyl	(S)- 3- <i>N,N</i> -diethylaminopyrrolidinyl
880	3',3'-dimethylsuccinyl	isopropyl	(S)- 3- <i>N,N</i> -diethylaminopyrrolidinyl
881	3',3'-dimethylglutaryl	isopropenyl	(R)- 3- <i>N</i> -ethylaminopyrrolidinyl
882	3',3'-dimethylglutaryl	isopropyl	(R)- 3- <i>N</i> -ethylaminopyrrolidinyl
883	3',3'-dimethylsuccinyl	isopropenyl	(R)- 3- <i>N</i> -ethylaminopyrrolidinyl
884	3',3'-dimethylsuccinyl	isopropyl	(R)- 3- <i>N</i> -ethylaminopyrrolidinyl
885	3',3'-dimethylglutaryl	isopropenyl	(S)- 3- <i>N</i> -ethylaminopyrrolidinyl
886	3',3'-dimethylglutaryl	isopropyl	(S)- 3- <i>N</i> -ethylaminopyrrolidinyl
887	3',3'-dimethylsuccinyl	isopropenyl	(S)- 3- <i>N</i> -ethylaminopyrrolidinyl
888	3',3'-dimethylsuccinyl	isopropyl	(S)- 3- <i>N</i> -ethylaminopyrrolidinyl
889	3',3'-dimethylglutaryl	isopropenyl	(R)- 3-(4-morpholinyl)pyrrolidinyl
890	3',3'-dimethylglutaryl	isopropyl	(R)- 3-(4-morpholinyl)pyrrolidinyl
891	3',3'-dimethylsuccinyl	isopropenyl	(R)- 3-(4-morpholinyl)pyrrolidinyl
892	3',3'-dimethylsuccinyl	isopropyl	(R)- 3-(4-morpholinyl)pyrrolidinyl
893	3',3'-dimethylglutaryl	isopropenyl	(S)- 3-(4-morpholinyl)pyrrolidinyl
894	3',3'-dimethylglutaryl	isopropyl	(S)- 3-(4-morpholinyl)pyrrolidinyl
895	3',3'-dimethylsuccinyl	isopropenyl	(S)- 3-(4-morpholinyl)pyrrolidinyl
896	3',3'-dimethylsuccinyl	isopropyl	(S)- 3-(4-morpholinyl)pyrrolidinyl
897	3',3'-dimethylglutaryl	isopropenyl	(R)- 3-(1-pyrrolidinyl)pyrrolidinyl
898	3',3'-dimethylglutaryl	isopropyl	(R)- 3-(1-pyrrolidinyl)pyrrolidinyl
899	3',3'-dimethylsuccinyl	isopropenyl	(R)- 3-(1-pyrrolidinyl)pyrrolidinyl
900	3',3'-dimethylsuccinyl	isopropyl	(R)- 3-(1-pyrrolidinyl)pyrrolidinyl
901	3',3'-dimethylglutaryl	isopropenyl	(S)- 3-(1-pyrrolidinyl)pyrrolidinyl
902	3',3'-dimethylglutaryl	isopropyl	(S)- 3-(1-pyrrolidinyl)pyrrolidinyl
903	3',3'-dimethylsuccinyl	isopropenyl	(S)- 3-(1-pyrrolidinyl)pyrrolidinyl
904	3',3'-dimethylsuccinyl	isopropyl	(S)- 3-(1-pyrrolidinyl)pyrrolidinyl
905	3',3'-dimethylglutaryl	isopropenyl	4-aminopiperidinyl

906	3',3'-dimethylglutaryl	isopropyl	4-aminopiperidinyl
907	3',3'-dimethylsuccinyl	isopropenyl	4-aminopiperidinyl
908	3',3'-dimethylsuccinyl	isopropyl	4-aminopiperidinyl
909	3',3'-dimethylglutaryl	isopropenyl	4-oxopiperidinyl
910	3',3'-dimethylglutaryl	isopropyl	4-oxopiperidinyl
911	3',3'-dimethylsuccinyl	isopropenyl	4-oxopiperidinyl
912	3',3'-dimethylsuccinyl	isopropyl	4-oxopiperidinyl
913	3',3'-dimethylglutaryl	isopropenyl	4-hydroxypiperidinyl
914	3',3'-dimethylglutaryl	isopropyl	4-hydroxypiperidinyl
915	3',3'-dimethylsuccinyl	isopropenyl	4-hydroxypiperidinyl
916	3',3'-dimethylsuccinyl	isopropyl	4-hydroxypiperidinyl
917	3',3'-dimethylglutaryl	isopropenyl	4- <i>N,N</i> -diaminopiperidinyl
918	3',3'-dimethylglutaryl	isopropyl	4- <i>N,N</i> -diaminopiperidinyl
919	3',3'-dimethylsuccinyl	isopropenyl	4- <i>N,N</i> -diaminopiperidinyl
920	3',3'-dimethylsuccinyl	isopropyl	4- <i>N,N</i> -diaminopiperidinyl
921	3',3'-dimethylglutaryl	isopropenyl	4-(4-morpholinyl)piperidinyl
922	3',3'-dimethylglutaryl	isopropyl	4-(4-morpholinyl)piperidinyl
923	3',3'-dimethylsuccinyl	isopropenyl	4-(4-morpholinyl)piperidinyl
924	3',3'-dimethylsuccinyl	isopropyl	4-(4-morpholinyl)piperidinyl
925	3',3'-dimethylglutaryl	isopropenyl	4-acetamidopiperidinyl
926	3',3'-dimethylglutaryl	isopropyl	4-acetamidopiperidinyl
927	3',3'-dimethylsuccinyl	isopropenyl	4-acetamidopiperidinyl
928	3',3'-dimethylsuccinyl	isopropyl	4-acetamidopiperidinyl
929	3',3'-dimethylglutaryl	isopropenyl	4-(methylsulfonamide)piperidinyl
930	3',3'-dimethylglutaryl	isopropyl	4-(methylsulfonamide)piperidinyl
931	3',3'-dimethylsuccinyl	isopropenyl	4-(methylsulfonamide)piperidinyl
932	3',3'-dimethylsuccinyl	isopropyl	4-(methylsulfonamide)piperidinyl
933	3',3'-dimethylglutaryl	isopropenyl	(<i>R</i>)- 3-acetamidopyrrolidinyl
934	3',3'-dimethylglutaryl	isopropyl	(<i>R</i>)- 3-acetamidopyrrolidinyl
935	3',3'-dimethylsuccinyl	isopropenyl	(<i>R</i>)- 3-acetamidopyrrolidinyl
936	3',3'-dimethylsuccinyl	isopropyl	(<i>R</i>)- 3-acetamidopyrrolidinyl
937	3',3'-dimethylglutaryl	isopropenyl	(<i>S</i>)- 3-acetamidopyrrolidinyl
938	3',3'-dimethylglutaryl	isopropyl	(<i>S</i>)- 3-acetamidopyrrolidinyl
939	3',3'-dimethylsuccinyl	isopropenyl	(<i>S</i>)- 3-acetamidopyrrolidinyl
940	3',3'-dimethylsuccinyl	isopropyl	(<i>S</i>)- 3-acetamidopyrrolidinyl

941	3',3'-dimethylglutaryl	isopropenyl	(R)- 3-(cyclopropanecarboxamido)pyrrolidinyl
942	3',3'-dimethylglutaryl	isopropyl	(R)- 3-(cyclopropanecarboxamido)pyrrolidinyl
943	3',3'-dimethylsuccinyl	isopropenyl	(R)- 3-(cyclopropanecarboxamido)pyrrolidinyl
944	3',3'-dimethylsuccinyl	isopropyl	(R)- 3-(cyclopropanecarboxamido)pyrrolidinyl
945	3',3'-dimethylglutaryl	isopropenyl	(S)- 3-(cyclopropanecarboxamido)pyrrolidinyl
946	3',3'-dimethylglutaryl	isopropyl	(S)- 3-(cyclopropanecarboxamido)pyrrolidinyl
947	3',3'-dimethylsuccinyl	isopropenyl	(S)- 3-(cyclopropanecarboxamido)pyrrolidinyl
948	3',3'-dimethylsuccinyl	isopropyl	(S)- 3-(cyclopropanecarboxamido)pyrrolidinyl
949	3',3'-dimethylglutaryl	isopropenyl	(R)- 3-(2-hydroxyacetamido)pyrrolidinyl
950	3',3'-dimethylglutaryl	isopropyl	(R)- 3-(2-hydroxyacetamido)pyrrolidinyl
951	3',3'-dimethylsuccinyl	isopropenyl	(R)- 3-(2-hydroxyacetamido)pyrrolidinyl
952	3',3'-dimethylsuccinyl	isopropyl	(R)- 3-(2-hydroxyacetamido)pyrrolidinyl
953	3',3'-dimethylglutaryl	isopropenyl	(S)- 3-(2-hydroxyacetamido)pyrrolidinyl
954	3',3'-dimethylglutaryl	isopropyl	(S)- 3-(2-hydroxyacetamido)pyrrolidinyl
955	3',3'-dimethylsuccinyl	isopropenyl	(S)- 3-(2-hydroxyacetamido)pyrrolidinyl
956	3',3'-dimethylsuccinyl	isopropyl	(S)- 3-(2-hydroxyacetamido)pyrrolidinyl
957	3',3'-dimethylglutaryl	isopropenyl	(R)- 3-(methylsulfonamido)pyrrolidinyl
958	3',3'-dimethylglutaryl	isopropyl	(R)- 3-(methylsulfonamido)pyrrolidinyl
959	3',3'-dimethylsuccinyl	isopropenyl	(R)- 3-

			(methylsulfonamido)pyrrolidinyl
960	3',3'-dimethylsuccinyl	isopropyl	(R)- 3-(methylsulfonamido)pyrrolidinyl
961	3',3'-dimethylglutaryl	isopropenyl	(S)- 3-(methylsulfonamido)pyrrolidinyl
962	3',3'-dimethylglutaryl	isopropyl	(S)- 3-(methylsulfonamido)pyrrolidinyl
963	3',3'-dimethylsuccinyl	isopropenyl	(S)- 3-(methylsulfonamido)pyrrolidinyl
964	3',3'-dimethylsuccinyl	isopropyl	(S)- 3-(methylsulfonamido)pyrrolidinyl
965	3',3'-dimethylglutaryl	isopropenyl	(R)- 2-(aminomethyl)pyrrolidinyl
966	3',3'-dimethylglutaryl	isopropyl	(R)- 2-(aminomethyl)pyrrolidinyl
967	3',3'-dimethylsuccinyl	isopropenyl	(R)- 2-(aminomethyl)pyrrolidinyl
968	3',3'-dimethylsuccinyl	isopropyl	(R)- 2-(aminomethyl)pyrrolidinyl
969	3',3'-dimethylglutaryl	isopropenyl	(S)- 2-(aminomethyl)pyrrolidinyl
970	3',3'-dimethylglutaryl	isopropyl	(S)- 2-(aminomethyl)pyrrolidinyl
971	3',3'-dimethylsuccinyl	isopropenyl	(S)- 2-(aminomethyl)pyrrolidinyl
972	3',3'-dimethylsuccinyl	isopropyl	(S)- 2-(aminomethyl)pyrrolidinyl
973	3',3'-dimethylglutaryl	isopropenyl	(R)- 2-(<i>N,N</i> -dimethylaminomethyl)pyrrolidinyl
974	3',3'-dimethylglutaryl	isopropyl	(R)- 2-(<i>N,N</i> -dimethylaminomethyl)pyrrolidinyl
975	3',3'-dimethylsuccinyl	isopropenyl	(R)- 2-(<i>N,N</i> -dimethylaminomethyl)pyrrolidinyl
976	3',3'-dimethylsuccinyl	isopropyl	(R)- 2-(<i>N,N</i> -dimethylaminomethyl)pyrrolidinyl
977	3',3'-dimethylglutaryl	isopropenyl	(S)- 2-(<i>N,N</i> -dimethylaminomethyl)pyrrolidinyl
978	3',3'-dimethylglutaryl	isopropyl	(S)- 2-(<i>N,N</i> -dimethylaminomethyl)pyrrolidinyl
979	3',3'-dimethylsuccinyl	isopropenyl	(S)- 2-(<i>N,N</i> -dimethylaminomethyl)pyrrolidinyl
980	3',3'-dimethylsuccinyl	isopropyl	(S)- 2-(<i>N,N</i> -dimethylaminomethyl)pyrrolidinyl
981	3',3'-dimethylglutaryl	isopropenyl	(R)- 2-(acetamidomethyl)pyrrolidinyl
982	3',3'-dimethylglutaryl	isopropyl	(R)- 2-(acetamidomethyl)pyrrolidinyl
983	3',3'-dimethylsuccinyl	isopropenyl	(R)- 2-(acetamidomethyl)pyrrolidinyl
984	3',3'-dimethylsuccinyl	isopropyl	(R)- 2-(acetamidomethyl)pyrrolidinyl

985	3',3'-dimethylglutaryl	isopropenyl	(S)- 2-(acetamidomethyl)pyrrolidinyl
986	3',3'-dimethylglutaryl	isopropyl	(S)- 2-(acetamidomethyl)pyrrolidinyl
987	3',3'-dimethylsuccinyl	isopropenyl	(S)- 2-(acetamidomethyl)pyrrolidinyl
988	3',3'-dimethylsuccinyl	isopropyl	(S)- 2-(acetamidomethyl)pyrrolidinyl
989	3',3'-dimethylglutaryl	isopropenyl	(R)- 2-(methylsulfonamidomethyl)pyrrolidinyl
990	3',3'-dimethylglutaryl	isopropyl	(R)- 2-(methylsulfonamidomethyl)pyrrolidinyl
991	3',3'-dimethylsuccinyl	isopropenyl	(R)- 2-(methylsulfonamidomethyl)pyrrolidinyl
992	3',3'-dimethylsuccinyl	isopropyl	(R)- 2-(methylsulfonamidomethyl)pyrrolidinyl
993	3',3'-dimethylglutaryl	isopropenyl	(S)- 2-(methylsulfonamidomethyl)pyrrolidinyl
994	3',3'-dimethylglutaryl	isopropyl	(S)- 2-(methylsulfonamidomethyl)pyrrolidinyl
995	3',3'-dimethylsuccinyl	isopropenyl	(S)- 2-(methylsulfonamidomethyl)pyrrolidinyl
996	3',3'-dimethylsuccinyl	isopropyl	(S)- 2-(methylsulfonamidomethyl)pyrrolidinyl
997	3',3'-dimethylglutaryl	isopropenyl	(R)- 2-(<i>N,N</i> -diethylaminomethyl)pyrrolidinyl
998	3',3'-dimethylglutaryl	isopropyl	(R)- 2-(<i>N,N</i> -diethylaminomethyl)pyrrolidinyl
999	3',3'-dimethylsuccinyl	isopropenyl	(R)- 2-(<i>N,N</i> -diethylaminomethyl)pyrrolidinyl
1000	3',3'-dimethylsuccinyl	isopropyl	(R)- 2-(<i>N,N</i> -diethylaminomethyl)pyrrolidinyl
1001	3',3'-dimethylglutaryl	isopropenyl	(S)- 2-(<i>N,N</i> -diethylaminomethyl)pyrrolidinyl
1002	3',3'-dimethylglutaryl	isopropyl	(S)- 2-(<i>N,N</i> -diethylaminomethyl)pyrrolidinyl
1003	3',3'-dimethylsuccinyl	isopropenyl	(S)- 2-(<i>N,N</i> -

			diethylaminomethyl)pyrrolidinyl
1004	3',3'-dimethylsuccinyl	isopropyl	(S)- 2-(<i>N,N</i> -diethylaminomethyl)pyrrolidinyl
1005	3',3'-dimethylglutaryl	isopropenyl	(R)- 2-(4-morpholinylmethyl)pyrrolidinyl
1006	3',3'-dimethylglutaryl	isopropyl	(R)- 2-(4-morpholinylmethyl)pyrrolidinyl
1007	3',3'-dimethylsuccinyl	isopropenyl	(R)- 2-(4-morpholinylmethyl)pyrrolidinyl
1008	3',3'-dimethylsuccinyl	isopropyl	(R)- 2-(4-morpholinylmethyl)pyrrolidinyl
1009	3',3'-dimethylglutaryl	isopropenyl	(S)- 2-(4-morpholinylmethyl)pyrrolidinyl
1010	3',3'-dimethylglutaryl	isopropyl	(S)- 2-(4-morpholinylmethyl)pyrrolidinyl
1011	3',3'-dimethylsuccinyl	isopropenyl	(S)- 2-(4-morpholinylmethyl)pyrrolidinyl
1012	3',3'-dimethylsuccinyl	isopropyl	(S)- 2-(4-morpholinylmethyl)pyrrolidinyl
1013	3',3'-dimethylglutaryl	isopropenyl	2,6-dimethylmorpholinyl
1014	3',3'-dimethylglutaryl	isopropyl	2,6-dimethylmorpholinyl
1015	3',3'-dimethylsuccinyl	isopropenyl	2,6-dimethylmorpholinyl
1016	3',3'-dimethylsuccinyl	isopropyl	2,6-dimethylmorpholinyl
1017	3',3'-dimethylglutaryl	isopropenyl	1,4-oxazepanyl
1018	3',3'-dimethylglutaryl	isopropyl	1,4-oxazepanyl
1019	3',3'-dimethylsuccinyl	isopropenyl	1,4-oxazepanyl
1020	3',3'-dimethylsuccinyl	isopropyl	1,4-oxazepanyl
1021	3',3'-dimethylglutaryl	isopropenyl	thiomorpholinyl
1022	3',3'-dimethylglutaryl	isopropyl	thiomorpholinyl
1023	3',3'-dimethylsuccinyl	isopropenyl	thiomorpholinyl
1024	3',3'-dimethylsuccinyl	isopropyl	thiomorpholinyl
1025	3',3'-dimethylglutaryl	isopropenyl	thiomorpholinyl 1-oxide
1026	3',3'-dimethylglutaryl	isopropyl	thiomorpholinyl 1-oxide
1027	3',3'-dimethylsuccinyl	isopropenyl	thiomorpholinyl 1-oxide
1028	3',3'-dimethylsuccinyl	isopropyl	thiomorpholinyl 1-oxide
1029	3',3'-dimethylglutaryl	isopropenyl	thiomorpholinyl 1,1-dioxide
1030	3',3'-dimethylglutaryl	isopropyl	thiomorpholinyl 1,1-dioxide
1031	3',3'-dimethylsuccinyl	isopropenyl	thiomorpholinyl 1,1-dioxide
1032	3',3'-dimethylsuccinyl	isopropyl	thiomorpholinyl 1,1-dioxide

[0082] Preferred compounds wherein R_2 is (vi) include, but are not limited to, those found in Table 8, wherein R_{18} and R_{19} are hydrogen, and d is 1:

TABLE 8

#	R_1	R_3	R_{12}	R_{13}
1033	3',3'-dimethylsuccinyl	isopropenyl	<i>tert</i> -butyl	hydrogen
1034	3',3'-dimethylglutaryl	isopropenyl	<i>tert</i> -butyl	hydrogen
1035	3',3'-dimethylsuccinyl	isopropenyl	<i>tert</i> -butoxycarbonyl	hydrogen
1036	3',3'-dimethylglutaryl	isopropenyl	<i>tert</i> -butoxycarbonyl	hydrogen
1037	3',3'-dimethylsuccinyl	isopropenyl	methoxy	hydrogen
1038	3',3'-dimethylglutaryl	isopropenyl	methoxy	hydrogen
1039	3',3'-dimethylsuccinyl	isopropenyl	5-tetrazolyl	hydrogen
1040	3',3'-dimethylglutaryl	isopropenyl	5-tetrazolyl	hydrogen
1041	3',3'-dimethylsuccinyl	isopropyl	<i>tert</i> -butyl	hydrogen
1042	3',3'-dimethylglutaryl	isopropyl	<i>tert</i> -butyl	hydrogen
1043	3',3'-dimethylsuccinyl	isopropyl	<i>tert</i> -butoxycarbonyl	hydrogen
1044	3',3'-dimethylglutaryl	isopropyl	<i>tert</i> -butoxycarbonyl	hydrogen
1045	3',3'-dimethylsuccinyl	isopropyl	methoxy	hydrogen
1046	3',3'-dimethylglutaryl	isopropyl	methoxy	hydrogen
1047	3',3'-dimethylsuccinyl	isopropyl	5-tetrazolyl	hydrogen
1048	3',3'-dimethylglutaryl	isopropyl	5-tetrazolyl	hydrogen

[0083] Preferred compounds wherein R_2 is (vi) and R_{12} and R_{13} taken with the nitrogen to which they are attached form a heterocycle or heteroaryl include those found in Table 9:

TABLE 9

#	R_1	R_3	R_{12} and R_{13} taken with the nitrogen to which they are attached
1049	3',3'-dimethylsuccinyl	isopropenyl	4'-carboxypiperidinyl
1050	3',3'-dimethylglutaryl	isopropenyl	4'-carboxypiperidinyl
1051	3',3'-dimethylsuccinyl	isopropenyl	3'-hydroxypyrrolidinyl
1052	3',3'-dimethylglutaryl	isopropenyl	3'-hydroxypyrrolidinyl
1053	3',3'-dimethylsuccinyl	isopropenyl	4',4'-difluoropiperidinyl
1054	3',3'-dimethylglutaryl	isopropenyl	4',4'-difluoropiperidinyl
1055	3',3'-dimethylsuccinyl	isopropenyl	4'-ethylpiperazinyl
1056	3',3'-dimethylglutaryl	isopropenyl	4'-ethylpiperazinyl

1057	3',3'-dimethylsuccinyl	isopropyl	4'-carboxypiperidinyl
1058	3',3'-dimethylglutaryl	isopropyl	4'-carboxypiperidinyl
1059	3',3'-dimethylsuccinyl	isopropyl	3'-hydroxypyrrolidinyl
1060	3',3'-dimethylglutaryl	isopropyl	3'-hydroxypyrrolidinyl
1061	3',3'-dimethylsuccinyl	isopropyl	4',4'-difluoropiperidinyl
1062	3',3'-dimethylglutaryl	isopropyl	4',4'-difluoropiperidinyl
1063	3',3'-dimethylsuccinyl	isopropyl	4'-ethylpiperazinyl
1064	3',3'-dimethylglutaryl	isopropyl	4'-ethylpiperazinyl

[0084] Additional preferred compounds wherein R₂ is (viii) include, but are not limited to, those found in Table 10:

TABLE 10

#	R ₁	R ₃	R ₁₇	R ₂₀
1065	3',3'-dimethylglutaryl	isopropenyl	<i>tert</i> -butoxy	hydrogen
1066	3',3'-dimethylglutaryl	isopropyl	<i>tert</i> -butoxy	hydrogen
1067	3',3'-dimethylsuccinyl	isopropenyl	<i>tert</i> -butoxy	hydrogen
1068	3',3'-dimethylsuccinyl	isopropyl	<i>tert</i> -butoxy	hydrogen
1069	3',3'-dimethylglutaryl	isopropenyl	methyl	hydrogen
1070	3',3'-dimethylglutaryl	isopropyl	methyl	hydrogen
1071	3',3'-dimethylsuccinyl	isopropenyl	methyl	hydrogen
1072	3',3'-dimethylsuccinyl	isopropyl	methyl	hydrogen
1073	3',3'-dimethylglutaryl	isopropenyl	methyl	methyl
1074	3',3'-dimethylglutaryl	isopropyl	methyl	methyl
1075	3',3'-dimethylsuccinyl	isopropenyl	methyl	methyl
1076	3',3'-dimethylsuccinyl	isopropyl	methyl	methyl
1077	3',3'-dimethylglutaryl	isopropenyl	trifluoromethyl	hydrogen
1078	3',3'-dimethylglutaryl	isopropyl	trifluoromethyl	hydrogen
1079	3',3'-dimethylsuccinyl	isopropenyl	trifluoromethyl	hydrogen
1080	3',3'-dimethylsuccinyl	isopropyl	trifluoromethyl	hydrogen
1081	3',3'-dimethylglutaryl	isopropenyl	phenyl	hydrogen
1082	3',3'-dimethylglutaryl	isopropyl	phenyl	hydrogen
1083	3',3'-dimethylsuccinyl	isopropenyl	phenyl	hydrogen
1084	3',3'-dimethylsuccinyl	isopropyl	phenyl	hydrogen
1085	3',3'-dimethylglutaryl	isopropenyl	hydrogen	hydrogen
1086	3',3'-dimethylglutaryl	isopropyl	hydrogen	hydrogen
1087	3',3'-dimethylsuccinyl	isopropenyl	hydrogen	hydrogen
1088	3',3'-dimethylsuccinyl	isopropyl	hydrogen	hydrogen

[0085] Additional preferred compounds wherein R₂ is (ii) include the compounds found in Table 11:

TABLE 11

#	R ₁	R ₂ is (ii) and R ₆ is	R ₃
1089	3',3'-dimethylsuccinyl	hydrogen	ethoxymethoxy(methyl)methyl
1090	3',3'-dimethylglutaryl	hydrogen	ethoxymethoxy(methyl)methyl
1091	3',3'-dimethylsuccinyl	hydrogen	1'-oxoethyl
1092	3',3'-dimethylglutaryl	hydrogen	1'-oxoethyl
1093	3',3'-dimethylsuccinyl	hydrogen	1'-methoxymethyl
1094	3',3'-dimethylglutaryl	hydrogen	1'-methoxymethyl
1095	3',3'-dimethylsuccinyl	hydrogen	isobutyl
1096	3',3'-dimethylglutaryl	hydrogen	isobutyl
1097	3',3'-dimethylsuccinyl	hydrogen	2'-hydroxyisopropyl
1098	3',3'-dimethylglutaryl	hydrogen	2'-hydroxyisopropyl

[0086] Additional preferred compounds include derivatives of R₃ and R₂ is (iv).

Examples can be found in Table 12:

TABLE 12

#	R ₁	R ₂ is (iv) and R ₉ is	R ₃
1099	3',3'-dimethylsuccinyl	hydrogen	ethoxymethoxy(methyl)methyl
1100	3',3'-dimethylglutaryl	hydrogen	ethoxymethoxy(methyl)methyl
1101	3',3'-dimethylsuccinyl	hydrogen	1'-oxoethyl
1102	3',3'-dimethylglutaryl	hydrogen	1'-oxoethyl
1103	3',3'-dimethylsuccinyl	hydrogen	1'-methoxymethyl
1104	3',3'-dimethylglutaryl	hydrogen	1'-methoxymethyl
1105	3',3'-dimethylsuccinyl	hydrogen	isobutyl
1106	3',3'-dimethylglutaryl	hydrogen	isobutyl
1107	3',3'-dimethylsuccinyl	hydrogen	2'-hydroxyisopropyl
1108	3',3'-dimethylglutaryl	hydrogen	2'-hydroxyisopropyl

[0087] Additional preferred compounds include allyl or alkyl esters of R₁ for any of the compounds listed in Tables 1-12. Additional preferred compounds include any of the compounds listed in Tables 1-12, wherein the specified R₁ is replaced by succinyl, glutaryl, 3'-methylsuccinyl, or 3'-methylglutaryl.

[0088] Additional preferred compounds include derivatives of R₁. Examples can be found in Table 13:

TABLE 13

#	R ₁	R ₂ is (ii) and R ₆ is	R ₃
1109	4'-(methylsulfonylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1110	4'-(methylsulfonylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1111	4'-(phenylsulfonylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1112	4'-(phenylsulfonylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1113	5'-(phenylsulfonylamino)-5'-oxo-3',3'-dimethylpentanoyl	hydrogen	isopropenyl
1114	5'-(phenylsulfonylamino)-5'-oxo-3',3'-dimethylpentanoyl	hydrogen	isopropyl
1115	4'-[5-(3-methyl-1,2,4-oxadiazolyl)]-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1116	4'-[5-(3-methyl-1,2,4-oxadiazolyl)]-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1117	4'-(2-thiazolylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1118	4'-(2-thiazolylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1119	cyanoaminocarbonyl-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1120	cyanoaminocarbonyl-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1121	4'-cyano-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1122	4'-cyano-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1123	4'-(5-tetrazolyl)-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1124	4'-(5-tetrazolyl)-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1125	methylsulfonylaminocarbonylpropanoyl	hydrogen	isopropenyl
1126	methylsulfonylaminocarbonylpropanoyl	hydrogen	isopropyl
1127	phenylsulfonylaminocarbonylpropanoyl	hydrogen	isopropenyl
1128	phenylsulfonylaminocarbonylpropanoyl	hydrogen	isopropyl
1129	aminocarbonylpropanoyl	hydrogen	isopropenyl
1130	aminocarbonylpropanoyl	hydrogen	isopropyl
1131	<i>tert</i> -butanoyl	hydrogen	isopropenyl
1132	<i>tert</i> -butanoyl	hydrogen	isopropyl
1133	isopropanoyl	hydrogen	isopropenyl
1134	isopropanoyl	hydrogen	isopropyl

[0089] Additional preferred compounds include derivatives of R₁. Examples can be found in Table 14:

TABLE 14

#	R ₁	R ₂ is (iv) and R ₉ is	R ₃
1135	4'-(methylsulfonylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1136	4'-(methylsulfonylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1137	4'-(phenylsulfonylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1138	4'-(phenylsulfonylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1139	5'-(phenylsulfonylamino)-5'-oxo-3',3'-dimethylpentanoyl	hydrogen	isopropenyl
1140	5'-(phenylsulfonylamino)-5'-oxo-3',3'-dimethylpentanoyl	hydrogen	isopropyl
1141	4'-[5-(3-methyl-1,2,4-oxadiazolyl)]-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1142	4'-[5-(3-methyl-1,2,4-oxadiazolyl)]-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1143	4'-(2-thiazolylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1144	4'-(2-thiazolylamino)-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1145	4'-cyanoamino-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropenyl
1146	4'-cyanoamino-4'-oxo-3',3'-dimethylbutanoyl	hydrogen	isopropyl
1147	4'-(methylsulfonylamino)-4'-oxo-butanoyl	hydrogen	isopropenyl
1148	4'-(methylsulfonylamino)-4'-oxo-butanoyl	hydrogen	isopropyl
1149	4'-(phenylsulfonylamino)-4'-oxo-butanoyl	hydrogen	isopropenyl
1150	4'-(phenylsulfonylamino)-4'-oxo-butanoyl	hydrogen	isopropyl
1151	4'-amino-4'-oxo-butanoyl	hydrogen	isopropenyl
1152	4'-amino-4'-oxo-butanoyl	hydrogen	isopropyl

1153	<i>tert</i> -butanoyl	hydrogen	isopropenyl
1154	<i>tert</i> -butanoyl	hydrogen	isopropyl
1155	isopropanoyl	hydrogen	isopropyl
1156	isopropanoyl	hydrogen	isopropyl

[0090] In some embodiments, 3',3'-dimethylsuccinyl is at the C-3 position. In some embodiments, the C-3 substituents having dimethyl groups or oxygen at the C-3' position can be the most active compounds. This observation suggests that these types of substituents might be important to enhanced anti-HIV activity.

[0091] Alkyl groups and alkyl containing groups of the compounds of the present invention can be straight chain or branched alkyl groups, preferably having one to ten carbon atoms. Typical C₁₋₁₀ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, heptyl, and octyl groups. In some embodiments, alkyl groups have one to six carbons. As described herein, any alkyl group, or alkyl containing group, can optionally be substituted with one or more halo, hydroxyl, or thiol.

[0092] The term "alkenyl" refers to C₂₋₁₀ alkenyl groups, preferably C₂₋₄ alkenyl. Typical C₂₋₄ alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and *sec*-butenyl. The term alkenyl also refers to all stereoisomers, i.e., *cis* and *trans* isomers, as well as the *E* and *Z* isomers.

[0093] The term "cycloalkyl" refers to cyclized alkyl groups that are saturated or partially unsaturated. Cycloalkyl groups can include C₃₋₈ cycloalkyl. Typical cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0094] The term "cycloalkylalkyl" refers to any of the above-mentioned C₁₋₁₀ alkyl groups attached to any of the above-listed cycloalkyl groups, such as cyclopropylmethyl or cyclohexylethyl.

[0095] The term "heterocyclcyl" or "heterocyclic" is used herein to mean saturated or partially unsaturated 3-7 membered monocyclic, or 3-14 membered bicyclic, ring system which consists of carbon atoms and from one to four heteroatoms independently selected from the group consisting of O, N, and S. Examples include, but are not limited to, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrazolidinyl, dihydrofuranyl, morpholinyl, dihydroimidazolyl, dihydropyranyl, dihydrooxazolyl, tetrahydrooxazolyl, 2-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl,

oxazinyl, isoxazinyl, oxathiazinyl and the like. Heterocyclic groups can be optionally substituted with one or more methyl, ethyl, oxo, halo, hydroxy, amino, alkylamino, dialkylamino, thiol, hydroxymethyl, hydroxyethyl, hydroxypropyl, methoxymethyl, toluenyl, carboxyl, benzyl, C₁-C₄ alkoxycarbonyl, *tert*-butoxycarbonyl, 4-morpholinylcarbonyl, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyl, alkoxycarbonylamino, aryl, arylalkyl, alkanoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkoxyalkyl, heteroarylalkyl, heterocyclyl, or dimethoxybenzyl; preferably optionally substituted with one or more methyl, ethyl, oxo, halo, thiol, hydroxymethyl, hydroxyethyl, hydroxypropyl, or methoxymethyl. In some embodiments, the term "heterocyclyl" refers to a cycloalkyl group that contains oxygen in the ring, i.e., a cyclic ether such as tetrahydrofuran or tetrahydropyran.

[0096] The term "heterocycloalkyl" refers to any of the above-mentioned C₁₋₁₀ alkyl groups attached to any of the above-mentioned heterocyclic groups.

[0097] The term "heterocycloalkylamino" refers to any of the above-mentioned heterocycloalkyl groups attached to an amino nitrogen.

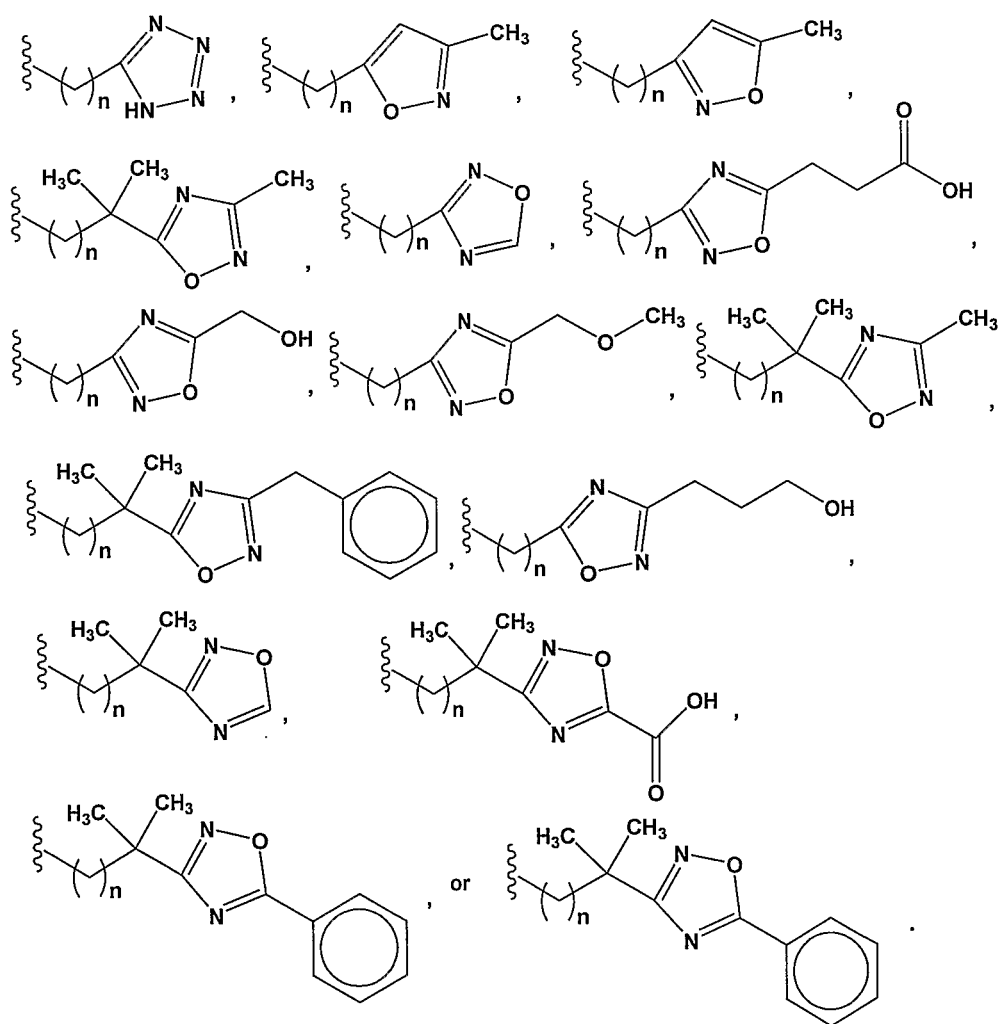
[0098] The term "aryl" refers to any aromatic carbon ring structure, or any carbon ring structure with aromatic properties. Preferred aryls include C₆₋₁₄ aryl, especially C₆₋₁₀ aryl, such as phenyl or naphthyl, and most preferably six carbon aryl. Aryl groups are optionally substituted with one or more methyl, ethyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, alkanoylamino, alkylsulfonamido, halo, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, methoxymethyl, toluenyl, carboxyl, benzyl, or dimethoxybenzyl. Preferably aryl groups are optionally substituted with one or more methyl, ethyl, halo, thiol, hydroxymethyl, hydroxyethyl, hydroxypropyl, methoxymethyl, toluenyl, carboxyl, benzyl, or dimethoxybenzyl.

[0099] The term "arylalkyl" refers to any of the above-mentioned C₁₋₁₀ alkyl groups attached to any of the above-mentioned C₆₋₁₄ aryl groups. Useful arylalkyl groups include phenyl, phenethyl, and phenpropyl.

[00100] The term "arylalkenyl" refers to any of the above-mentioned C₂₋₄ alkenyl groups attached to any of the above-mentioned C₆₋₁₄ aryl groups.

[00101] The term "heteroaryl" refers to 5-14 membered heteroaromatic ring systems, especially 5-14 membered heteroaromatic ring systems, and most preferably five or six membered heteroaromatic groups, wherein from one to four atoms in the ring structure are heteroatoms independently selected from the group consisting of O, N, and S. Examples include, but are not limited to, tetrazolyl, pyridinyl, imidazolyl, isoxazolyl, furanyl, oxazolyl, thiazolyl, pyrrolyl, thienyl, pyrazolyl, triazolyl, e.g., 1,2,3-triazolyl and 1,2,4-triazolyl, isothiazolyl, oxadiazolyl, e.g., 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, and 1,3,4-oxadiazolyl, oxatriazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, e.g., 1,2,3-triazinyl and 1,2,4-triazolyl, quinolinyl, isoquinolinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, and indazolyl.

[00102] Useful heteroarylalkyl include any of the above-listed heteroaryl groups attached to an alkyl group. Useful heteroarylalkyl groups include:



- 77 -

wherein n is one to eight, more preferably one to six.

[00103] The term "alkoxy" refers to a C₁₋₁₀ alkyl group as described above, wherein one of the carbon atoms is substituted by an oxygen atom.

[00104] The term "alkanoyl" refers to an alkyl group as defined above attached to a carbonyl group.

[00105] The term "carboxyalkanoyl" refers to an alkanoyl group as defined above attached to a carboxyl group.

[00106] The terms "alkylamino" and "dialkylamino" refer to —NHR_x and —NR_xR_y respectively, wherein R_x and R_y are C₁₋₁₀ alkyl groups.

[00107] The term "dialkylaminoalkyl" refers to any of the above-mentioned C₁₋₁₀ alkyl groups attached to any of the above-mentioned dialkylamino groups.

[00108] The term "dialkylaminoalkylamino" refers to any of the above-mentioned dialkylaminoalkyl groups attached to an amino nitrogen, such as dimethylaminoethylamino.

[00109] The term "aminoalkyl" refers to an amino groups (-NH₂) attached to an alkyl chain.

[00110] The term "aminocarbonyl" refers to —C(O)NH₂.

[00111] The term "alkylaminocarbonyl" and "dialkylaminocarbonyl" refers to carbonyl groups attached to —NHR₁₂ or —NR₁₂R₁₃ respectively, wherein R₁₂ and R₁₃ are C₁₋₁₀ alkyl groups.

[00112] The terms "halo" or "halogen" refer to an atom selected from the group consisting of fluorine, chlorine, bromine and iodine.

[00113] The terms "carboxyl" and "carboxy" refer to a substituent of formula -COOH.

[00114] The term "carboxyacyl" refers to a dicarboxy compound in which a hydroxy has been removed from one of the carboxyl groups, e.g., substituents of formula —C(O)C_jCO₂H, where j is 0-20.

[00115] The term "cyano" refers to a substituent of formula -CN.

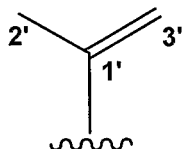
[00116] The term "alkylazo" refers to a substituent of the general formula -N=N-(CH₂)_n-CH₃, wherein n is one to six.

[00117] The term "oxo," refers to =O.

[00118] The term "sulfo" refers to the sulfonic acid group -SO₃H.

- 78 -

- [00119] The term "sulfonyl" refers to the radical $-\text{SO}_2-$.
- [00120] The term "sulfinyl" refers to the group $-\text{S}=\text{O}$.
- [00121] The terms "phosphono" refers to the phosphonic acid radical $-\text{P}(\text{O})(\text{OH})_2$.
- [00122] The term "phosphonoalkyl" refers to a substituent of the general formula $-(\text{CH}_2)_n\text{PO}_3\text{H}_2$, wherein n is one to six.
- [00123] The term "sulfoalkyl" refers to a substituent of the general formula $-(\text{CH}_2)_n\text{SO}_3\text{H}$, wherein n is one to six.
- [00124] The term "formyl" refers to a substituent of the general formula $-\text{CH}=\text{O}$. In some embodiments, the formyl group can be substituted with a halogen.
- [00125] As used herein, the term "isopropenyl" refers to a substituent of formula



The term "propen-2-yl" is used interchangeably with isopropenyl, with the exception that the numbering of propen-2-yl follows accepted IUPAC rules.

- [00126] The terms "hydroximino" or "hydroxyimino" refer to a substituent of the general formula $=\text{N}-\text{OH}$. The term "1'-hydroxyiminoethyl" refers to a substituent of the formula $-\text{C}(=\text{N}-\text{OH})\text{CH}_3$. The term "1'-alkoxyiminoethyl" refers to a substituent of the general formula $-\text{C}(=\text{N}-\text{O}-(\text{CH}_2)_p\text{CH}_3)\text{CH}_3$, wherein p is 0 to 6.
- [00127] The term "optionally substituted" refers to the replacement of a hydrogen in a compound in exchange for an atom or substituent.
- [00128] Also, included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free acid form with a suitable organic or inorganic base and isolating the salt thus formed. These can include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, and cations of methylamine, dimethylamine, trimethylamine, ethylamine, N-methylglucamine and the like. The salts can also be prepared by reacting the purified

betulin compound containing an amine in its base form with a suitable organic or inorganic acid, and isolating the salt thus formed. These base salts can include halides, such as chloride, bromide, and iodide, phosphate, sulfate, and the like; organic acid salts such as citrate, lactate, tartrate, maleate, fumarate, mandelate, acetate, dichloroacetate, trifluoroacetate, oxalate, formate, and the like; and sulfonates such as methanesulfonate, benzenesulfonate, *p*-toluenesulfonate and the like.

[00129] The invention disclosed herein is also meant to encompass prodrugs of the disclosed compounds. The expression "prodrug" refers to compounds that are rapidly transformed *in vivo* by an enzymatic or chemical process, to yield the parent compound of the above formulas, for example, by hydrolysis in blood. Typical prodrugs are esters of the parent drug. A thorough discussion is provided by Higuchi, T. and V. Stella in *Pro-drugs as Novel Delivery Systems, Vol. 14*, A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, Ed. Edward B. Roche, American Pharmaceutical Association, Pergamon Press, 1987. Other examples of prodrugs are drug compounds covalently linked to lipid molecules. Such lipid-linked compounds may have longer half-lives in the body than the drug compounds themselves. They can also be incorporated into liposomes, which may be used to improve the targeting of infected cells, or to enhance the uptake of the drug by infected cells. A thorough discussion of such compositions and methods is provided in U.S. 6,002,029, U.S. 6,448,392 and U.S. 6,599,887. Further examples of prodrugs are drug compounds linked to, or incorporated into, nanometer-sized particles for enhanced absorption by, or improved targeting of, cells within the body. Methods of this sort are described in Weissleder, R. *et al.*, *Nature Biotech.* 23 October 2005, *NBT1159*, p. 1-6; Allen, T. and Cullis, P.R., *Science* 303:1818-1822 (2004); LaVan *et al.*, *Nature Rev. Drug Disc.* 1:77-84 (2002); and Kralj, M. and Pavelic, K., *EMBO Reports* 4:1008-1012 (2003).

[00130] The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification, glucuronidation and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic

product thereof. Such products typically are identified by preparing a radiolabeled compound of the invention, administering it parenterally in a detectable dose to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur and isolating its conversion products from the urine, blood or other biological samples.

[00131] The invention disclosed herein is also meant to encompass the disclosed compounds being isotopically labeled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

[00132] Some of the compounds disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms, as well as their racemic and resolved forms and mixtures thereof. In some embodiments, the compounds of the present invention can be separated as a single enantiomer. Alternatively, the individual enantiomers may be separated according to methods that are well known to those of ordinary skill in the art.

[00133] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[00134] The term "chiral center" refers to a carbon atom to which four different groups are attached.

[00135] The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

[00136] The term "racemic" refers to a mixture of equal parts of enantiomers and which is optically inactive.

[00137] The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

[00138] The invention is also directed to a method for treating a subject infected with HIV-1 by administering at least one of the above-noted betulin derivatives, optionally in combination with any one or more of the known anti-AIDS therapeutics or an immunostimulant.

[00139] Other features, advantages, embodiments, aspects and objects of the present invention will be clear to those skilled in the areas of relevant art, based upon the description, teaching and guidance presented herein.

[00140] The analogs of the present invention can have anti-retroviral activity, thus providing suitable compounds and compositions for treating retroviral infections, optionally with additional pharmaceutically active ingredients, such as anti-retroviral, anti-HIV, and/or immunostimulating compounds or antiviral antibodies or fragments thereof.

[00141] By the term "anti-retroviral activity" or "anti-HIV activity" is intended the ability to inhibit at least one of:

- (1) viral pro-DNA integration into host cell genome;
- (2) retroviral attachment to cells;
- (3) viral entry into cells;
- (4) cellular metabolism which permits viral replication;
- (5) inhibition of intercellular spread of the virus;
- (6) synthesis and/or cellular expression of viral antigens;
- (7) viral budding or maturation;
- (8) activity of virus-coded enzymes (such as reverse transcriptase, integrase and proteases); and/or
- (9) any known retroviral or HIV pathogenic actions, such as, for example, immunosuppression. Thus, any activity which tends to inhibit any of these mechanisms is "anti-retroviral activity" or "anti-HIV activity."

[00142] A compound of the present invention can be used for treatment of retroviral (*e.g.*, HIV) infection either alone, or in combination with other modes of therapy known in the art. Such modes of therapy can include chemotherapy with drugs, such as, but not limited

- 82 -

to, at least one of AZT, 3TC, ddC, d4T, ddI, tenofovir, abacavir, nevirapine, delavirdine, emtricitabine, efavirenz, saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, amprenavir, fosamprenavir, tipranavir, and atazanavir or any other antiretroviral drugs or antibodies in combination with each other, or associated with a biologically based therapeutic, such as, for example, gp41-derived peptides enfuvirtide (Fuzeon; Trimeris-Roche) and T-1249 (Trimeris), or soluble CD4, antibodies to CD4, and conjugates of CD4 or anti-CD4, or as additionally presented herein.

[00143] A compound according to the present invention can be used in treating blood products, such as those maintained in blood banks. The nation's blood supply is currently tested for antibodies to HIV. However, the test is still imperfect and samples which yield negative tests can still contain HIV virus. Treating the blood and blood products with the compounds of the present invention can add an extra margin of safety by reducing or eliminating activity of any retrovirus that may have gone undetected.

[00144] A compound according to the present invention can be used in the treatment of HIV in patients who are not adequately treated by other HIV-1 therapies. Accordingly, the invention is also drawn to a method of treating a patient in need of therapy, wherein the HIV-1 infecting said cells does not respond to other HIV-1 therapies. In another embodiment, methods of the invention are practiced on a subject infected with an HIV that is resistant to a drug used to treat HIV infection. In various applications, the HIV is resistant to one or more protease inhibitors, reverse transcriptase inhibitors, entry inhibitors, nucleoside analogs, vaccines, binding inhibitors, immunomodulators, and/or any other inhibitors. In some embodiments, the compositions and methods of the invention are practiced on a subject infected with an HIV that is resistant to one or more drugs used to treat HIV infections, for example, but not limited to, zidovudine, lamivudine, didanosine, zalcitabine, stavudine, abacavir, nevirapine, delavirdine, emtricitabine, efavirenz, saquinavir, ritonavir, lopinavir, indinavir, nelfinavir, tenofovir, amprenavir, adefovir, atazanavir, fosamprenavir, tipranavir, enfuvirtide, hydroxyurea, AL-721, ampligen, butylated hydroxytoluene; polymannoacetate, castanospermine; contracan; creme pharmatex, CS-87, penciclovir, famciclovir, acyclovir, cytofovir, ganciclovir, dextran sulfate, D-penicillamine trisodium phosphonoformate, fusidic acid, HPA-23, eflornithine, nonoxynol, pentamidine isethionate, peptide T, phenytoin,

isoniazid,. ribavirin, rifabutin, ansamycin, trimetrexate, SK-818, suramin, UA001, and combinations thereof.

[00145] In addition, compounds of the present invention can be used as prophylactics to prevent transmission of HIV infection between individuals. For example, the compounds can be administered orally or by injection to an HIV infected pregnant woman and/or fetus during pregnancy or immediately prior to, at, or subsequent to birth, to reduce the probability that the newborn infant becomes infected. Also, the compounds can be administered vaginally immediately prior to childbirth to prevent infection of the infant during passage through the birth canal. Further, the compounds of the present invention can be used during sexual intercourse to prevent transmission of HIV by applying a retroviral inhibiting effective amount of a topical composition including one or more compounds of Formula *I* to vaginal or other mucosa prior to sexual intercourse. For example, the compounds of the present invention can be used to prevent transmission of HIV from an infected male to an uninfected female or *vice versa*.

Pharmaceutical Compositions

[00146] Pharmaceutical compositions can comprise at least one compound of the present invention. Pharmaceutical compositions according to the present invention can also further comprise one or more additional antiviral agents such as, but not limited to, AZT (zidovudine, RETROVIR, GlaxoSmithKline), 3TC (lamivudine, EPIVIR®, GlaxoSmithKline), AZT+3TC, (COMBIVIR®, GlaxoSmithKline) AZT+3TC+abacvir (TRIZIVIR®, GlaxoSmithKline), ddI (didanosine, VIDEX®, Bristol-Myers Squibb), ddC (zalcitabine, HIVID®, Hoffmann-LaRoche), D4T (stavudine, ZERIT®, Bristol-Myers Squibb), abacavir (ZIAGEN®, GlaxoSmithKline), nevirapine (VIRAMUNE®, Boehringer Ingelheim), delavirdine (Pfizer), efavirenz (SUSTIVA®, DuPont Pharmaceuticals), tenofovir (VIREAD®, Gilead Sciences), FTC (emtricitabine, EMTRIVA®, Gilead Sciences), tenofovir + FTC (TRUVADA®, Gilead Sciences), saquinavir (INVIRASE®, FORTOVASE®, Hoffmann-La Roche), ritonavir (NORVIR®, Abbott Laboratories), indinavir (CRIXIVAN®, Merck and Company), nelfinavir (VIRACEPT®, Pfizer), amprenavir (AGENERASE®, GlaxoSmithKline), adefovir (PREVEON®, HEPSERA®, Gilead Sciences), atazanavir (REYATAZ®, Bristol-Myers

- 84 -

Squibb), fosamprenavir (LEXIVA®, GlaxoSmithKline), hydroxyurea (HYDREA®, Bristol-Meyers Squibb), and tipranavir (APTIVUS®, Boehringer Ingelheim), or any other antiretroviral drugs or antibodies in combination with each other, or associated with a biologically based therapeutic, such as, for example, gp41-derived peptides enfuvirtide (FUZEON®, Roche and Trimeris) and T-1249, or soluble CD4, antibodies to CD4, and conjugates of CD4 or anti-CD4, or as additionally presented herein.

[00147] Additional suitable antiviral agents for optimal use with a compound of the present invention can include, but is not limited to, amphotericin B (FUNGIZONE®); Ampligen (mismatched RNA; Hemispherx Biopharma); interferon beta (BETASERON®, Chiron, Berlex); interferon alfa (INTRON A®, Schering-Plough; ROFERON A®, Hoffman-LaRoche; INFERGEN®, Amgen; WELLFERON®, GlaxoSmithKline); pegylated interferon alfa (PEGASYS®, Hoffman-LaRoche; PEG-Intron®, Schering-Plough); butylated hydroxytoluene; Carrosyn (polymannoacetate); Castanospermine; Contracan (stearic acid derivative); Creme Pharmatex (containing benzalkonium chloride); 5-unsubstituted derivative of zidovudine; penciclovir (DENA VIR®, Novartis); famciclovir (FAMVIR®, Novartis); acyclovir (ZOVIRAX®, GlaxoSmithKline); cytofovir (VISTIDE®, Gilead); ganciclovir (CYTOVENE®, Hoffman LaRoche); valacyclovir, VALTREX®, GlaxoSmithKline); dextran sulfate; D-penicillamine (3-mercapto-D-valine); FOSCARNET® (trisodium phosphonoformate; AstraZeneca); fusidic acid; glycyrrhizin (a constituent of licorice root); HPA-23 (ammonium-21-tungsto-9-antimonate); ORNIDYL® (eflornithine, Aventis); nonoxynol; pentamidine isethionate (PENTAM-300); Peptide T (octapeptide sequence, Peninsula Laboratories); Phenytoin (Pfizer); INH or isoniazid; ribavirin (REBETOL®, Schering-Plough; VIRAZOLE®, Valeant Pharmaceuticals); rifabutin, ansamycin (MYCOBUTIN®, Pfizer); CD4-IgG2 (Progenics Pharmaceuticals) or other CD4-containing or CD4-based molecules; Trimetrexate (Medimmune); suramin and analogues thereof (Bayer).

[00148] Pharmaceutical compositions of the present invention can also further comprise immunomodulators. Suitable immunomodulators for optional use with a compound of the present invention in accordance with the present invention can include, but are not

- 85 -

limited to: ABPP (Bropiramine); anti-human interferon- α -antibody; ascorbic acid and derivatives thereof; interferon- β ; Ciamexon; cyclosporin; cimetidine; CL-246,738; colony stimulating factors, including GM-CSF; dinitrochlorobenzene; HE2000 (Hollis-Eden Pharmaceuticals); inteferon- γ ; glucan; hyperimmune gamma-globulin (Bayer); immuthiol (sodium diethylthiocarbamate); interleukin-1 (Hoffmann-LaRoche, Amgen), interleukin-2 (IL-2) (Chiron); isoprinosine (inosine pranobex); Krestin; LC-9018 (Yakult); lentinan (Yamanouchi); LF-1695; methionine-enkephalin; Minophagen C; muramyl tripeptide, MTP-PE; naltrexone (Barr Laboratories); RNA immunomodulator; REMUNE® (Immune Response Corporation); RETICULOSE® (Advanced Viral Research Corporation); shosaikoto; ginseng; thymic humoral factor; Thymopentin; thymosin factor 5; thymosin 1 (ZADAXIN®, SciClone); thymostimulin; TNF (tumor necrosis factor, Genentech); and vitamin preparations.

[00149] In some embodiments, the animal subject of the present invention is a mammal. By the term "mammal" is meant an individual belonging to the class *Mammalia*. The invention is particularly useful in the treatment of human patients.

[00150] The term "treating" means the administering to subjects a compound of the present invention for purposes which can include prevention, amelioration, or cure of a retroviral-related pathology.

[00151] Medicaments are considered to be provided "in combination" with one another if they are provided to the patient concurrently or if the time between the administration of each medicament is such as to permit an overlap of biological activity.

[00152] In some embodiments, at least one compound of the present invention comprises a single pharmaceutical composition.

[00153] Pharmaceutical compositions for administration according to the present invention can comprise at least one compound according to the present invention in a pharmaceutically acceptable form optionally combined with a pharmaceutically acceptable carrier. These compositions can be administered by any means that achieve their intended purposes. Amounts and regimens for the administration of a compound according to the present invention can be determined readily by those with ordinary skill in the clinical art of treating a retroviral pathology.

[00154] For example, administration can be by parenteral, such as subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration can be by the oral route. The dosage administered depends upon the age, health and weight of the recipient, type of previous or concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

[00155] Compositions within the scope of this invention include all compositions comprising at least one compound according to the present invention in an amount effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typical dosages comprise about 0.1 mg/kg to about 100 mg/kg body weight. In some embodiments, the dosages comprise about 1 mg/kg to about 100 mg/kg body weight of the active ingredient. In some embodiments, the dosages comprise about 1 mg/kg to about 50 mg/kg body weight. In some embodiments, the dosages comprise about 5 mg/kg to about 25 mg/kg body weight.

[00156] Therapeutic administration can also include prior, concurrent, subsequent or adjunctive administration of at least one additional compound according to the present invention or other therapeutic agent, such as an antiviral or immune stimulating agent. In such an approach, the dosage of the second drug can be the same as or different from the dosage of the first therapeutic agent. In some embodiments, the drugs are administered on alternate days in the recommended amounts of each drug.

[00157] Administration of a compound of the present invention can also optionally include previous, concurrent, subsequent or adjunctive therapy using immune system boosters or immunomodulators. In addition to the pharmacologically active compounds, a pharmaceutical composition of the present invention can also contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. In some embodiments, the preparations, particularly those preparations which can be administered orally and which can be used in the above-described type of administration, such as tablets, dragees, and capsules, and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from about 1 percent to about 99 percent,

- 87 -

preferably from about 20 percent to about 75 percent of active compound(s), together with the excipient.

[00158] Pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[00159] Suitable excipients are, *e.g.*, fillers such as saccharides, *e.g.*, lactose, sucrose, mannitol or sorbitol; cellulose preparations and/or calcium phosphates, such as tricalcium phosphate or calcium hydrogen phosphate; as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone. If desired, disintegrating agents can be added such as the above-mentioned starches and also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which can optionally contain gum arabic, talc, polyvinylpyrrolidone, poly(ethylene glycol) and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate are used. Dyestuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

[00160] Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in

the form of granules which can be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In some embodiments using soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils or liquid paraffin. In addition, stabilizers can be added.

[00161] Possible pharmaceutical preparations which can be used rectally include, for example, suppositories which consist of a combination of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, poly(ethylene glycols), or paraffin hydrocarbons.

[00162] Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts. In addition, suspensions of the active compounds as appropriate oily injection suspensions can be administered. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides. Aqueous injection suspensions that can contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethylcellulose, sorbitol, and/or dextran. Optionally, the suspension can also contain stabilizers.

[00163] A pharmaceutical formulation for systemic administration according to the invention can be formulated for enteral, parenteral or topical administration. Indeed, all three types of formulation can be used simultaneously to achieve systemic administration of the active ingredient.

[00164] Suitable formulations for oral administration include hard or soft gelatin capsules, dragees, pills, tablets, including coated tablets, elixirs, suspensions, syrups or inhalations and controlled release forms thereof.

[00165] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as,

- 89 -

for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, cyclodextrins such as hydroxypropyl- β -cyclodextrin, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, *N,N*-dimethylformamide, oils such as cottonseed, groundnut, corn, germ, olive, castor, and sesame oils, glycerol, tetrahydrofurfuryl alcohol, poly(ethylene glycols) and fatty acid esters of sorbitan, and mixtures thereof.

[00166] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, poly(oxyethylene) sorbitol and sorbitan esters, cellulose, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and gum tragacanth, and combinations thereof.

[00167] Solid dosage forms in addition to those formulated for oral administration include rectal suppositories.

[00168] Prophylactic topical compositions for preventing HIV infection between individuals during childbirth or sexual intercourse include one or more compounds of Formula *I* and at least one pharmaceutically acceptable topical carrier or diluent. The topical composition can be, for example, in the form of an ointment, a cream, a gel, a lotion, a paste, a jelly, a spray, a foam, or a sponge. The dosage amount of a compound of Formula *I* in a prophylactic topical formulation is, in general, less than about 1,000 milligrams, and in some embodiments from about 0.01 milligrams to about 100 milligrams. The topical formulations can include other prophylactic ingredients. The carrier and diluents should be acceptable in the sense of being compatible with other ingredients of the formulation and not deleterious to the recipient.

[00169] Topical prophylactic formulations include those suitable for vaginal, rectal or topical administration. The formulations can, where appropriate, be conveniently presented in discrete dosage units, and can be prepared by any of the methods known in the art of pharmacy. All such methods include the step of bringing the active agent into association with liquid carriers, gels or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[00170] Prophylactic formulations suitable for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, jelly, foams, or sprays, or aqueous or oily suspensions, solutions or emulsions (liquid formulations) containing suitable carriers

- 90 -

known in the art in addition to the active agent. Liquid formulations can contain conventional additives, such as, suspending agents, emulsifying agents, non-aqueous vehicles including edible oils, or preservatives. These formulations are useful to prevent both sexual transmission of HIV and infection of an infant during passage through the birth canal. In one example, the vaginal administration can take place prior to sexual intercourse, or immediately prior to childbirth.

[00171] In some embodiments, prophylactic formulations suitable for rectal or vaginal administration having a solid carrier are represented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. Suppositories can be formed, for example, mixing one or more compounds of Formula *I* with one or more softened or melted carriers followed by chilling and shaping in molds.

[00172] Prophylactic formulations according to the invention can also be in the form of drops formulated with an aqueous or non-aqueous base comprising one or more dispersing agents, solubilizing agents, or suspending agents. Liquid sprays can be delivered from pressurized packs.

[00173] Prophylactic formulations according to the invention can be adapted to give sustained delivery. Also, the prophylactic formulations can include other active agents, such as spermicidal agents, antimicrobial agents, and antiviral agents.

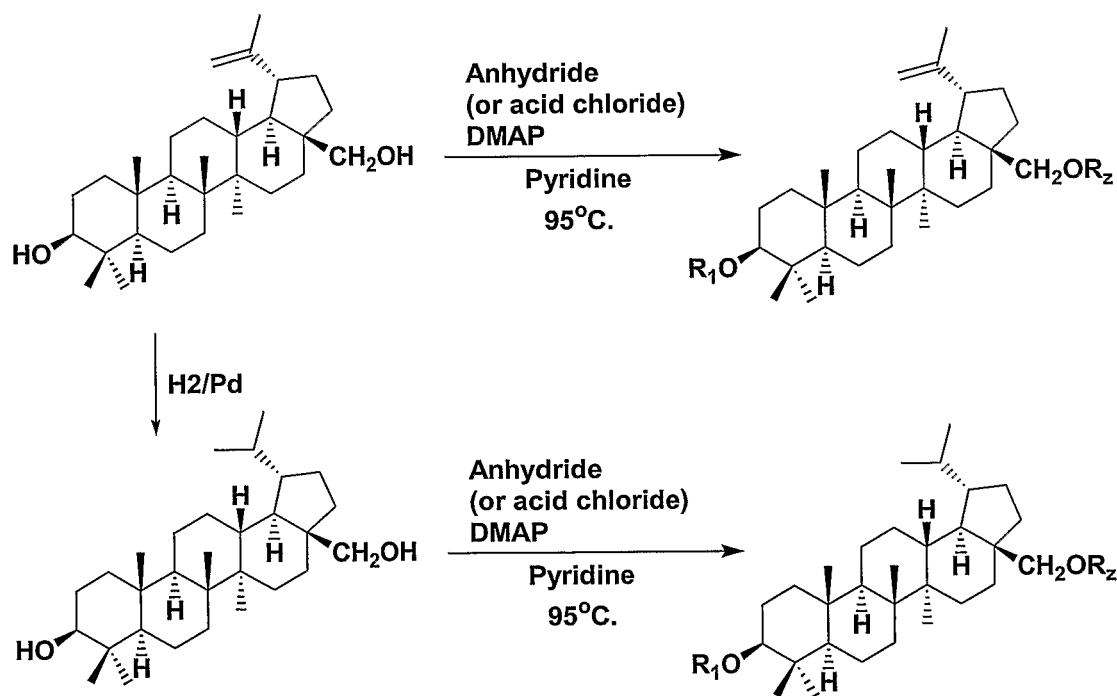
[00174] The compounds of the present invention can also be administered in the form of an implant when compounded with a biodegradable slow-release carrier. Alternatively, the compounds of the present invention can be formulated as a transdermal patch for continuous release of the active ingredient.

[00175] Suitable formulations for topical administration include creams, gels, jellies, mucilages, pastes and ointments. Suitable injectable solutions include intravenous subcutaneous and intramuscular injectable solutions. Alternatively, the compounds can be administered in the form of an infusion solution or as a nasal inhalation or spray.

[00176] The compounds of the present invention can be prepared using methods known to those skilled in the art. Betulin and betulinic acid can be obtained from commercial sources. In general, methods used in make compounds of the present invention employ protection and deprotection steps, for example, protection of hydroxy, amino and carboxy groups. Protecting groups and their chemistry are described generally in *Protective*

Groups in Organic Synthesis, 3rd ed. (eds. T.W. Greene and P.G.M. Wuts, John Wiley and Sons, Inc. (1999)). The compounds of Formula *I* of the present invention wherein R₂ is (ii) can be prepared in a manner similar to that exemplified by the modification of betulin as shown in Scheme 1. Betulin or dihydrobetulin can be heated overnight at 95°C with 6-fold of the appropriate anhydride in anhydrous pyridine in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP). R_z corresponds to -COR₅, -R₆ or -CO(CH₂)_dNR₁₂R₁₃, wherein R₅, R₆, R₁₂, R₁₃ and d are defined above. When thin layer chromatography (TLC) indicates complete consumption of starting material, the reaction can be diluted with EtOAc and washed with 10% HCl solution. The EtOAc layer can then be dried over MgSO₄ and subjected to column chromatography.

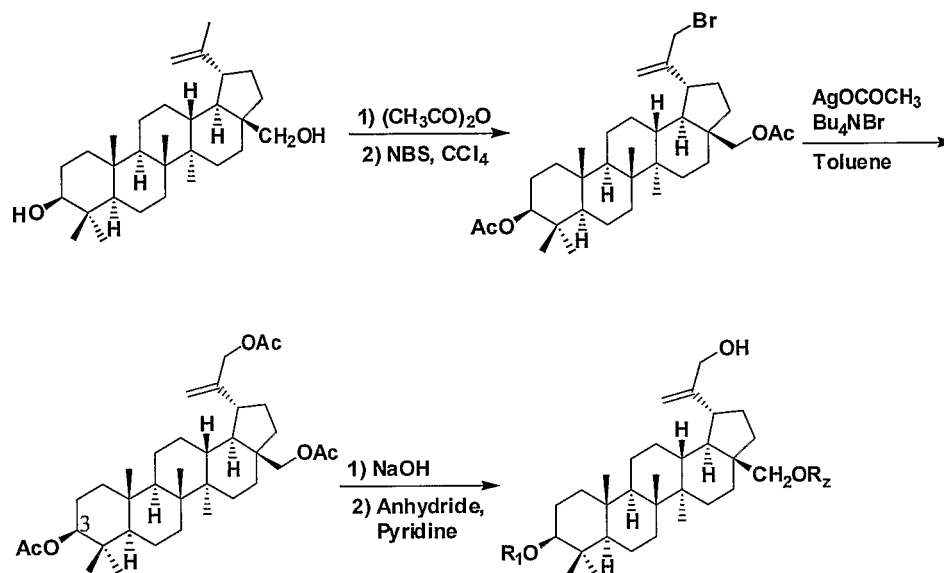
SCHEME 1



[00177] The compounds of Formula *I* of the present invention can be prepared in a manner similar to that exemplified by the modification of betulin as shown in Scheme 2. Scheme 2 depicts the synthesis route for compounds where R₁ is substituted or unsubstituted carboxyacyl. R_z corresponds to -COR₅, -R₆ or -CO(CH₂)_dNR₁₂R₁₃, wherein R₅, R₆, R₁₂, R₁₃ and d are defined above.

- 92 -

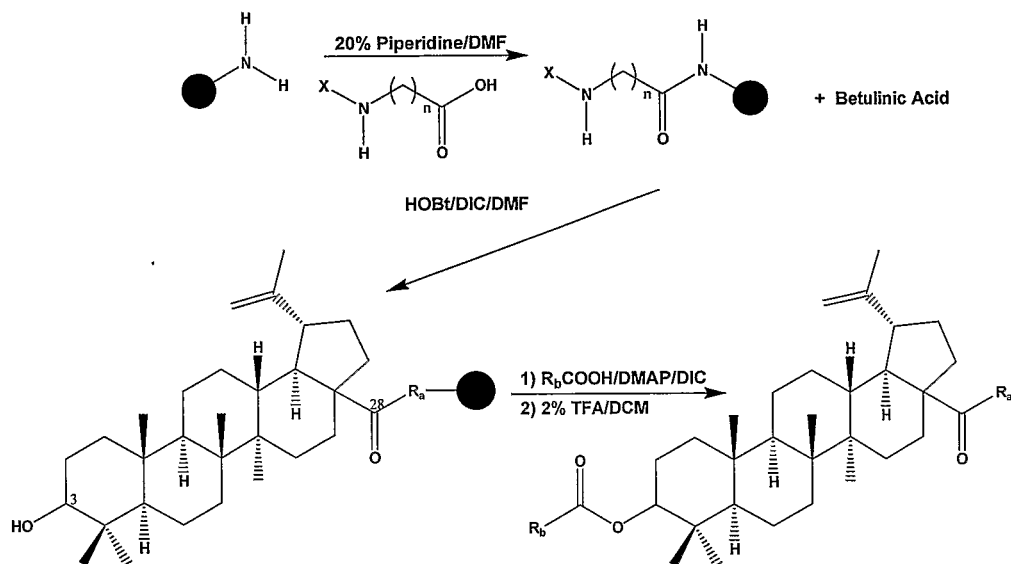
SCHEME 2



[00178] Scheme 3 depicts an alternative method of synthesizing the compounds of the present invention by the use of solid phase organic synthesis (Pathak, A., *et al. Combinatorial Chem. and High Throughput Screening* 5, 241-248 (2002)). Briefly, a betulin backbone can be linked to a resin via ester or amide bond formation at R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} or R_{13} (denoted by R_a). Any resin which allows cleavage of compounds under mild conditions can be used, *e.g.*, 2-chlorotrityl chloride resin or Sieber amide resin. An amino acid can be introduced as a spacer between the betulin and the resin if desired. Once the betulin is immobilized onto the resin scaffold, diversity can be introduced as desired at the C-3 position by adding the acid form of the desired R_1 substituents (denoted by R_b).

- 93 -

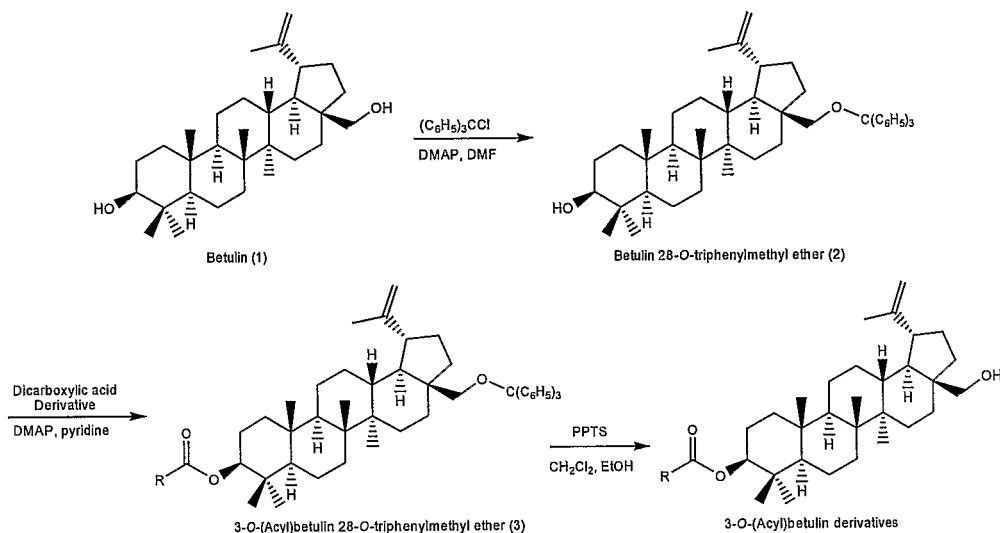
SCHEME 3



[00179] The compounds of the present invention containing modifications at the C-3 position can be prepared as shown in Scheme 4. Protection of the 28-hydroxyl group of betulin (1) with triphenylmethyl ether group yields betulin 28-*O*-triphenylmethyl ether (2), whose solution in pyridine is further treated with an appropriate dicarboxylic acid in the presence of DMAP at reflux. Finally, the 28-protective group is removed by refluxing with pyridinium *p*-toluenesulfonate (PPTS) in CH₂Cl₂-EtOH to give desired 3-*O*-(acyl)betulin derivatives.

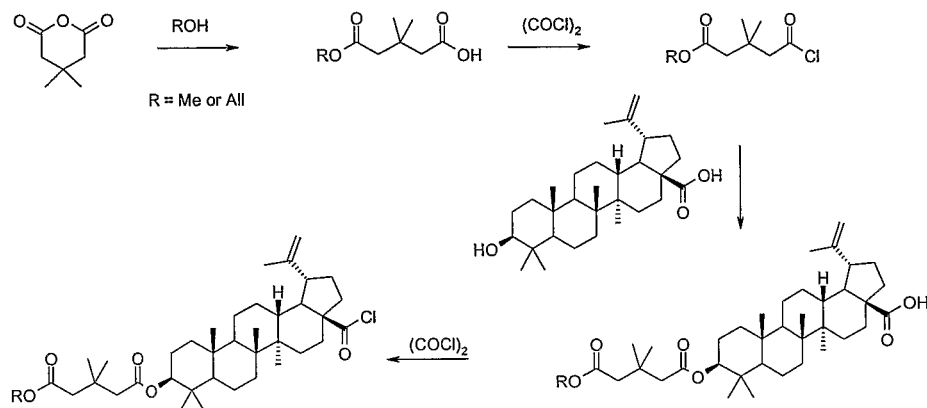
- 94 -

SCHEME 4



[00180] The C-28 amides of the present invention can be synthesized by the following methods. A first method of synthesis of betulinic acid amides is performed by forming C-3 protected betulinic acid C-28 acid halides as described in Scheme 5. A number of additional alcohols can be used in the first step in addition to the allyl alcohol or methanol, e.g., alkyl, alkenyl or aralkyl alcohols can be used. A C-28 amide is introduced by treatment of the C-3 protected betulinic acid C-28 acid halides with the desired amine under appropriate conditions, such as in dry dichloromethane and *N,N*-diisopropylethylamine (Method D). The carboxy-protecting group from the first step is then removed. Deprotection steps are well-known in the art for particular protecting groups. See for example Method E and Method F as described herein.

SCHEME 5

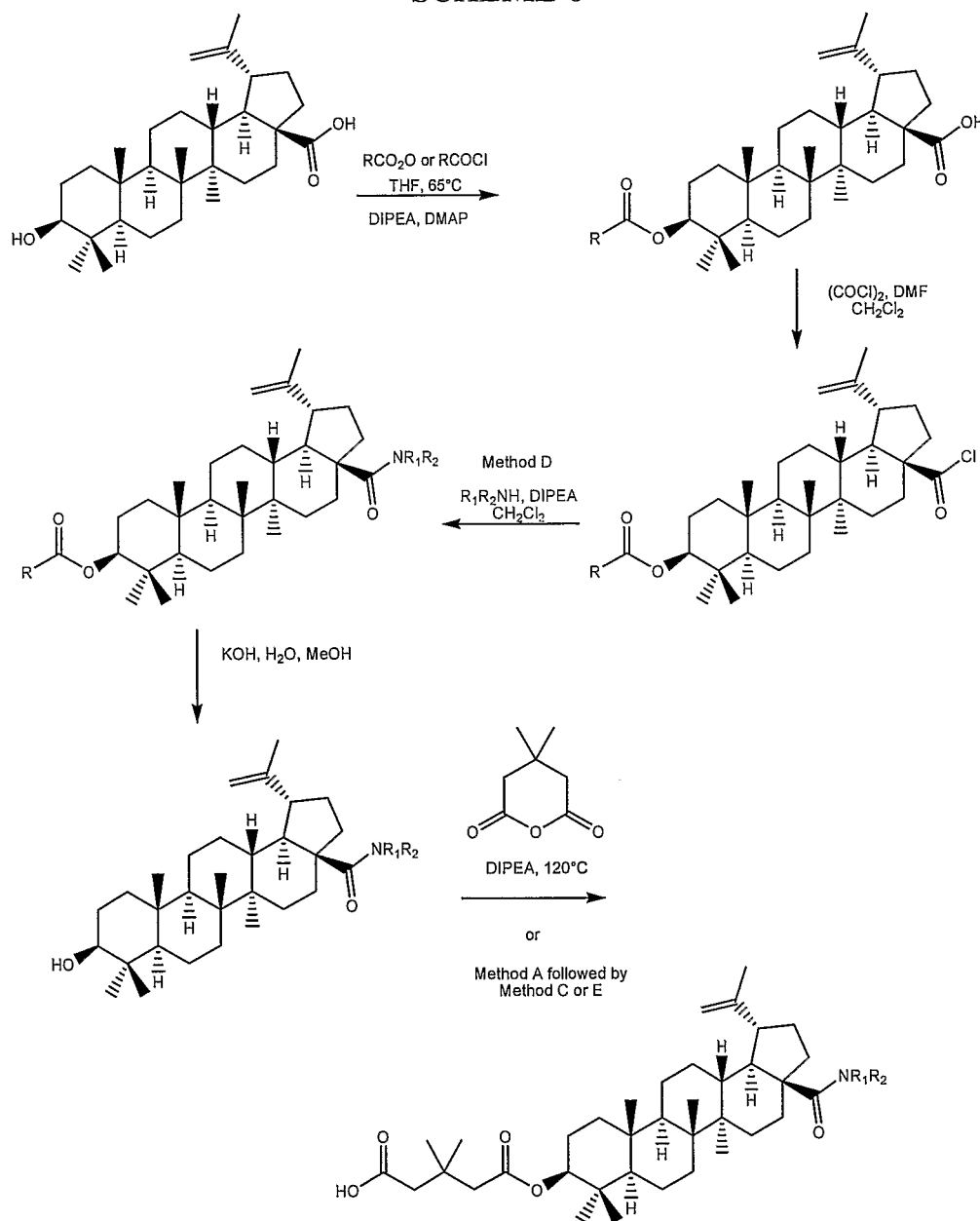


[00181] Thus, another aspect of the invention is directed to a method of synthesizing a compound of Formula *I* wherein R_2 is formula (v) comprising: (a) forming a monoprotected di-carboxylic acid derivative, (b) activating the non-protected carboxyl group of the di-carboxylic acid to form an acid halide, (c) reacting the acid halide of step (b) with betulinic acid to form the R_1 group at the C-3 position, (d) activating the C-28 position of the compound of (c) to form an acid halide, (e) attaching the desired amine at C-28, and (f) deprotecting the protected R_1 carboxyl group of (a).

[00182] A second method of synthesis of betulinic acid amides is shown in Scheme 6.

- 96 -

SCHEME 6



[00183] The C-3 alcohol of betulinic acid is first protected with a suitable hydroxy protecting group, such as the acetate or benzoate using either the acid anhydride or acid chloride and *N,N*-diisopropylethylamine (DIPEA) in tetrahydrofuran (THF) with DMAP as catalyst. The C-28 carboxylic acid is activated as an acid halide or other suitable activating group. Reagents useful for this conversion include but are not limited to oxalyl chloride, oxalyl bromide, thionyl chloride, thionyl bromide, phosphorous oxychloride,

- 97 -

phosphorous oxybromide, phosphorous pentachloride, phosphorous pentabromide, phosphorous trichloride, phosphorous tribromide and the like. The appropriate amide is formed by treatment of the acid halide with the desired amine in dry dichloromethane and DIPEA (Method D). The C-3 acetyl group is removed by basic hydrolysis using potassium or sodium hydroxide in aqueous alcohol (Method G). The C-3 group is introduced using the appropriate anhydride to provide directly the desired compound (Method H). In some instances, the C-3 group can be introduced with methyl or allyl 3,3-dimethylglutaryl chloride in dichloromethane and DIPEA using Method A followed by removal of the C-5' ester using either Method C for the allyl ester or Method E for the methyl ester.

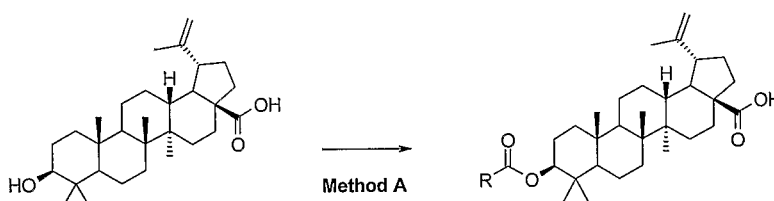
[00184] Thus, another aspect of the invention is directed to a method of synthesizing a compound of Formula *I* wherein R₂ is formula (v), comprising: (a) protecting a C-3 alcohol of betulinic acid; (b) activating the C-3 protected betulinic acid at the C-28 carbon to form a C-3 protected, C-28 activated betulinic acid; (c) the resulting compound of (b) reacting the C-3 protected, C-28 activated betulinic acid with an appropriated amine; (d) deprotecting the the resulting compound of step (c) at its C-3 position and (e) adding an R₁ ester group at C-3.

EXAMPLE 1

Synthesis of Betulinic Acid C-3 Modifications

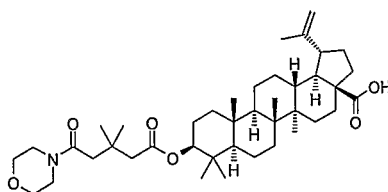
[00185] Methods to synthesize 3-*O*-(acyl)betulinic acid compounds are depicted in Scheme 7.

SCHEME 7



[00186] **Method A:** 3-*O*-(Acyl)betulinic acid compounds are prepared by adding betulinic acid (1 equivalent) to a stirred solution of the desired acid chloride or sulfonyl chloride (4 equivalents) in dry dichloromethane, followed by DMAP (1 equivalent) and DIPEA (4 equivalents). The reaction was heated at 40°C overnight, diluted in EtOAc, washed successively with 1M HCl (aq), water and dried over Na₂SO₄. The combined organic layers were concentrated to dryness *in vacuo*. Final compounds were purified by flash column chromatography on silica gel.

3-*O*-(5'-Morpholinyl-5'-oxo-3',3'-dimethylpentanoyl)betulinic acid.



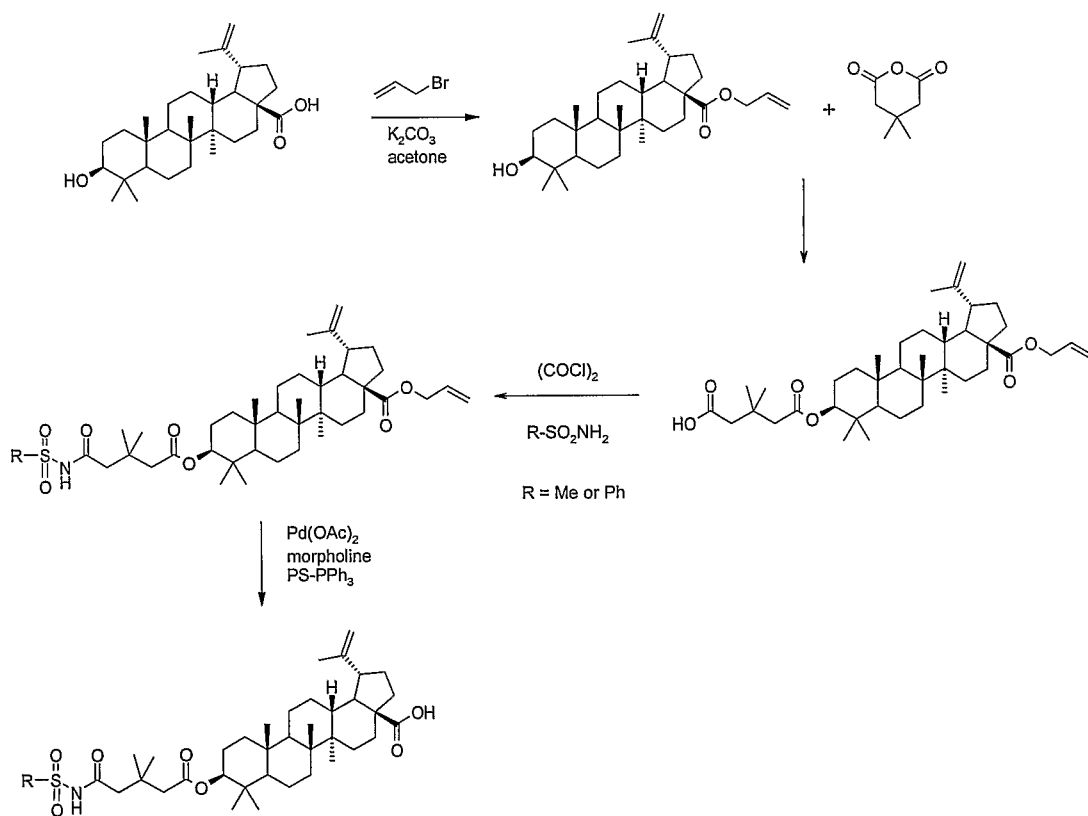
[00187] The compound was synthesized by coupling betulinic acid with 5-morpholino-5-oxo-3,3-dimethylpentanoyl chloride applying **method A** (47 mg, 3%); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.72 - 1.76 (42H, m), 1.89 - 2.06 (3H, m), 2.12 - 2.23 (1H, m), 2.27

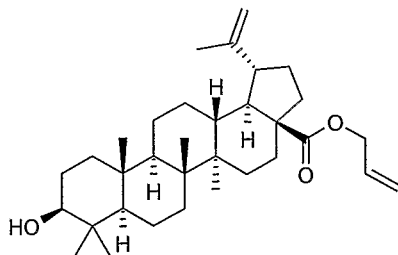
(1H, d, $J=12.7$ Hz), 2.39 - 2.49 (3H, m), 2.52 (2H, d), 2.93 - 3.08 (1H, m), 3.46 - 3.63 (4H, m), 3.64 - 3.78 (4H, m), 4.46 (1H, dd, $J=10.8, 5.4$ Hz), 4.61 (1H, s), 4.74 (1H, s).

Synthesis of substituted 3-*O*-[5'-(sulfonylamino)-3',3'-dimethyl glutaryl]betulinic acids.

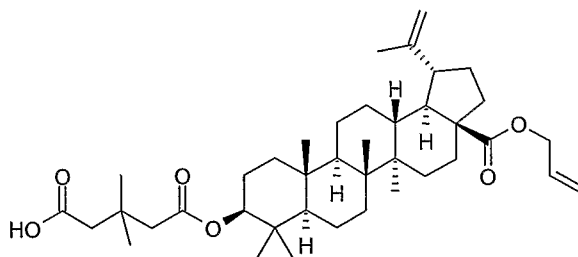
[00188] Substituted 3-*O*-[5'-(sulfonylamino)-3',3'-dimethylglutaryl]betulinic acids were synthesized in 4 steps from betulinic acid as shown in Scheme 8.

SCHEME 8

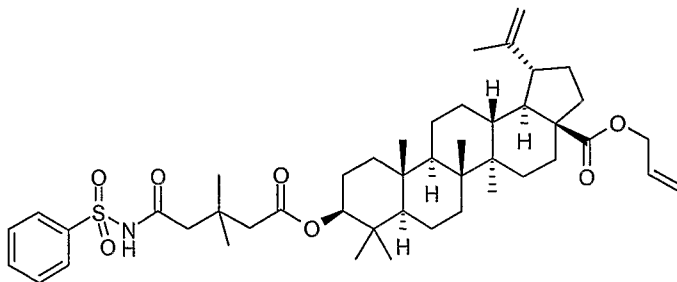


Betulinic acid allyl ester.

[00189] Betulinic acid (0.8 g, 1.6 mmol) and 0.28 mL (2 eq., 3.2 mmol) allyl bromide were dissolved in 10 mL of acetone. Potassium carbonate (0.69 g, 5 mmol) was then added. The resulting suspension was stirred at reflux for 3 hours. The insoluble inorganic salts were removed by filtration and the reaction mixture was concentrated under reduced pressure to yield crude product (1.04 g, quantitative) used without further purification.

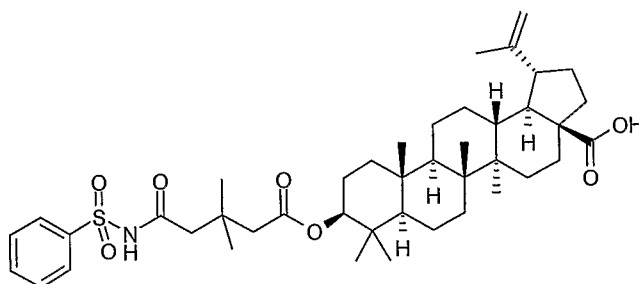
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid allyl ester.

[00190] Betulinic acid allyl ester (1.04 g, 1.6 mmol), 0.45 g (2 eq., 3.2 mmol) 3,3'-dimethylglutaric anhydride and DMAP (0.19 g, 1.6 mmol) were suspended in 5 mL of pyridine under nitrogen and stirred at reflux for 25 hours. After removal of all solvent under reduced pressure an orange-brown solid was obtained. Purification by flash column chromatography (2 to 20% EtOAc in heptane) yielded 0.803 g of product, used without further purification.

3-*O*-[5'-(Phenylsulfonylamino)-3',3'-dimethylglutaryl]betulinic acid allyl ester.

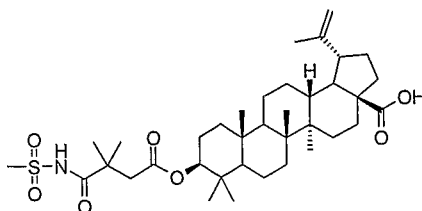
[00191] 3-*O*-(3',3'-Dimethylglutaryl)betulinic acid allyl ester (0.4 g, 0.62 mmol) was dissolved in 4 mL of dichloromethane under nitrogen. Oxalyl chloride (0.31 g, 1.2 mmol) was added and the reaction was left to stir at rt for 1 hour. After removal of all solvents under reduced pressure, a pale yellow solid was obtained. This solid was re-dissolved in 5 mL of dichloromethane and benzenesulfonamide (0.3 g, 1.9 mmol) was added. The reaction was stirred at rt overnight. Solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (2 to 10% EtOAc in heptane) yielding 0.622 g of desired product which was used without further purification.

3-*O*-[5'-(Phenylsulfonylamino)-5'-oxo--3',3'-dimethylpentanoyl]betulinic acid.



[00192] 3-*O*-[5'-(Phenylsulfonylamino)-3',3'-dimethylglutaryl]betulinic acid allyl ester (0.112 g, 0.14 mmol), 0.033 g (1 eq., 0.14 mmol) palladium(II) acetate, polymer bound triphenylphosphine (0.145 g, 0.432 mmol) and morpholine (0.125 mL, 0.14 mmol) were suspended in 3 mL of THF under nitrogen and stirred at 50°C for 20 hours. After removal of all solvent under reduced pressure a brown solid was obtained. Purification with preparative HPLC yielded 27 mg of product. ¹H NMR (400 MHz, CDCl₃) δ ppm 10.46 (1H, s), 8.09 (2H, d, *J*=7.34 Hz), 7.42 - 7.69 (3H, m), 4.43 - 4.84 (3H, m), 3.01 (1H, d, *J*=4.9 Hz), 2.12 - 2.40 (7H, m), 1.87 - 2.07 (2H, m), 0.64 - 1.81 (43H, m); LCMS, *R*_f=4.86 min, 100% (M+Na)⁺ 760 (100%).

3-*O*-[4'-(Methylsulfonylamino)-4'-oxo -3',3'-dimethylbutanoyl]betulinic acid.



[00193] 3-*O*-[4'-(Methylsulfonylamino)-4'-oxo-3',3'-dimethylbutanoyl]betulinic acid can be prepared by coupling the acid chloride of allyl (3',3'-dimethylbutanoyl)betulinic acid with methanesulfonamide followed by removal of the allyl ester.

EXAMPLE 2

Synthesis of 3-*O*-Acyl Betulinic Acid C-28 Derivatives: Preparation of Intermediates

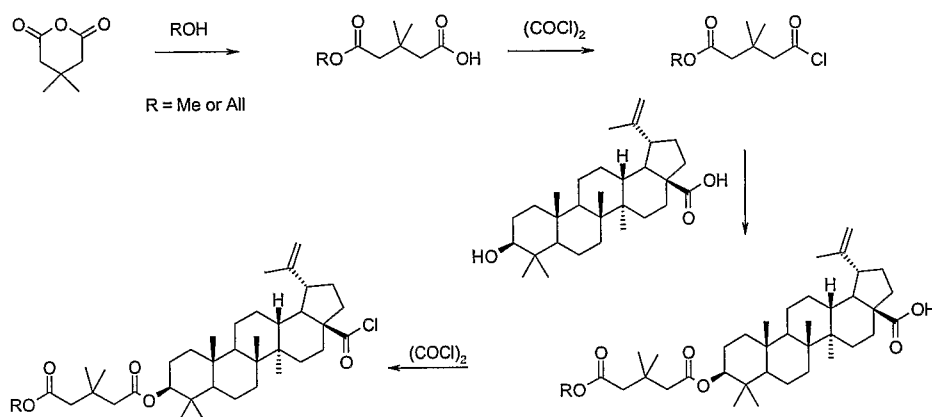
[00194] Synthesis of C-28 derivatives of 3-*O*-(acyl)betulinic acid is accomplished by coupling a suitably protected *O*-acyl side chain on the C-3 hydroxyl of betulinic acid and reacting the resulting compound with oxalyl chloride to form the corresponding betulinic acid chloride derivative. This C-28 acid chloride is then coupled to the desired group, and subsequently is deprotected to form the targeted C-28 derivative.

[00195] Alternatively 3-*O*-acetylbetulinic acid is activated and coupled to the desired group. The 3-*O*-acetyl group is then removed by hydrolysis and the desired 3-*O*-acyl side chain is introduced at the C-3 position resulting in formation of the betulinic acid C-28 derivative.

3-*O*-(5'-Alkoxy-3',3'-dimethylglutaryl)betulinic acid chloride preparations.

[00196] 3-*O*-(5'-Alkoxy-3',3'-dimethylglutaryl)betulinic acid chlorides (where alkoxy = allyl or methyl) were prepared in four steps from 3,3-dimethylglutaric anhydride as shown in Scheme 9.

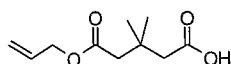
SCHEME 9



[00197] Ring opening of 3,3-dimethylglutaric anhydride with allyl alcohol or methanol followed by treatment of the resulting acids with oxalyl chloride afforded methyl or allyl 3,3-dimethylglutaryl chloride. The acid chlorides were coupled to betulinic acid and the resulting products were converted to their corresponding acid chlorides by treatment with oxalyl chloride.

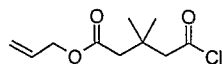
3-O-(5'-Allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride preparation.

Mono-Allyl 3,3-dimethylglutarate.



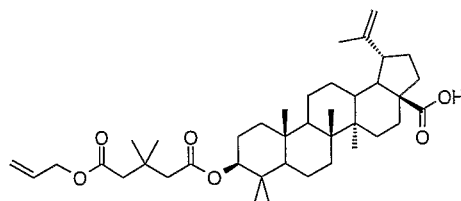
[00198] A suspension of 3,3-dimethylglutaric anhydride (5.3 g, 38 mmol) in allylic alcohol (10 mL, 145 mmol) was heated at reflux for 5 hours (solution became clear). The allylic alcohol was removed *in vacuo*, the residue was then diluted in EtOAc (100 mL), washed successively twice with water, dried over Na₂SO₄, and concentrated *in vacuo* to afford the desired compound (6.7 g, 99%) as a colorless oil which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 1.13-1.18 (s, 6H), 2.48 (s, 2H), 2.49 (s, 2H), 4.59 (d, 2H, *J*=5.8 Hz), 5.25 (dd, 1H, *J*=10.4, 1.3 Hz), 5.32 (dd, 1H, *J*=17.3, 1.3 Hz), 5.9 (m, 1H).

Allyl 3,3-dimethylglutaryl chloride.



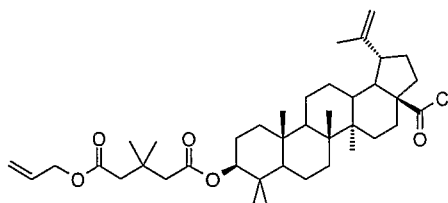
[00199] *N,N*-Dimethylformamide (DMF) (30 μ L, 0.38 mmol) was added to a stirred solution of oxalyl chloride (16.6 mL, 175 mmol) and allyl 3,3-dimethylglutarate (3.5 g, 17.5 mmol) in dichloromethane (60 mL) at 0°C. The reaction was allowed to reach rt and was stirred for 1 hour. The volatiles were removed *in vacuo*. The resulting solid residue was dissolved in dichloromethane (10 mL) and concentrated to dryness *in vacuo*. This operation was repeated twice more, to afford the desired acid chloride (3.8 g, quantitative yield) as yellow oil, which was used without further purification.

3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)betulinic acid.



[00200] Betulinic acid (2.0 g, 4.38 mmol) was added to a stirred solution of allyl 3,3-dimethylglutaryl chloride (3.8 g, 17.5 mmol) in dry dichloromethane (60 mL) followed by DIPEA (1.53 mL, 8.76 mmol) at 0°C. The ice bath was removed and the reaction was heated at 40°C overnight. The reaction mixture was concentrated *in vacuo* and the residue was diluted in EtOAc (100 mL), washed twice with 1M HCl, and dried over Na₂SO₄. The combined organic layers were concentrated to dryness *in vacuo*. Flash column chromatography on silica gel (EtOAc 0 to 10% in heptane) provided the desired compound (2.38 g, 85%) as a white solid. TLC (EtOAc:heptane 2:8) *R_f* = 0.37; ¹H NMR (400 MHz, CDCl₃) δ ppm 10.7 (1H, s), 5.85 - 5.97 (1H, m), 5.27 - 5.36 (1H, m), 5.19 - 5.26 (1H, m), 4.74 (1H, d, *J*=1.8 Hz), 4.61 (1H, s), 4.54 - 4.59 (2H, m), 4.47 (1H, dd, *J*=11.2, 4.9 Hz), 3.01 (1H, ddd), 2.34 - 2.52 (4H, m), 2.12 - 2.23 (1H, m), 1.91 - 2.06 (2H, m), 0.73 - 1.79 (45H, m) of which 1.70 (s), 1.12 (s), 0.97 (s), 0.93 (s), 0.85 (s), 0.82 (s).

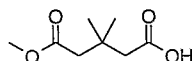
3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride.



[00201] DMF (20 μ L, 0.25 mmol) was added to a stirred solution of oxalyl chloride (0.62 mL, 6.51 mmol) and 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid (0.692 g, 1.08 mmol) in dichloromethane (15 mL) at 0°C. The reaction was allowed to reach rt and was stirred for 12 hours. The volatiles were removed *in vacuo*. The resulting solid residue was dissolved in dichloromethane (10 mL) and concentrated to dryness *in vacuo*. This operation was repeated to afford the desired acid chloride (0.75 g, quantitative yield) as an oil, which was used without further purification. A sample of acid chloride was quenched in methanol to give the methyl ester: TLC (EtOAc:heptane 2:8) R_f = 0.50; SM R_f = 0.37.

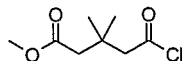
3-*O*-(5'-Methoxy-3',3'-dimethylglutaryl)betulinic acid chloride preparation.

Mono-methyl 3,3-dimethylglutarate.



[00202] A suspension of 3,3-dimethylglutaric anhydride (9.0 g, 63.4 mmol) and DMAP (0.77 g, 6.3 mmol) in triethylamine (TEA) (8.8 mL, 63.4 mmol) and methanol (75 mL) was heated at reflux overnight. The methanol was removed *in vacuo*, and the residue was then dissolved in EtOAc (150 mL), washed successively with citric acid (1 M, 3X 100 mL), water and dried over MgSO₄, and concentrated *in vacuo* to afford the desired compound (11.06 g, 100%) as a colorless oil which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ ppm 10.9 (1H, br s), 3.7 (3H, s), 2.45 (4H, d), 1.15 (6H, s).

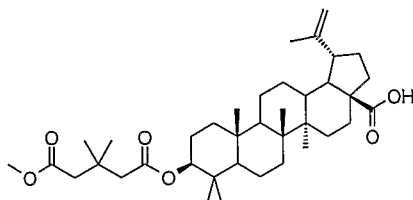
Methyl 3,3-dimethylglutaryl chloride.



[00203] DMF (30 μ L, 0.38 mmol) was added to a stirred solution of oxalyl chloride (7.7 mL, 90 mmol) and mono-methyl 3,3-dimethylglutarate (10.4 g, 60 mmol) in dichloromethane (100 mL) at 0°C. The reaction was allowed to reach rt and was stirred for 1 hour. The volatiles were removed *in vacuo*. The resulting solid residue was dissolved in dichloromethane (10 mL) and concentrated to dryness *in vacuo*. This

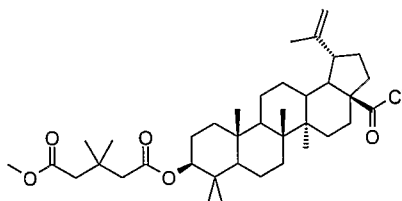
operation was repeated twice more, to afford the desired acid chloride (11.5 g, quantitative yield) which was used without further purification.

3-O-(5'-Methoxy-3',3'-dimethylglutaryl)betulinic acid.

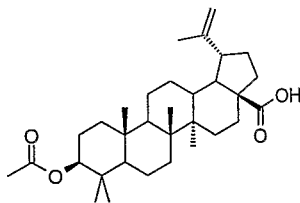


[00204] Betulinic acid (3.6 g, 7.9 mmol) was added to a stirred solution of methyl 3,3-dimethylglutaryl chloride (6.1 g, 31.7 mmol) in dry dichloromethane (30 mL) followed by DIPEA (5.5 mL, 31.7 mmol) at 0°C. The ice bath was removed and the reaction was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and the residue was diluted in EtOAc (100 mL), washed twice with 1M HCl, and dried over Na₂SO₄. The combined organic layers were concentrated to dryness *in vacuo*. Flash column chromatography on silica gel (EtOAc 2 to 5% in heptane) provided the desired compound (4.97 g, quantitative yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.74 (1H, d, *J*=1.3 Hz), 4.61 (1H, s), 4.41 - 4.53 (1H, m), 3.7 (3H, s), 2.92 - 3.09 (1H, td, *J*=11.1, 4.1 Hz), 2.5 - 2.32 (4H, m), 2.3 - 1.9 (4H, m), 1.77 - 0.72 (44H, m).

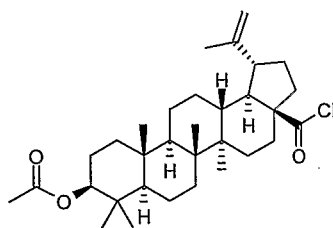
3-O-(5'-Methoxy-3',3'-dimethylglutaryl)betulinic acid chloride.



[00205] DMF (20 μL, 0.25 mmol) was added to a stirred solution of oxalyl chloride (1.03 mL, 12.0 mmol) and 3-O-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid (1.46 g, 2.4 mmol) in dichloromethane (20 mL) at 0°C. The reaction was allowed to reach rt and was stirred for 14 hours. The volatiles were removed *in vacuo*. The resulting solid residue was dissolved in dichloromethane (10 mL) and concentrated to dryness *in vacuo*. This operation was repeated to afford the desired acid chloride (1.51 g, quantitative yield) as a pale yellow solid which was used without further purification. A sample of acid chloride was quenched in methanol to give the methyl ester: TLC (EtOAc:heptane 4:6) *R_f*=0.6.

3-*O*-Acetylbetulinic acid preparation.

[00206] Betulinic acid (1.0 g, 2.2 mmol) was dissolved in 10 mL of dry THF and 1 mL of DIPEA. To this solution are added 0.034 g (0.27 mmol) of DMAP and 0.3 mL (3.1 mmol) of acetic anhydride. The mixture was heated at 65°C for two hours until TLC showed complete consumption of the starting material. Minor traces of mixed anhydride were also present in the crude mixture. The reaction mixture was concentrated to dryness to yield a white solid. This solid was then suspended in 20 mL of a 0.6 M hydrochloric acid solution and heated at 100°C for 30 minutes in order to hydrolyze any traces of undesired mixed anhydride. The white suspension was left to cool down to rt and the solid was collected by filtration. The cake was washed with 20 mL of water and dried at 50°C under reduced pressure overnight yielding 1.06 g (2.1 mmol, 97%) of a white free flowing powder. TLC: R_f = 0.65 (EtOAc: CH₂Cl₂ 5: 95); ¹H NMR: (250 MHz, CDCl₃); δ ppm 4.74 (1H, d, J =1.3 Hz), 4.61 (1H, s), 4.41 - 4.53 (1H, m), 2.92 - 3.09 (1H, m), 2.10 - 2.34 (2H, m), 1.92 - 2.09 (5H, m), 0.69 - 1.83 (38H, m).

3-*O*-Acetylbetulinic acid chloride preparation.

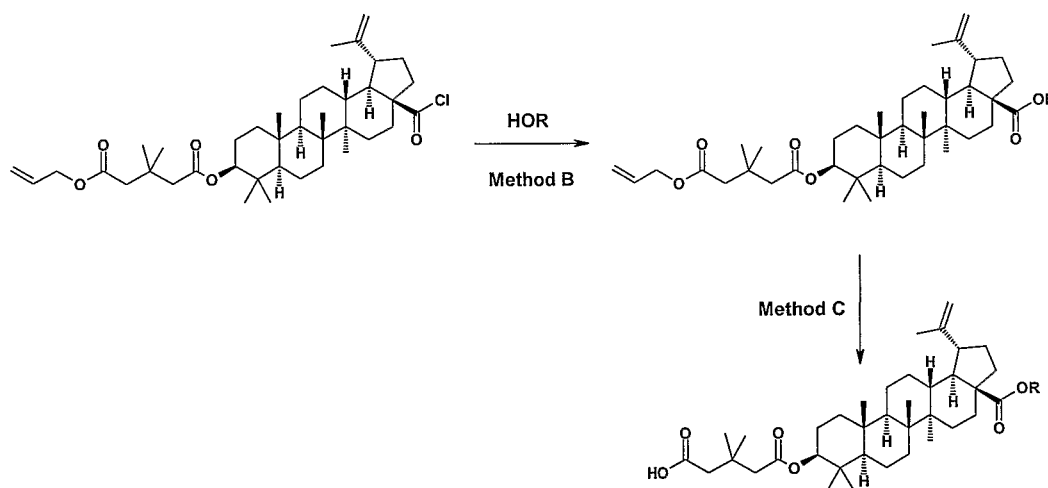
[00207] 3-*O*-Acetylbetulinic acid (0.5 g, 1.0 mmol) was dissolved in 3 mL of dry THF under nitrogen. A few drops of DMF were added followed by slow addition of 0.3 mL (3 mmol) oxalyl chloride. The reaction was stirred at rt for two hours. All solvents were removed under reduced pressure and the resulting acid chloride was used without further purification.

EXAMPLE 3

Synthesis of Betulinic Acid Esters

[00208] C-28 esters of betulinic acid were prepared in two steps from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride as shown in Scheme 10.

SCHEME 10

**Method B: Esterification method.**

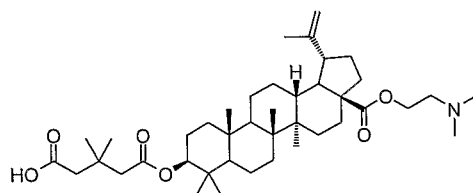
[00209] Betulinic esters were prepared by adding a solution of 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride or 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride (1 equivalent) in dry dichloromethane to a stirred solution of the desired alcohol (2 to 5 equivalents) and DIPEA (3 to 6 equivalents) in dry dichloromethane at rt. The reaction was stirred at rt overnight, diluted in EtOAc, washed with 1M HCl, water and dried over Na₂SO₄. The combined organic layers were concentrated to dryness *in vacuo* and the resulting oil was purified by flash column chromatography on silica gel (hexane:EtOAc) to provide the desired betulinic ester.

Method C: Deallylation method.

[00210] Palladium(II) acetate (1.05 equivalent) and polymer bound triphenylphosphine (3.1 equivalent) or Fibrecat palladium(II)® (0.5 -1 equivalent) were added to a degassed

solution of the desired allylic ester (1 equivalent) and morpholine (20 equivalents) in THF under a nitrogen atmosphere. The reaction was stirred overnight at 60°C and allowed to cool down to rt. The resin was removed by filtration, and the organic solution was diluted with EtOAc, washed successively with 1M KHSO₄ (aq), water and dried over Na₂SO₄. The combined organic layers were concentrated to dryness *in vacuo* and the resulting solid purified by flash column chromatography on silica gel (hexane:EtOAc) to provide the desired deprotected acid.

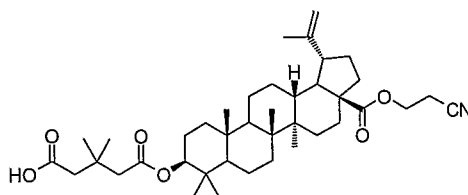
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 2-*N,N*-dimethylaminoethyl ester.



[00211] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method B** with 2-*N,N*-(dimethylamino)ethanol (32%), followed by **method C** deprotection: (29 mg, 66%); ¹H NMR (400 MHz, CDCl₃) δ ppm 4.72 (1H, d, *J*=1.8 Hz), 4.59 (1H, s), 4.47 (1H, dd, *J*=11.0, 4.8 Hz), 4.16 - 4.28 (2H, m), 3.73 - 3.82 (2H, m), 2.93 - 3.04 (3H, m), 2.62 - 2.73 (1H, m), 2.15 - 2.54 (10H, m), 0.65 - 2.10 (45H, m); LCMS, 92% pure; *R*_f= 3.20; *m/z* (relative intensity) 670 ([M+Na]⁺, 30%).

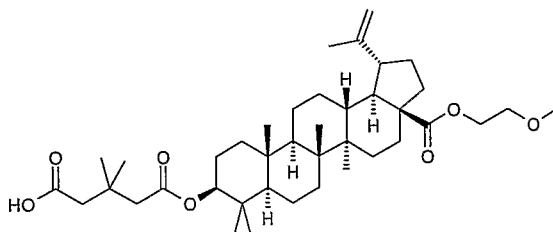
[00212]

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 2-cyanoethyl ester.



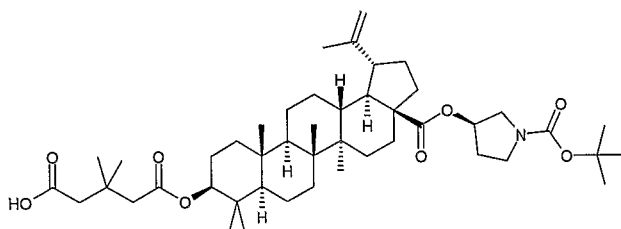
[00213] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method B** with 2-cyanoethanol (29%), followed by **method C** deprotection: (16 mg, 40%); ¹H NMR (400 MHz, CDCl₃) δ ppm 4.70 - 4.78 (1H, m), 4.61 (1H, d, *J*=1.5 Hz), 4.50 (1H, dd, *J*=10.6, 5.1 Hz), 4.25 - 4.35 (2H, m), 2.91 - 3.06 (1H, m), 2.72 (2H, t, *J*=6.2 Hz), 2.37 - 2.53 (4H, m), 0.71 - 2.34 (48H, m); LCMS, 80% pure; *R*_f= 3.90; *m/z* (relative intensity) 674 ([M+Na]⁺, 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 2-methoxyethyl ester.



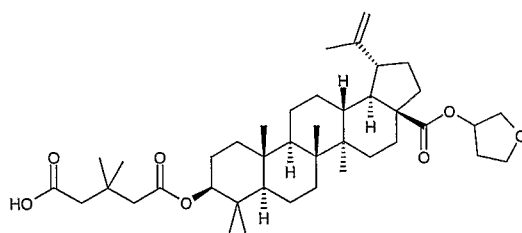
[00214] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method B** with 2-methoxyethanol, followed by **method C** deprotection. ^1H NMR (400MHz, CDCl_3); δ ppm 4.70 (1H, s), 4.62 (1H, s), 4.52 – 4.47 (1H, m), 4.28 – 4.24 (1H, m), 4.20 – 4.16 (1H, m), 3.58 (2H, t, $J=4.8\text{Hz}$), 3.38 (3H, s), 3.04 – 3.02 (1H, m), 2.48 – 2.40 (4H, m), 2.30 – 2.18 (2H, m), 1.93 – 1.88 (2H, m), 1.87 – 0.61 (46H, m); LCMS, 100% $R_t = 5.10$; m/z (relative intensity) 679 ($[\text{M}+\text{Na}^+]$ 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid (R)-3-[1-(*tert*-butoxycarbonyl)pyrrolidinyl] ester.



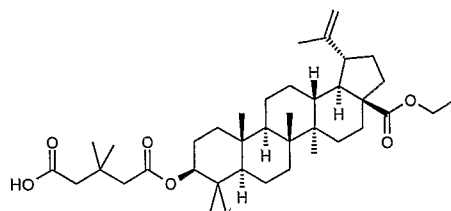
[00215] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method B** with (R)-3-hydroxy-1-(*tert*-butoxycarbonyl)pyrrolidine, followed by **method C** deprotection. ^1H NMR (250 MHz, CDCl_3) δ ppm 0.65 - 2.76 (64H, m), 2.83 - 3.13 (1H, m), 3.54 (3H, br s), 4.50 (1H, dd, $J=10.5, 5.8\text{ Hz}$), 4.61 (1H, s), 4.73 (1H, d, $J=1.6\text{ Hz}$), 5.27 (1H, s).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 3-(R/S)-3-(tetrahydrofuranyl) ester.



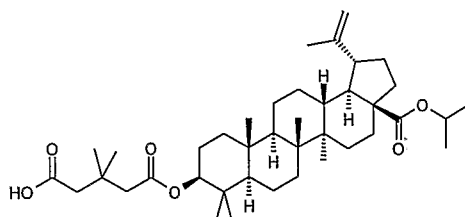
[00216] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method B** with 3-hydroxytetrahydrofuran, followed by **method C** deprotection; ^1H NMR (400 MHz, CDCl_3) δ ppm 0.63 - 2.24 (50H, m), 2.34 (1H, d), 2.37 - 2.52 (3H, m), 2.86 - 2.99 (1H, m), 3.72 (1H, m), 3.83 (2H, dd, $J=8.4, 5.1$ Hz), 3.86 - 3.95 (1H, m), 4.42 (1H, dd, $J=10.6, 5.1$ Hz), 4.54 (1H, s), 4.66 (1H, s), 5.16 - 5.27 (1H, m).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid ethyl ester.



[00217] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method B** with ethanol, followed by **method C** deprotection. ^1H NMR (400MHz, CDCl_3); δ ppm 4.73 (1H, s), 4.60 (1H, s), 4.49 - 4.47 (1H, m), 4.19 - 4.10 (2H, m), 3.01 - 3.02 (1H, m), 2.50 - 2.30 (8H, m), 2.09 - 1.99 (1H, m), 1.87 - 0.61 (46H, m); LCMS, 97% $R_t=4.34$; m/z (relative intensity) 649 ($[\text{M}+\text{Na}^+]$ 100%).

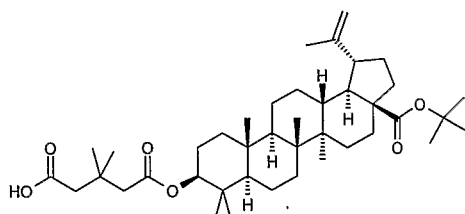
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid isopropyl ester.



[00218] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method B** with isopropanol, followed by **method C** deprotection. ^1H NMR (400MHz, CDCl_3); δ ppm 5.04 - 5.00 (1H, m), 4.73

(1H, s), 4.60 (1H, s), 4.52 – 4.48 (1H, m), 3.04 – 3.02 (1H, m), 2.50 – 2.30 (8H, m), 2.09 – 1.99 (1H, m), 1.87 – 0.61 (49H, m); LCMS, 96% $R_t = 4.44$; m/z (relative intensity) 664 ($[M+Na^+]$ 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *tert*-butyl ester.



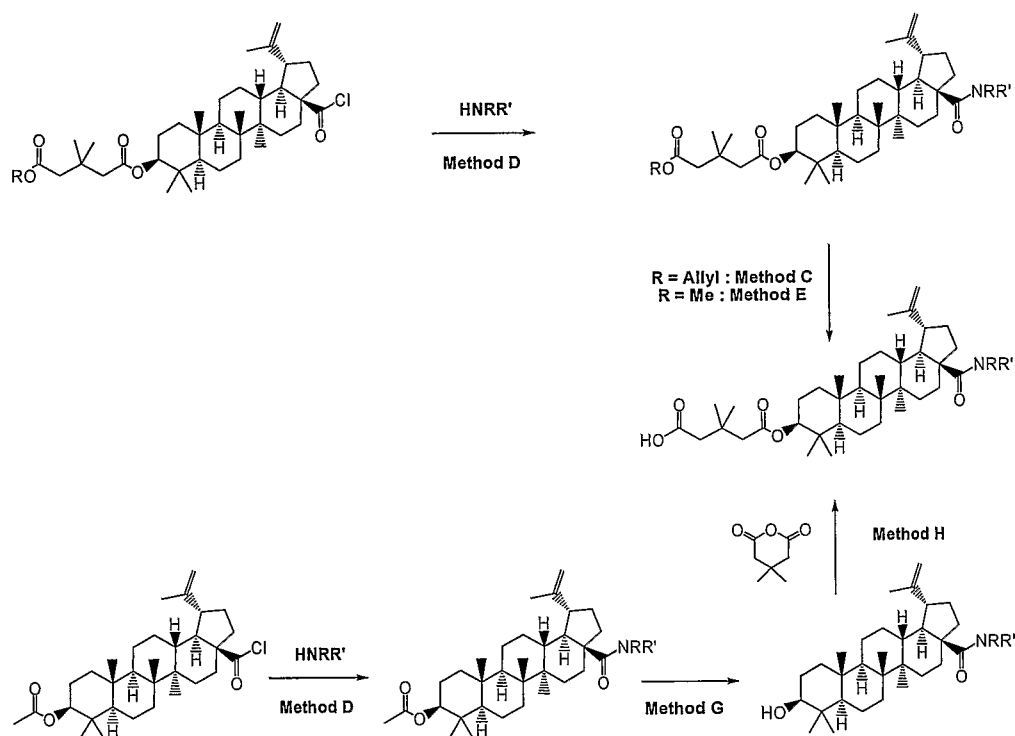
[00219] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method B** with *t*-butanol, followed by **method C** deprotection. 1H NMR (400MHz, $CDCl_3$); δ ppm 4.73 (1H, s), 4.60 (1H, s), 4.52 – 4.48 (1H, m), 3.04 – 3.02 (1H, m), 2.50 – 2.30 (8H, m), 2.09 – 1.99 (1H, m), 1.87 – 0.61 (52H, m); LCMS, 95% $R_t = 4.56$; m/z (relative intensity) 678 ($[M+Na^+]$ 100%).

EXAMPLE 4

Synthesis of Betulinic Acid Amides

[00220] Amides of betulinic acid were prepared either in two steps from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride and 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride or in 3 steps from 3-*O*-acetylbetulinic acid chloride as shown in Scheme 11.

SCHEME 11

**Method D: Amidation method.**

[00221] Betulinic acid amides were prepared by adding a solution of 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride, 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid or 3-*O*-acetylbetulinic acid (1 equivalent) in dry dichloromethane to a stirred solution of the desired amine (2-5 equivalents) in dry dichloromethane and DIPEA (3-6 equivalents) at rt. The reaction was stirred at rt overnight. The reaction mixture was then diluted in EtOAc, washed successively with 1M HCl (aq.) and water, dried over Na₂SO₄. The combined organic layers were concentrated to dryness *in vacuo* and the resulting oil was purified by flash column chromatography on silica gel (hexane:EtOAc) to provide the desired betulinic acid derived amide.

Method E: Methyl ester hydrolysis method.

[00222] 2M Aqueous potassium hydroxide (2 equivalents) was added to a solution of the desired methyl ester (1 equivalent) in THF/Methanol (1:1). The reaction was stirred overnight at rt and for further 4 hours at 50°C if not completed. Solvent was removed *in*

vacuo, the crude product taken up in EtOAc, washed successively with 1M KHSO₄ (aq) and dried over Na₂SO₄. The combined organic layers were concentrated to dryness *in vacuo* and the resulting solid purified by flash column chromatography on silica gel (hexane:EtOAc) to provided the desired acid.

Method F: *N*-*tert*-Butoxycarbonyl deprotection method.

[00223] 4N HCl in dioxane (ca. 40 equivalents) was added to a solution of the appropriate *tert*-butoxycarbonyl (Boc) protected amine (1 equivalent) in dioxane at 0°C. Cooling was removed and the reaction mixture was allowed to warm to rt over 20 h. The reaction mixture was concentrated to dryness in *vacuo* and the resulting off white solid (typical yield >90%) was used without further purification.

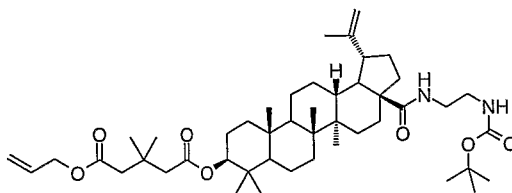
Method G: 3-*O*-Acetyl group removal method.

[00224] Potassium hydroxide pellets (5 equivalents) were added to a suspension of the desired 3-*O*-acetylbetulinic acid amide derivative in methanol and water (7/1). The mixture was stirred at 50°C overnight. The mixture was left cool to rt and diluted with water. The solid was collected by filtration, washed with water and dried at 60°C under reduced pressure over night to yield the desired betulinic acid amide derivative.

Method H: Glutaric side chain introduction method.

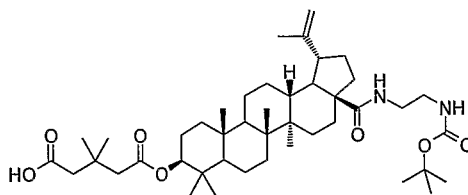
[00225] The desired betulinic acid amide derivative and 4 equivalents of 3,3'-dimethylglutaric anhydride were suspended in neat DIPEA under nitrogen and stirred at 125°C for 24 hours. All solvents were removed under pressure. The resulting solid was suspended in EtOAc and concentrated to dryness under reduced pressure in order to remove remaining traces of DIPEA. This solid was added to a 0.2 M solution of K₂CO₃ and stirred at 100°C for 20 minutes. The solid was collected by filtration, washed with water and left to dry overnight at 60°C to yield the desired material.

3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)betulinic acid *N*-2-(*tert*-butoxycarbonylamino)ethyl amide.



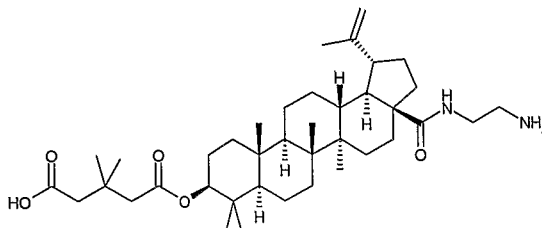
[00226] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with *N*- *tert*-butyl 2-aminoethylcarbamate ; (0.36 g, 51%); ¹H NMR (400 MHz, CDCl₃) δ ppm 6.18 - 6.36 (1H, br m), 5.81 - 6.02 (1H, m), 5.16 - 5.42 (2H, m), 4.91 - 5.05 (1H, br m), 4.67 - 4.79 (1H, m), 4.51 - 4.65 (3H, m), 4.41 - 4.51 (1H, m), 3.04 - 3.42 (5H, m), 2.33 - 2.57 (5H, m), 1.87 - 2.03 (2H, m), 0.69 - 1.80 (53H, m).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-(*tert*-butoxycarbonylamino) ethyl amide.



[00227] 3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)betulinic acid *N*-(*tert*-butoxycarbonylamino)ethyl amide was deprotected using **method C**, (89 mg, 79%); ¹H NMR (400 MHz, CDCl₃) δ ppm 6.32 (1H, s), 5.02 (1H, s), 4.74 (1H, s), 4.59 (1H, s), 4.44 - 4.55 (1H, m), 3.23 (5H, s), 2.44 (5H, s), 0.69 - 2.11 (56H, m); LCMS , 97% pure; *R*_f= 3.99; *m/z* (relative intensity) 741 (MH⁺, 40%).

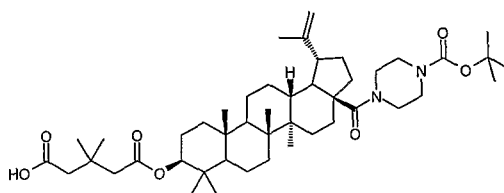
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-2-aminoethyl amide HCl salt.



[00228] 3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-(*tert*-butoxycarbonylamino)ethyl amide was deprotected using **method F**. ¹H NMR (400MHz, CD₃OD); δ ppm 4.61 (1H,

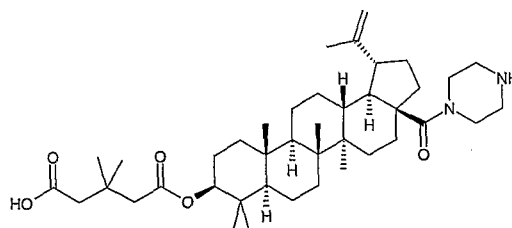
s), 4.49 (1H, s), 4.48 – 4.40 (1H, m), 3.66 – 3.64 (1H, m), 3.58 – 3.55 (2H, m), 3.50 – 3.48 (1H, m), 3.34 – 3.32 (2H, m), 2.97 – 2.89 (3H, m), 2.44 – 2.29 (4H, m), 2.04 – 2.00 (1H, m), 1.79 – 0.61 (47H, m); LCMS, 96% $R_t = 3.20$; m/z (relative intensity) 641 ($[M+H]^+$ 35%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[4-(*tert*-butoxycarbonyl) piperazinyl] amide.



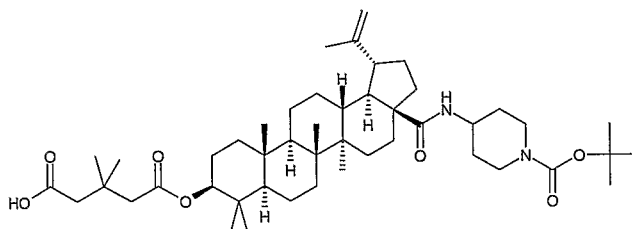
[00229] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 1-(*tert*-butoxycarbonyl)piperazine (0.35 g, 60%), followed by **method C** deprotection: (17.2 mg, 46%); ^1H NMR (400 MHz, CDCl_3) δ ppm 4.73 (1H, d, $J=1.9$ Hz), 4.58 (1H, s), 4.50 (1H, m), 3.57 (4H, s), 3.39 (4H, s), 2.92 - 3.05 (1H, m), 2.79 - 2.92 (1H, m), 2.34 - 2.54 (4H, m), 0.70 - 2.13 (57H, m); LCMS, 96% pure; $R_t = 4.24$; m/z (relative intensity) 789 ($[M+Na]^+$, 30%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-piperazine amide HCl salt.



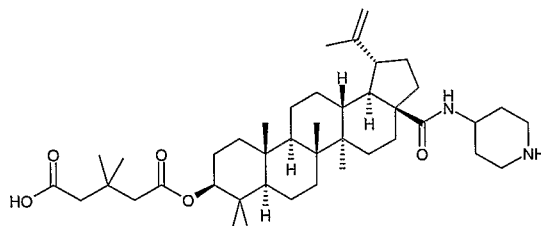
[00230] 3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[4-(*tert*-butoxycarbonyl) piperazinyl] amide was deprotected using **method F**: ^1H NMR (400MHz, CD_3OD); δ ppm 4.72 (1H, s), 4.61 (1H, s), 4.50 – 4.46 (1H, m), 3.92 – 3.87 (4H, m), 3.22 – 3.20 (4H, m), 2.96 – 2.94 (1H, m), 2.92 – 2.85 (1H, m), 2.52 – 2.41 (3H, m), 2.14 – 2.02 (1H, m), 2.01 – 1.99 (1H, m), 1.82 – 0.77 (48H, m); LCMS, 100% pure, $R_t = 3.22$; m/z (relative intensity) 667 ($[M+H]^+$ 26%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-4-[1-(*tert*-butoxycarbonyl)piperidinyl] amide.



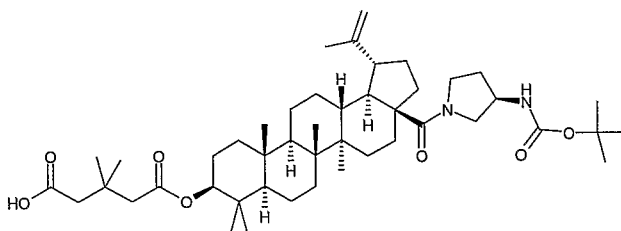
[00231] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride and 4-amino-1-(*tert*-butoxycarbonyl) piperidine, applying **method D**, followed by **method C** deprotection. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.63 - 1.99 (58H, m), 2.27 - 2.36 (2H, m), 2.36 - 2.44 (3H, m), 2.68 - 2.90 (2H, m), 3.05 (1H, m), 3.77 - 3.92 (1H, m), 3.97 (2H, br s), 4.35 - 4.46 (1H, m), 4.53 (1H, s), 4.66 (1H, s), 5.36 (1H, d, *J*=7.82 Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-4-piperidinyl amide HCl salt.



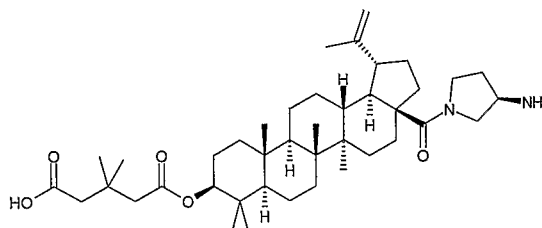
[00232] 3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-4-[1-(*tert*-butoxycarbonyl)piperidinyl] amide was deprotected using **method F**: ¹H NMR (400 MHz, CD₃OD) δ ppm 0.47 - 1.82 (48H, m), 1.86 - 2.17 (3H, m), 2.46 - 2.60 (1H, m), 2.86 - 3.10 (3H, m), 3.34 (2H, d, *J*=13.2 Hz), 3.43 - 3.52 (1H, m), 3.53 - 3.70 (5H, m), 3.78 - 3.89 (1H, m), 4.37 (1 H, dd, *J*=10.0, 6.1 Hz), 4.50 (1H, s), 4.61 (1H, s).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[(*R*)-3-(*tert*-butoxycarbonyl amino)pyrrolidinyl] amide.



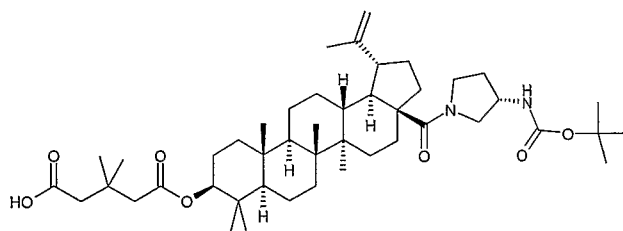
[00233] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride and (*R*)-3-(*tert*-butoxycarbonyl amino)pyrrolidine, applying **method D**, followed by **method C** deprotection. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.57 - 1.96 (56H, m), 2.12 (2H, d, *J*=11.7 Hz), 2.33 (1H, m), 2.36 - 2.46 (3H, m), 2.73 (1H, dt, *J*=10.8 Hz), 2.96 (1H, m), 3.24 (1H, s), 3.38 - 3.63 (2H, m), 3.78 (1H, br s), 4.04 (1H, br s), 4.42 (1H, m), 4.50 (1H, s), 4.65 (2H, d, *J*=1.8 Hz); LCMS, 100% pure; *R*_f= 4.58; *m/z* (relative intensity) 668 ([*M*+*H*]⁺, 50%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[(*R*)-3-aminopyrrolidinyl] amide HCl salt.



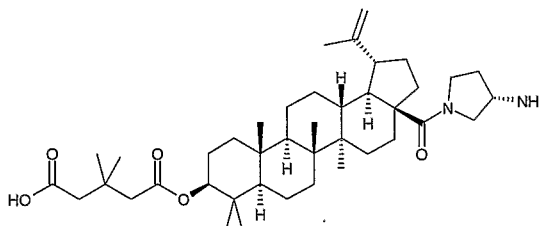
[00234] 3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[(*R*)-3-(*tert*-butoxycarbonylamino)pyrrolidinyl] amide was deprotected using **method F**. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.67 - 2.00 (48H, m), 2.15 - 2.33 (5H, m), 2.38 (1H, m), 2.70 (1H, m), 2.89 (1H, m), 3.16 - 3.23 (2 H, m), 3.34 - 3.62 (2H, m), 3.68 - 3.87 (2H, m), 4.36 (1H, dd, *J*=10.1, 6.0 Hz), 4.49 (1H, s), 4.60 (1H, d, *J*=1.8 Hz); LCMS, 100% pure; *R*_f= 3.20; *m/z* (relative intensity) 667 ([*M*+*H*]⁺, 20%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[(*S*)-3-(*tert*-butoxycarbonyl amino)pyrrolidinyl] amide.



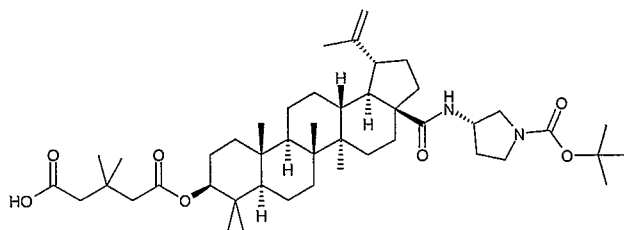
[00235] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride and (S)-3-(*tert*-butoxycarbonyl amino)pyrrolidine, applying **method D**, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.70 - 1.95 (54H, m), 1.97 - 2.12 (1H, m), 2.18 (1H, d, *J*=5.1 Hz), 2.34 - 2.43 (1H, m), 2.43 - 2.53 (3H, m), 2.68 - 2.88 (1H, m), 3.26 - 3.96 (4H, m), 4.14 (1H, br s), 4.50 (1H, m), 4.58 (2H, br s), 4.72 (1H, d, *J*=2.2 Hz); LCMS, 100% pure; *R*_f= 5.00; *m/z* (relative intensity) 789 ([M+Na]⁺, 70%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-[(S)-3-aminopyrrolidinyl] amide HCl salt.



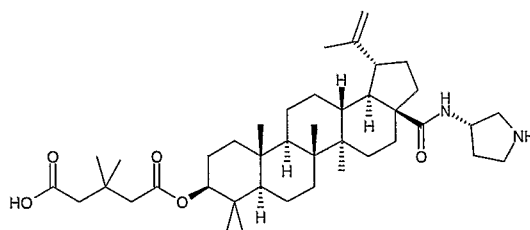
[00236] 3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-[(S)-3-(*tert*-butoxycarbonyl amino)pyrrolidinyl] amide was deprotected using **method F**. ¹H NMR (400MHz, CD₃OD); δ ppm 4.52 (1H, s), 4.41 (1H, s), 4.30 - 4.26 (1H, m), 3.75 (2H, br s), 3.54 - 3.52 (2H, m), 2.84 - 2.80 (1H, m), 2.65 - 2.59 (1H, m), 2.32 - 2.13 (6H, m), 1.90 - 1.82 (2H, m), 1.56 - 0.61 (48H, m); LCMS, 100% pure, *R*_t = 3.21; *m/z* (relative intensity) 667 ([M+H]⁺ 15%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-[(*S*)-3-(*tert*-butoxycarbonyl)pyrrolidinyl] amide.



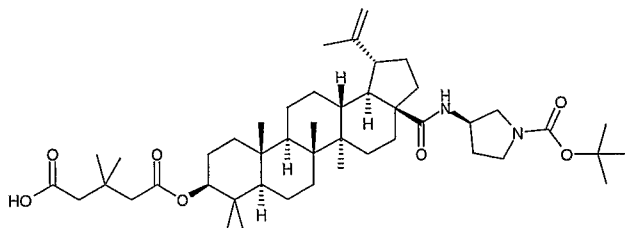
[00237] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride and (*S*)-3-amino-1-(*tert*-butoxycarbonyl)pyrrolidine, applying **method D**, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.68 - 2.02 (57H, m), 2.07 - 2.23 (1H, m), 2.36 - 2.44 (2H, m), 2.45 - 2.51 (2H, m), 3.02 - 3.52 (4H, m), 3.60 (1H, dd, *J*=11.7, 6.4 Hz), 4.34 - 4.46 (1H, m), 4.52 (1H, dd, *J*=10.3, 5.9 Hz), 4.60 (1H, s), 4.74 (1H, s), 5.60 (1H, d, *J*=6.8 Hz); LCMS, 97% pure, *R*_f= 5.01; *m/z* (relative intensity) 789 ([*M*+Na]⁺, 80%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-[(*S*)-3-pyrrolidinyl] amide HCl salt.



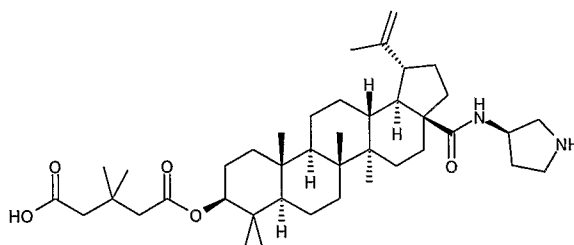
[00238] 3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-[(*S*)-3-(*tert*-butoxycarbonyl)pyrrolidinyl] amide was deprotected using method F. ¹H NMR (400 MHz, CD₃OD) δ ppm 4.48 (1H, d, *J*=2.0 Hz), 4.38 (1H, dd, *J*=2.4, 1.5 Hz), 4.24 (1H, dd, *J*=10.0, 6.1 Hz), 4.11 - 4.20 (1H, m), 3.24 - 3.34 (2H, m), 2.95 (1H, dd, *J*=12.2, 4.9 Hz), 2.85 (1H, td, *J*=10.9, 4.6 Hz), 2.32 - 2.42 (1H, m), 2.08 - 2.30 (6H, m), 1.91 - 1.98 (1H, m), 1.74 - 1.85 (1H, m), 0.56 - 1.70 (50H, m); LCMS, 96% pure; *R*_f= 3.22; *m/z* (relative intensity) 668 ([*M*+H]⁺, 40%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic *N*-[(*R*)-3-(*tert*-butoxycarbonyl) pyrrolidinyl] amide.

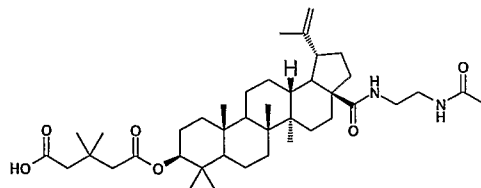


[00239] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride and (*R*)-3-amino-1-(*tert*-butoxycarbonyl)pyrrolidine, applying **method D**, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.59 (1H, d, *J*=4.4 Hz), 4.74 (1H, s), 4.60 (1H, s), 4.46 - 4.55 (1H, m), 4.37 - 4.46 (1H, m), 3.60 (1H, dd, *J*=11.7, 6.4 Hz), 3.45 (2H, br s), 3.12 (2H, br s), 2.37 - 2.51 (4H, m), 0.70 - 2.24 (59H, m); LCMS, 98% pure; *R*_f= 4.59; *m/z* (relative intensity) 768 ([*M*+*H*]⁺, 20%).

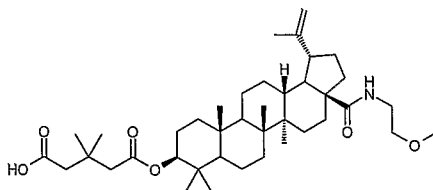
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-[(*R*)-3-aminopyrrolidinyl] amide HCl salt.



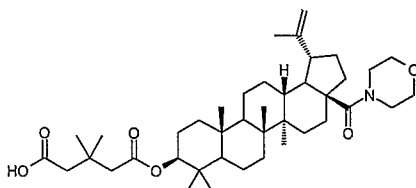
[00240] 3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-[(*R*)-3-(1-*tert*-butoxycarbonyl)pyrrolidinyl] amide was deprotected using **method F**. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.67 - 1.81 (44H, m), 1.95 (1H, s), 2.06 (1H, d, *J*=13.5 Hz), 2.18 - 2.33 (5H, m), 2.38 (1H, m), 2.48 (1H, m), 2.97 (1H, dt, *J*=4.0 Hz), 3.06 (1H, d, *J*=8.0 Hz), 3.21 (4H, s), 3.33 - 3.50 (2H, m), 4.24 (1H, m), 4.36 (1H, dd, *J*=9.9, 6.2 Hz), 4.49 (1H, s), 4.60 (1H, s); LCMS, 100% pure; *R*_f= 3.24; *m/z* (relative intensity) 667 ([*M*+*H*]⁺, 20%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-2-(acetamido)ethyl amide.

[00241] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with *N*-(2-aminoethyl)acetamide (0.19 g, 78%); followed by **method C** deprotection; (0.13 g, 84%); ^1H NMR (400 MHz, CDCl_3) δ ppm 6.66 - 6.84 (1H, m), 6.33 - 6.45 (1H, m), 4.73 (1H, d, $J=2.0$ Hz), 4.60 (1H, d), 4.49 (1H, m), 3.27 - 3.54 (4H, m), 2.99 - 3.18 (1H, m), 2.29 - 2.56 (5H, m), 0.60 - 2.09 (50H, m); LCMS, 94% pure; $R_f=1.80$ (2.5 min); m/z (relative intensity) 683 (MH^+ , 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 2-methoxyethyl amide.

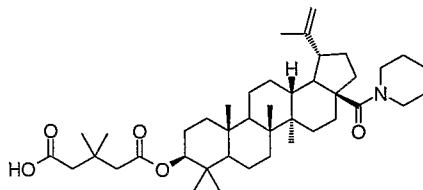
[00242] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2-methoxyethylamine (55 mg, 34%), followed by **method C** deprotection: (9.1 mg, 88%); ^1H NMR (400 MHz, CDCl_3) δ ppm 5.90 - 6.08 (1H, m), 4.69 - 4.79 (1H, m), 4.55 - 4.65 (1H, m), 4.45 - 4.55 (1H, m), 3.29 - 3.56 (7H, m), 3.05 - 3.18 (1H, m), 2.34 - 2.51 (5H, m), 1.89 - 2.02 (2H, m), 0.72 - 1.79 (45H, m); LCMS, 96% pure; $R_f=3.86$; m/z (relative intensity) 678 ($[\text{M}+\text{Na}]^+$, 50%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 4-morpholinyl amide.

[00243] The compound was synthesized from 3-*O*-acetylbetulinic acid chloride applying **method D** with morpholine, followed by **method G** deprotection and **method H** side

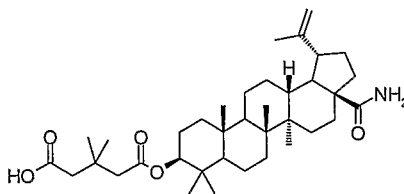
chain introduction. ^1H NMR (400 MHz, CDCl_3) δ ppm 4.69 - 4.76 (1H, m), 4.56 - 4.61 (1H, m), 4.44 - 4.55 (1H, m), 3.55 - 3.72 (8H, m), 2.93 - 3.04 (1H, m), 2.81 - 2.92 (1H, m), 2.35 - 2.52 (4H, m), 0.70 - 2.13 (47H, m); LCMS, 96% pure; R_f = 3.97; m/z (relative intensity) 668 (MH^+ , 90%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-piperidiny amide.

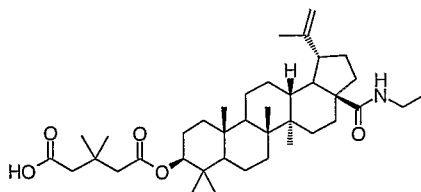


[00244] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with piperidine (49%), followed by **method C** deprotection: (80 mg, 90%); ^1H NMR (400 MHz, CDCl_3) δ ppm 4.68 - 4.74 (1H, m), 4.54 - 4.59 (1H, m), 4.45 - 4.55 (1H, m), 3.36 - 3.65 (4H, m), 2.96 - 3.07 (1H, m), 2.84 - 2.95 (1H, m), 2.35 - 2.50 (4H, m), 2.08 - 2.17 (1H, m), 1.93 - 2.03 (1H, m), 1.79 - 1.90 (1H, m), 0.73 - 1.75 (50H, m); LCMS, 97% pure; R_f = 4.36; m/z (relative intensity) 666 (MH^+ , 100%).

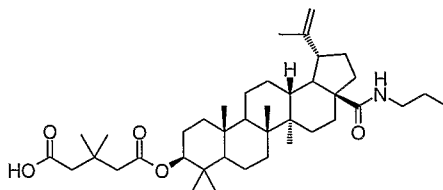
3-*O*-(3',3'-Dimethylglutaryl)betulinic amide.



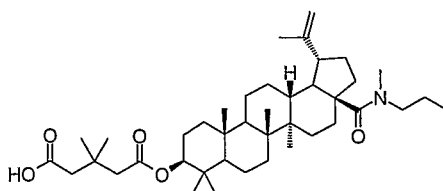
[00245] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with ammonia (62%), followed by **method C** deprotection; (6.6 mg, 22%); ^1H NMR (400 MHz, CDCl_3) δ ppm 6.69 (1H, s), 5.56 (1H, s), 4.71 (1H, d, J = 2.2 Hz), 4.58 (1H, s), 4.44 - 4.53 (1H, m), 3.00 - 3.10 (1H, m), 2.75 (1H, d, J = 12.8 Hz), 2.31 - 2.52 (3H, m), 2.21 (1H, d, J = 13.2 Hz), 1.75 - 2.04 (4H, m), 0.72 - 1.75 (43H, m); LCMS, 100% pure; R_f = 3.77; m/z (relative intensity) 620 ($[\text{M}+\text{Na}]^+$, 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-ethyl amide.

[00246] The compound was synthesized applying from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride **method D** with ethylamine (77%), followed by **method C** deprotection: (80 mg, 90%); ^1H NMR (400 MHz, CDCl_3) δ ppm 5.54 (1H, t, $J=5.5$ Hz), 4.72 (1H, d, $J=2.2$ Hz), 4.58 (1H, s), 4.49 (1H, dd, $J=10.2, 5.9$ Hz), 2.97 - 3.42 (3H, m), 2.32 - 2.54 (5H, m), 1.83 - 2.04 (2H, m), 0.67 - 1.76 (48H, m); LCMS, 96% pure; $R_f=3.97$; m/z (relative intensity) 626 ($[\text{M}+\text{H}]^+$, 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-propyl amide.

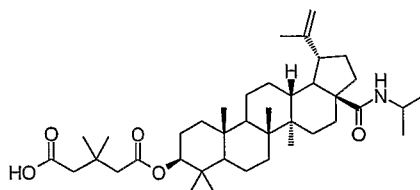
[00247] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with propylamine (52%), followed by **method C** deprotection: (24 mg, 25%); ^1H NMR (400 MHz, CDCl_3) δ ppm 5.63 (1H, t, $J=5.9$ Hz), 4.73 (1H, d, $J=2.2$ Hz), 4.59 (1H, s), 4.42 - 4.54 (1H, m), 3.20 - 3.34 (1H, m), 3.05 - 3.20 (2H, dd, $J=12.3, 6.4$ Hz), 2.37 - 2.54 (5H, m), 0.67 - 2.24 (52H, m); LCMS, 96% pure; $R_f=4.06$; m/z (relative intensity) 640 ($[\text{M}+\text{H}]^+$, 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-methyl-*N*-propyl amide.

[00248] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with *N*-methylpropylamine (19%), followed by **method C** deprotection: (17 mg, 49%); ^1H NMR (400 MHz, CDCl_3)

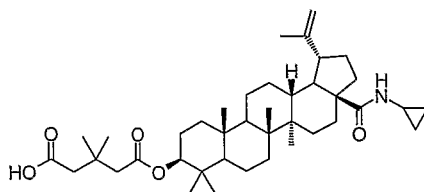
δ ppm 4.72 (1H, d, $J=1.8$ Hz), 4.57 (1H, s), 4.50 (1H, dd, $J=10.2, 5.9$ Hz), 2.78 - 3.13 (5H, m), 2.32 - 2.54 (4H, m), 0.64 - 2.29 (54H, m); LCMS, 97% pure; $R_f=4.33$; m/z (relative intensity) 653 ($[M+H]^+$, 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-isopropyl amide.

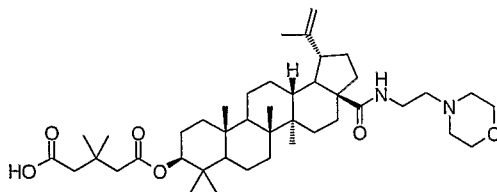


[00249] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with isopropylamine (38%), followed by **method C** deprotection: (45 mg, 38%); ^1H NMR (400 MHz, CD_3OD) δ ppm 4.59 (1H, d, $J=2.4$ Hz), 4.47 (1H, s), 4.35 (1H, dd, $J=10.3, 5.9$ Hz), 3.82 - 3.95 (1H, m), 2.94 - 3.05 (1H, m), 2.45 - 2.56 (1H, m), 2.38 (1H, d, $J=14.2$ Hz), 2.25 - 2.33 (3H, m), 1.99 - 2.09 (1H, m), 0.67 - 1.85 (53H, m); LCMS, 96% pure; $R_f=4.08$; m/z (relative intensity) 640 ($[M+H]^+$, 100%).

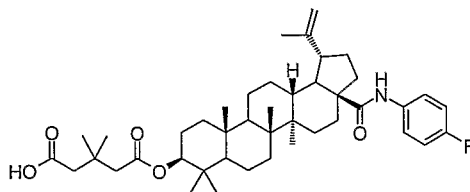
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-cyclopropyl amide.



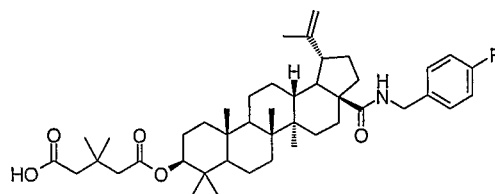
[00250] The compound was synthesized from 3-*O*-acetylbetulinic acid chloride applying **method D** with cyclopropylamine, followed by **method G** deprotection and **method H** side chain introduction. ^1H NMR (400 MHz, CD_3OD) δ ppm 4.69 (1H, d, $J=2.4$ Hz), 4.57 (1H, s), 4.45 (1H, dd, $J=10.3, 5.9$ Hz), 3.01 - 3.19 (1H, m), 2.32 - 2.68 (6H, m), 1.98 - 2.12 (1H, m), 0.61 - 1.94 (49H, m), 0.33 - 0.50 (2H, m); LCMS, 99% pure; $R_f=3.97$; m/z (relative intensity) 660 ($[M+Na]^+$, 60%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-(2-(4-morpholinyl)ethyl) amide.

[00251] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2-(4-morpholinyl)ethylamine (40%) followed by **method C** deprotection: (62 mg, 48%); ^1H NMR (400 MHz, CD_3OD) δ ppm 4.60 (1H, s), 4.49 (1H, s), 4.36 (1H, dd, $J=10.5, 5.6$ Hz), 3.50 - 3.67 (7H, m), 3.32 - 3.51 (2H, m), 3.21 - 3.32 (1H, m), 2.90 - 3.07 (1H, m), 2.30 - 2.50 (8H, m), 1.99 - 2.09 (1H, m), 0.61 - 1.87 (47H, m); LCMS, 100% pure; $R_f=3.23$; m/z (relative intensity) 711 ($[\text{M}+\text{H}]^+$, 40%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-(4-fluorophenyl) amide.

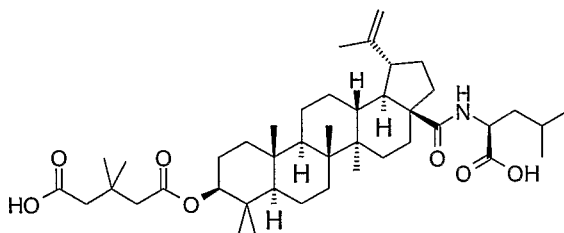
[00252] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 4-fluoroaniline (39%), followed by **method C** deprotection: (40 mg, 32%); ^1H NMR (400 MHz, Acetone- d_6) δ ppm 8.74 (1H, s), 7.49 - 7.61 (2H, m), 6.93 (2H, t, $J=8.8$ Hz), 4.26 - 4.66 (4H, m), 2.98 - 3.10 (1H, m), 2.62 - 2.75 (2H, m), 2.17 - 2.41 (6H, m), 0.73 - 1.99 (43H, m); LCMS, 100% pure; $R_f=4.13$; m/z (relative intensity) 692 ($[\text{M}+\text{H}]^+$, 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-(4-fluorobenzyl) amide.

[00253] The compound was synthesized from 3-*O*-acetylbetulinic acid chloride applying **method D** with 4-fluorobenzylamine, followed by **method G** deprotection and **method H**

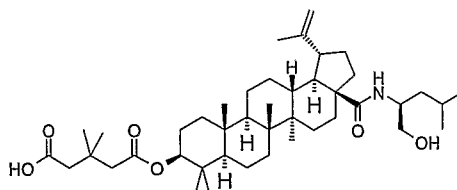
side chain introduction. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.05 (1H, t, $J=6.1$ Hz), 7.21 (2H, dd, $J=8.3$, 5.4 Hz), 6.86 - 6.98 (2H, m), 4.60 (1H, d, $J=2.0$ Hz), 4.48 (1H, s), 4.23 - 4.41 (2H, m), 4.12 (1H, dd, $J=14.7$, 5.9 Hz), 2.93 - 3.06 (1H, m), 2.41 - 2.52 (1H, m), 2.30 - 2.41 (2H, m), 1.99 - 2.09 (1H, m), 0.61 - 1.84 (53H, m); ^{19}F NMR (376 MHz, Acetone- d_6) δ ppm -118.2 (s); LCMS, 100% pure; $R_f=4.10$; m/z (relative intensity) 706 ($[\text{M}+\text{H}]^+$, 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-[(*S*)-(1-carboxy-3-methyl)butyl] amide.

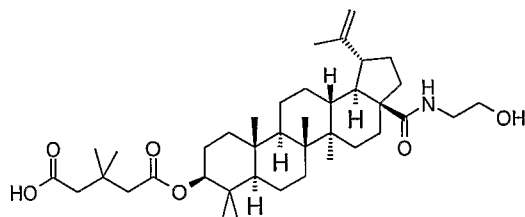


[00254] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with (*S*)-*N*-(*tert*-butoxycarbonyl)leucine, followed by **method F** Boc group deprotection and **method C** deallylation. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.72 - 2.03 (57H, m), 2.36 - 2.51 (5H, m), 3.10 (1H, td, $J=10.9$, 4.6 Hz), 4.50 (1H, dd, $J=10.4$, 5.7 Hz), 4.59 (2H, s), 4.73 (1H, d, $J=1.8$ Hz), 5.89 (1H, d, $J=7.7$ Hz).

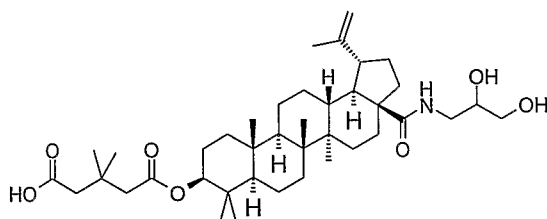
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-[(*S*)-(1-hydroxymethyl-3-methyl)butyl] amide.



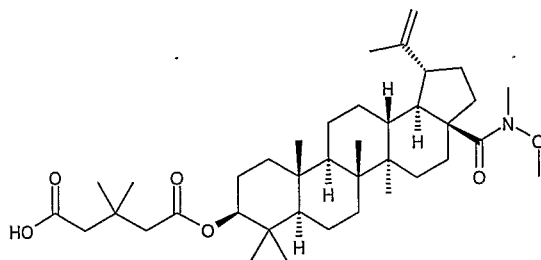
[00255] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with (*S*)-leucinol, followed by **method C** deprotection. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.67 - 1.71 (55H, m), 1.75 (1H, dd, $J=12.1$, 7.7 Hz), 1.85 - 2.01 (2H, m), 2.31 - 2.41 (1H, m), 2.41 - 2.51 (4H, m), 3.08 (1H, dt, $J=11.0$, 4.0 Hz), 3.49 (1H, dd, $J=11.0$, 6.2 Hz), 3.64 (1H, dd, $J=10.8$, 3.5 Hz), 4.07 (1H, br s), 4.57 (1H, s), 4.71 (1H, d, $J=1.8$ Hz), 5.68 (1H, d, $J=8.0$ Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-2-hydroxyethyl amide.

[00256] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2-hydroxyethylamine, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.00 (1H, m), 4.67 (1H, s), 4.53 (1H, s), 4.46 – 4.42 (1H, m), 3.70 – 3.65 (2H, m), 3.50 – 3.25 (5H, m), 3.09 (1H, m), 2.48 – 2.25 (6H, m), 2.1 – 0.70 (45H, m).

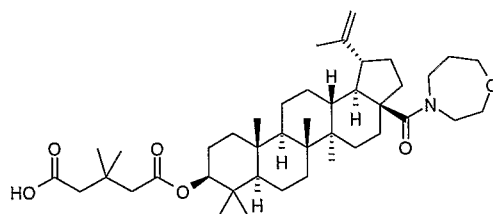
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-(*R/S*)-2,3-dihydroxypropyl amide.

[00257] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with (*R/S*)-2,3-dihydroxypropylamine, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.71 - 2.22 (44H, m), 2.34 - 2.42 (1H, m), 2.44 - 2.52 (3H, m), 2.97 (1H, d, *J*=11.2 Hz), 3.08 (1H, dt), 3.27 - 4.01 (10H, m), 4.50 (1H, dd, *J*=10.5, 5.6 Hz), 4.61 (1H, s), 4.74 (1H, s), 6.10 (1H, d, *J*=2.4 Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-methoxy-*N*-methyl amide.

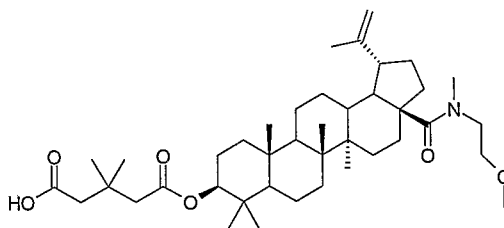
[00258] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with *N,O*-dimethylhydroxylamine, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.72 - 1.04 (18H, m), 1.07 - 1.89 (29H, m), 2.02 - 2.17 (1H, m), 2.24 - 2.54 (5H, m), 2.98 (1H, dt, *J*=11.2, 3.7 Hz), 3.16 (3H, s), 3.66 (3H, s), 4.50 (1H, dd), 4.58 (1H, s), 4.72 (1H, d, *J*=2.2 Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 4-(1,4-oxazepinyl) amide.

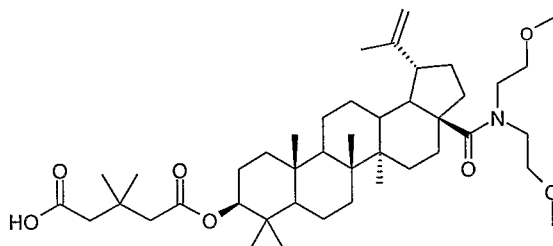


[00259] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 1,4-oxazepine, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.63 - 1.70 (45H, m), 1.69 - 1.96 (4H, m), 1.99 - 2.13 (1H, m), 2.32 (1H, d), 2.36 - 2.45 (3H, m), 2.78 - 2.99 (2H, m), 3.39 - 3.87 (8H, m), 4.37 - 4.47 (1H, m), 4.51 (1H, s), 4.66 (1H, d, *J*=2.2 Hz).

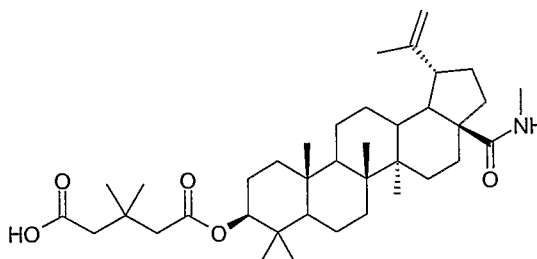
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-(2-methoxyethyl)-*N*-methyl amide.



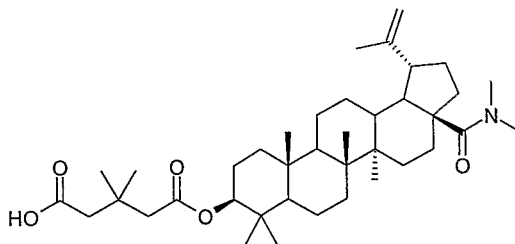
[00260] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with *N*-methyl-2-methoxyethylamine, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.67 - 1.76 (47H, m), 1.77 - 1.91 (1H, m), 2.05 (1H, dd, *J*=10.8, 7.5 Hz), 2.26 (1H, d, *J*=13.5 Hz), 2.40 (1H, d), 2.45 - 2.51 (3H, m), 2.89 (1H, dt), 3.00 (1H, dt, *J*=11.2, 3.7 Hz), 3.12 (2H, br s), 3.32 - 3.37 (3H, m), 3.54 (2H, t, *J*=5.3 Hz), 3.60 - 3.73 (1H, m), 4.50 (1H, dd, *J*=10.4, 5.7 Hz), 4.57 (1H, s), 4.72 (1H, d, *J*=2.2 Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N,N*-bis(2-methoxyethyl) amide.

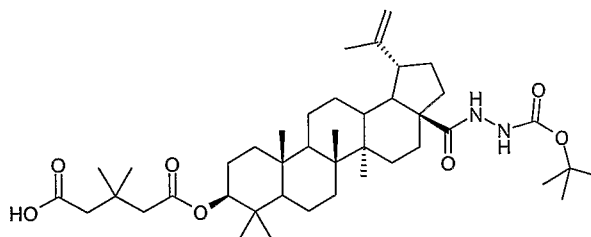
[00261] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with bis(2-methoxyethyl)amine, followed by **method C** deprotection. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.71 - 1.75 (45H, m), 1.76 - 1.89 (1H, m), 2.04 (1H, dd, $J=10.8, 7.5$ Hz), 2.17 (1H, d, $J=13.5$ Hz), 2.40 (1H, d), 2.43 - 2.51 (3H, m), 2.86 (1H, dt), 2.99 (1H, dt, $J=11.0, 3.3$ Hz), 3.25 - 3.43 (7H, m, $J=4.4$ Hz), 3.43 - 3.67 (6H, m), 3.76 (1H, br s), 4.50 (1H, dd), 4.57 (1H, s), 4.72 (1H, d, $J=2.2$ Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-methyl amide.

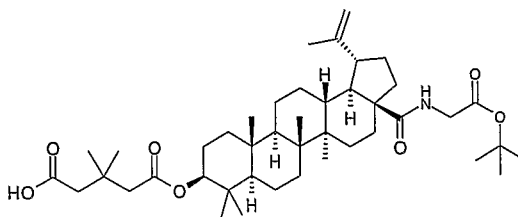
[00262] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with methylamine, followed by **method C** deprotection. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.70 - 2.16 (47H, m), 2.33 - 2.42 (1H, m), 2.42 - 2.56 (4H, m), 2.80 (3H, d, $J=4.8$ Hz), 2.96 (1H, d), 3.14 (1H, dt, $J=11.4, 3.8$ Hz), 4.49 (1H, dd), 4.59 (1H, s), 4.74 (1H, d, $J=1.8$ Hz), 5.57 (1H, q, $J=4.5$ Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N,N*-dimethyl amide.

[00263] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with dimethylamine, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.72 - 1.76 (45H, m), 1.78 - 1.93 (1H, m), 1.98 - 2.08 (1H, m), 2.24 (1H, d), 2.42 - 2.53 (3H, m), 2.88 (1H, dt), 2.88 (1H, dt), 2.94 - 3.10 (6H, m), 4.50 (1H, dd, *J*=10.4, 5.7 Hz), 4.57 (1H, s), 4.72 (1H, d, *J*=2.2 Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-2-(*tert*-butoxycarbonyl)hydrazide.

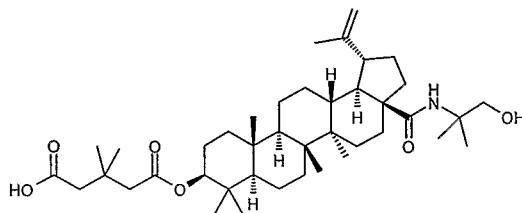
[00264] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with *tert*-butylcarbazate, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.71 - 1.76 (53H, m), 1.83 - 2.07 (3H, m), 2.39 (1H, d), 2.43 - 2.52 (4H, m), 3.08 (1H, dt), 4.50 (1H, dd), 4.59 (1H, s), 4.73 (1H, d, *J*=2.2 Hz), 6.52 (1H, s), 7.40 (1H, s).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-(*tert*-butoxycarbonylmethyl) amide.

[00265] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with *N*-(*tert*-

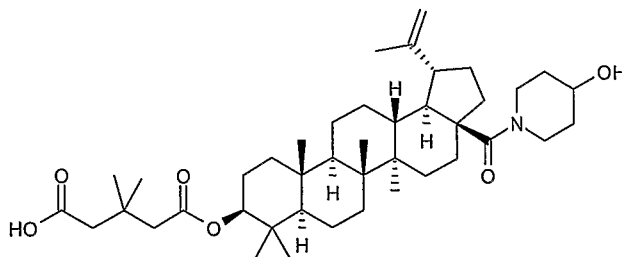
butoxycarbonyl)glycine, followed by **method C** deprotection. ^1H NMR (400 MHz, CDCl_3) δ ppm 6.12 (1H, t, $J=5.1$ Hz), 4.72 (1H, d, $J=2.2$ Hz), 4.58 (1H, s), 4.43 - 4.51 (1H, m), 3.89 (2H, dd, $J=5.1, 2.9$ Hz), 3.09 (1H, td, $J=11.0, 4.4$ Hz), 2.35 - 2.50 (5H, m), 1.87 - 2.05 (2H, m), 1.82 (1H, dd, $J=11.7, 7.7$ Hz), 0.70 - 1.75 (54H, m)

3-O-(3',3'-Dimethylglutaryl)betulinic acid N-(1-hydroxy-2-methyl-2-propyl) amide.



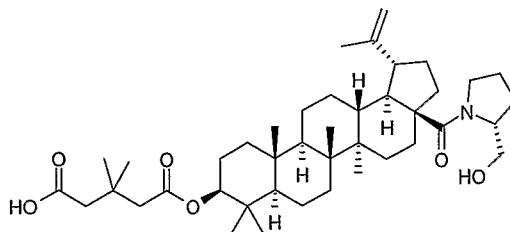
[00266] The compound was synthesized from 3-O-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 1-hydroxy-2-methyl-2-propylamine, followed by **method C** deprotection. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.64 - 1.76 (51H, m), 1.79 - 1.89 (1H, m), 1.90 - 2.01 (1H, m), 2.39 (1H, d), 2.42 - 2.50 (4H, m), 3.05 (1H, dt, $J=11.1, 3.8$ Hz), 3.57 (2H, s), 4.49 (1H, dd), 4.59 (1H, s), 4.72 (1H, d, $J=2.2$ Hz), 5.59 (1H, s).

3-O-(3',3'-Dimethylglutaryl)betulinic acid N-4-hydroxycyclohexyl amide.



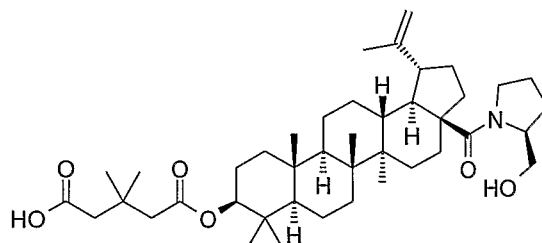
[00267] The compound was synthesized from 3-O-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 4-hydroxycyclohexylamine, followed by **method C** deprotection. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.65 - 1.95 (51H, m), 2.05 (1H, d), 2.33 (1H, d), 2.36 - 2.48 (3H, m), 2.81 (1H, dt), 2.92 (1H, dt, $J=11.2, 3.4$ Hz), 2.98 - 3.16 (2H, m), 3.80 - 3.90 (1H, m), 3.94 (1H, d, $J=13.2$ Hz), 3.99 - 4.16 (1H, m), 4.44 (1H, dd, $J=10.3, 5.9$ Hz), 4.51 (1H, s), 4.65 (1H, d, $J=2.0$ Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[(*R*)-2-(hydroxymethyl)pyrrolidinyl] amide.

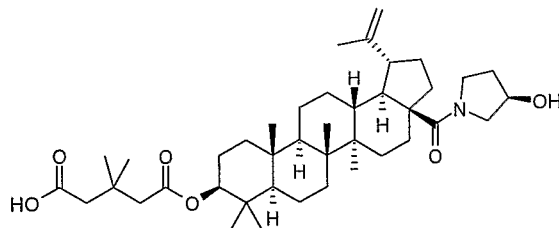


[00268] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with (*R*)-prolinol, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.70 - 1.95 (50H, m), 2.05 - 2.16 (1H, m), 2.24 - 2.34 (1H, m), 2.40 (1H, d), 2.43 - 2.53 (3H, m), 2.76 (1H, dt), 2.96 - 3.07 (1H, m), 3.26 (1H, dt, *J*=11.0, 5.49 Hz), 3.56 (1H, dd, *J*=11.5, 7.9 Hz), 3.71 (1H, dd), 3.89 (1H, dd), 4.36 (1H, dd), 4.44 - 4.54 (1H, m), 4.59 (1H, s), 4.74 (1H, d, *J*=2.2 Hz).

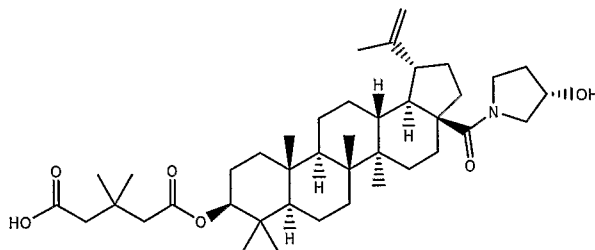
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[(*S*)-2-(hydroxymethyl)pyrrolidinyl] amide.



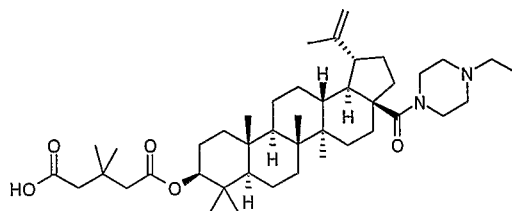
[00269] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with (*S*)-prolinol, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.64 - 1.70 (46H, m), 1.73 - 1.86 (2H, m), 1.91 - 2.15 (4H, m), 2.26 - 2.47 (4H, m), 2.75 - 2.96 (2H, m), 3.16 - 3.32 (1H, m), 3.39 - 3.61 (2H, m), 3.69 - 3.83 (1H, m), 4.19 - 4.32 (1H, m), 4.44 (1H, dd, *J*=10.3, 5.9 Hz), 4.52 (1H, s), 4.65 (1H, d, *J*=2.4 Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[(*R*)-3-hydroxypyrrolidinyl] amide.

[00270] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with (*R*)-(+)-3-pyrrolidinol, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.67 - 2.10 (49H, m), 2.20 (1H, d, *J*=12.1 Hz), 2.36 (1H, d), 2.41 - 2.51 (3H, m), 2.81 - 2.93 (1H, m), 2.97 (1H, dt), 3.50 (1H, dd, *J*=12.1, 3.7 Hz), 3.55 - 3.73 (3H, m), 4.37 - 4.44 (1H, m), 4.47 (1H, dd), 4.56 (1H, s), 4.70 (1H, d, *J*=2.2 Hz); LCMS, 100% pure; *R*_f= 4.20; *m/z* (relative intensity) 668 ([*M*+*H*]⁺, 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[(*S*)-3-hydroxypyrrolidinyl] amide.

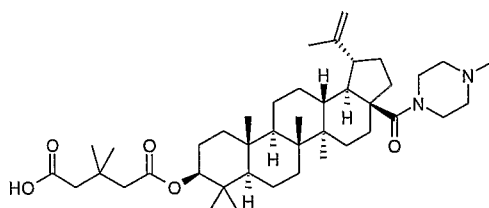
[00271] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with (*S*)-(-)-3-pyrrolidinol, followed by **method C** deprotection. ¹H NMR (250 MHz, CDCl₃) δ ppm 4.72 (1H, d, *J*=1.5 Hz), 4.58 (1H, s), 4.40 - 4.55 (2H, m), 3.38 - 3.81 (5H, m), 2.84 - 3.17 (2H, m), 2.67 - 2.83 (1H, m), 2.32 - 2.54 (4H, m), 0.64 - 2.29 (48H, m).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-(4-ethylpiperazinyl) amide.

[00272] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with *N*-ethylpiperazine,

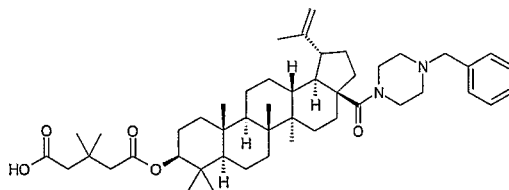
followed by **method C** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 4.65 (1H, s), 4.52 (1H, s), 4.42 – 4.38 (1H, m), 2.89 – 2.87 (1H, m), 2.78 – 2.74 (2H, m), 2.62 – 2.60 (2H, m), 2.49 – 2.45 (2H, m), 2.24 – 2.20 (2H, m), 1.98 – 1.96 (1H, m), 1.84 – 1.79 (2H, m), 1.93 – 1.88 (2H, m), 1.87 – 0.61 (53H, m); LCMS, 100% $R_t = 3.27$; m/z (relative intensity) 695 ($[\text{M}+\text{H}^+]$ 10%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-(4-methylpiperazine) amide.



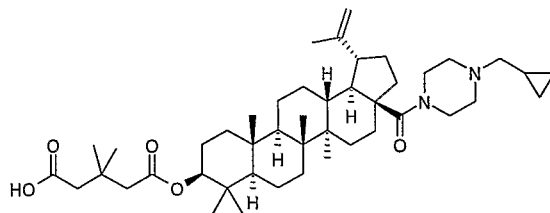
[00273] The compound was synthesized from 3-*O*-acetylbetulinic acid chloride applying **method D** with *N*-methylpiperazine, followed by **method G** deprotection and **method H** side chain introduction. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 4.46 (1H, s), 4.35 (1H, s), 4.2 (1H, m), 2.75 – 2.63 (2H, m), 2.23 – 1.88 (13H, m), 1.81 – 1.72 (1H, m), 1.59 – 0.51 (50H, m).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-(4-benzylpiperazinyl) amide.



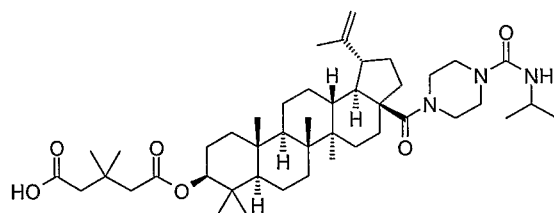
[00274] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 1-benzylpiperazine, followed by **method C** deprotection. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.67 - 1.98 (48H, m), 2.00 - 2.13 (1H, m), 2.17 - 2.70 (7H, m), 2.79 - 2.91 (1H, m), 2.92 - 3.04 (1H, m), 3.30 - 3.82 (5H, m), 4.49 (1H, dd, $J=11.0, 4.4$ Hz), 4.58 (1H, s), 4.72 (1H, d, $J=1.8$ Hz), 7.28 - 7.37 (5H, m); LCMS, 100% pure; $R_t = 4.33$; m/z (relative intensity) 757 ($[\text{M}+\text{H}]^+$, 70%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[4-(cyclopropylmethyl)piperazinyl] amide.



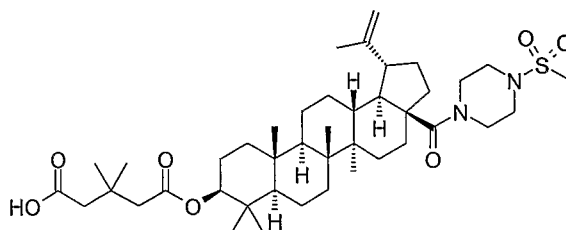
[00275] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 1-(cyclopropylmethyl)piperazine, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.65 (1H, s), 4.53 (1H, s), 4.40 - 4.47 (1H, m), 2.80 - 2.91 (3H, m), 2.65 - 2.75 (1H, m), 2.30 - 2.43 (4H, m), 1.87 - 2.00 (1H, m), 1.75 (1H, br s), 0.65 - 1.68 (57H, m), 0.38 (2H, d, *J*=4.0 Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[4-(isopropylaminocarbonyl)piperazinyl] amide.



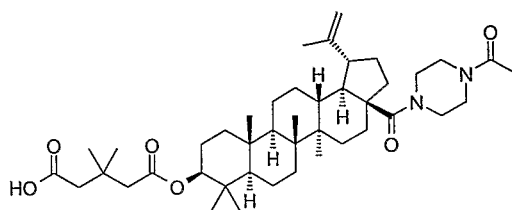
[00276] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 1-(isopropylaminocarbonyl)piperazine, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.63 - 2.06 (53H, m), 2.33 (1H, d), 2.36 - 2.43 (3H, m), 2.78 (1H, dt), 2.84 - 2.99 (1H, m), 3.25 (4H, s), 3.46 - 3.65 (4H, m), 3.83 - 3.99 (1H, m), 4.19 (1H, d, *J*=7.3 Hz), 4.37 - 4.48 (1H, m), 4.52 (1H, s), 4.66 (1H, d, *J*=2.0 Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[4-(methylsulfonyl)piperazinyl] amide.



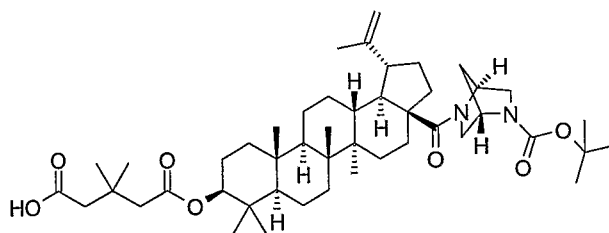
[00277] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 1-methylsulfonylpiperazine, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.74 - 2.25 (47H, m), 2.36 - 2.57 (4H, m), 2.74 - 3.09 (5H, m), 3.21 (4H, s), 3.74 (4H, s), 4.45 - 4.58 (1H, m), 4.62 (1H, s), 4.75 (1H, s).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-(4-acetylpiperazinyl) amide.



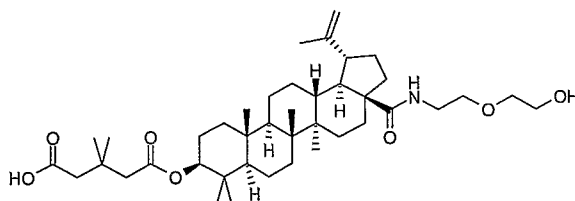
[00278] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 1-acetylpiperazine, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.61 - 1.93 (48H, m), 1.93 - 2.03 (2H, m), 2.30 - 2.36 (1H, m), 2.36 - 2.43 (3H, m), 2.77 (1H, d, *J*=2.0 Hz), 2.90 (1H, d, *J*=3.9 Hz), 3.25 - 3.70 (8H, m), 4.39 - 4.48 (1H, m), 4.49 - 4.58 (1H, m), 4.66 (1H, d, *J*=2.2 Hz).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 2-[(1*S*,4*S*)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptyl] amide.



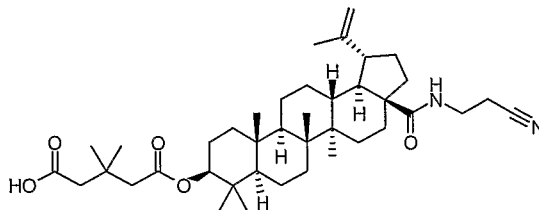
[00279] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with (1*S*,4*S*)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptane, followed by **method C** deprotection. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.49 - 2.08 (60H, m), 2.23 - 2.40 (4H, m), 2.46 - 3.80 (6H, m), 4.32 (1H, s), 4.45 (1H, s), 4.58 (1H, s).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-2-(2-hydroxyethoxy)ethyl amide.



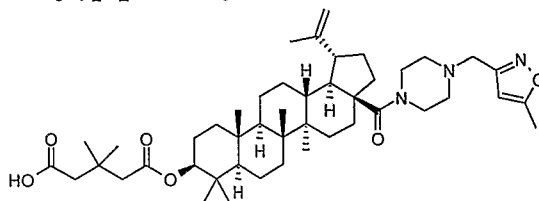
[00280] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2-(hydroxyethoxy)ethylamine, followed by **method C** deprotection. ^1H NMR (400MHz, CDCl_3); δ ppm 5.99 (1H, s), 4.74 (1H, s), 4.59 (1H, s), 4.53 – 4.49 (1H, m), 3.75 (2H, s), 3.59 – 3.56 (5H, m), 3.52 – 3.50 (1H, m), 3.45 – 3.42 (1H, m), 2.46 – 2.41 (5H, m), 1.97 – 1.94 (2H, m), 1.75 – 0.76 (46H, m); LCMS, 87% $R_t = 4.49$; m/z (relative intensity) 709 ($[\text{M}+\text{Na}^+]$ 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-2-cyanoethyl amide.



[00281] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2-cyanoethylamine, followed by **method C** deprotection. ^1H NMR (400MHz, CDCl_3); δ ppm 6.15 – 6.12 (1H, m), 4.74 (1H, s), 4.60 (1H, s), 4.51 – 4.47 (1H, m), 3.57 – 3.52 (1H, m), 3.47 – 3.43 (1H, m), 3.12 – 3.06 (1H, m), 2.67 – 2.63 (2H, m), 2.48 – 2.38 (4H, m), 1.97 – 1.93 (2H, m), 1.78 – 0.77 (46H, m); LCMS, 100% pure, $R_t = 4.67$; m/z (relative intensity) 674 ($[\text{M}+\text{Na}^+]$ 100%).

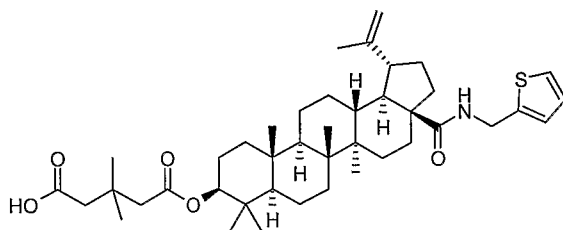
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 1-[4-(3-(5-methylisoxazolyl)methyl)piperazinyl] amide.



[00282] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 4-[3-(5-

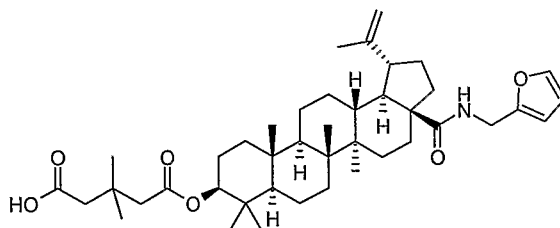
methylisoxazolyl)methyl]piperazine followed by **method C** deprotection. ^1H NMR (400MHz, CDCl_3); δ ppm 5.95 (1H, s), 4.65 (1H, s), 4.51 (1H, s), 4.43 – 4.40 (1H, m), 3.62 – 3.49 (7H, m), 2.92 – 2.88 (1H, m), 2.81 – 2.77 (1H, m), 2.50 – 2.28 (8H, m), 2.02 – 1.98 (1H, m), 1.89 – 1.84 (2H, m), 1.65 – 0.70 (46H, m); LCMS, 99% pure, $R_t = 3.67$; m/z (relative intensity) 762 ($[\text{M}+\text{H}^+]$ 10%)

3-O-(3',3'-Dimethylglutaryl)betulinic acid N-(2-thienylmethyl) amide.



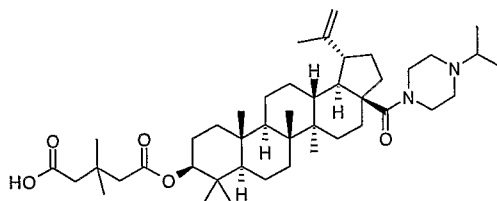
[00283] The compound was synthesized from 3-O-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2-thiophenemethylamine, followed by **method C** deprotection. ^1H NMR (400MHz, CDCl_3); δ ppm 7.34 (1H, s), 6.32 (1H, m), 6.22 (1H, m), 5.94 – 5.91 (1H, m), 4.73 (1H, s), 4.59 (1H, s), 4.52 – 4.47 (2H, m), 4.37 – 4.32 (1H, m), 3.18 – 3.11 (1H, m), 2.50 – 2.38 (4H, m), 1.97 – 1.90 (2H, m), 1.76 – 0.75 (46 H, m); LCMS, 100% pure, $R_t = 4.72$; m/z (relative intensity) 695 ($[\text{M}+\text{H}^+]$ 90%).

3-O-(3',3'-Dimethylglutaryl)betulinic acid N-(2-furanylmethyl) amide.



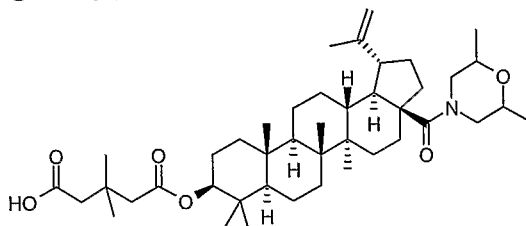
[00284] The compound was synthesized from 3-O-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2-furanemethylamine, followed by **method C** deprotection. ^1H NMR (400MHz, CDCl_3); δ ppm 7.15 – 4.14 (1H, dd, $J=1.2, 4.9$ Hz), 6.88 – 6.85 (2H, m), 5.91 – 5.86 (1H, t, $J=5.7$ Hz), 4.67 (1H, s), 4.61 – 4.40 (3H, m), 3.11 – 3.06 (1H, m), 2.44 – 2.40 (4H, m), 1.91 – 1.81 (1H, m), 1.70 – 0.68 (49H, m); LCMS, 100% pure, $R_t = 4.65$; m/z (relative intensity) 679 ($[\text{M}+\text{H}^+]$ 65%).

3-O-(3',3'-Dimethylglutaryl)betulinic acid 1-(4-isopropylpiperazinyl) amide.



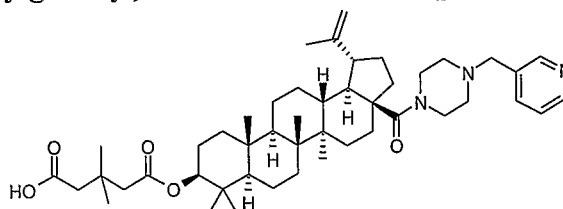
[00285] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 4-isopropylpiperazine, followed by **method C** deprotection. ^1H NMR (400 MHz, CD_3OD); δ ppm 4.57 (1H, s), 4.45 (1H, s), 4.33 – 4.29 (1H, dd, $J=6.4, 10.5$ Hz), 3.34 – 3.27 (1H, m), 3.05 (4H, br s), 2.81 – 2.75 (1H, m), 2.72 – 2.62 (1H, m), 2.56 (2H, s), 2.36 – 2.24 (2H, m), 2.02 – 1.99 (1H, m), 1.89 – 1.84 (1H, m), 1.74 – 0.69 (56H, m); LCMS, 97% pure, $R_t = 3.57$; m/z (relative intensity) 710 ($[\text{M}+\text{H}^+]$ 20%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid 4-(2,6-dimethylmorpholine) amide.



[00286] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2,6-dimethylmorpholine, followed by **method C** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 4.74 (1H, s), 4.59 (1H, s), 4.53 – 4.49 (1H, dd, $J=6.4, 10.5$ Hz), 3.53 – 3.47 (2H, m), 3.00 – 2.95 (1H, m), 2.89 – 2.84 (1H, m), 2.48 – 2.45 (1H, d, $J=13.9$ Hz), 2.47 (2H, s), 2.42 – 2.38 (1H, d, $J=13.9$ Hz), 2.20 – 1.91 (1H, m), 1.83 – 1.71 (2H, m), 1.74 – 0.69 (52H, m); LCMS, 100% pure, $R_t = 4.86$; m/z (relative intensity) 697 ($[\text{M}+\text{H}^+]$ 100%).

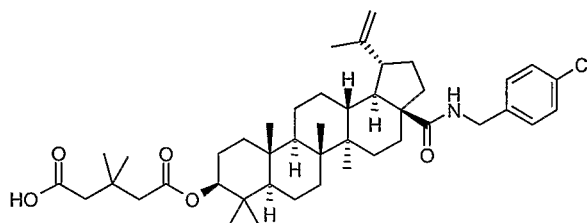
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-4-(3-pyridylmethyl) piperazine amide.



[00287] The compound was synthesized from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 4-(3-pyridinylmethyl)piperazine, followed by **method C** deprotection. ^1H NMR (400 MHz,

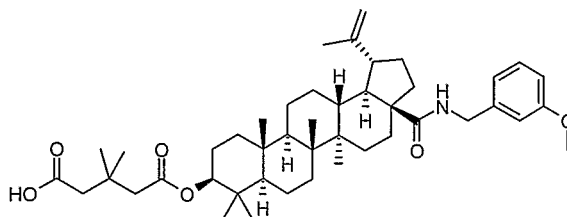
CD₃OD); δ ppm 8.75 (1H, d, $J=1.4$ Hz), 8.69 – 8.67 (1H, dd, $J=1.4$, 5.4 Hz), 8.23 – 8.21 (1H, d, $J=8.0$ Hz), 7.72 – 7.69 (1H, dd, $J=5.4$, 8.0 Hz), 4.60 (1H, s), 4.49 (1H, s), 4.37 – 4.33 (1H, m), 3.14 (4H, br s), 2.86 – 2.79 (1H, m), 2.76 – 2.64 (1H, m), 2.44 – 2.39 (1H, d, $J=19.3$ Hz), 2.31 – 2.28 (3H, m), 2.05 – 2.01 (1H, m), 1.93 – 1.88 (1H, m), 1.74 – 0.69 (51H, m); LCMS, 94% pure, $R_t = 3.39$; m/z (relative intensity) 759 ($[M+H]^+$ 20%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-4-chlorobenzyl amide.



[00288] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 4-chlorobenzylamine, followed by **method E** deprotection. ¹H NMR (400 MHz, CDCl₃); δ ppm 7.24 – 7.23 (2H, d, $J=7.4$ Hz), 7.16– 7.14 (2H, d, $J=7.4$ Hz), 5.88 – 5.85 (1H, t, $J=6.0$ Hz), 4.67 (1H, s), 4.53 (1H, s), 4.45 – 4.40 (1H, m), 4.38 – 4.37 (1H, d, $J=6.0$ Hz), 4.26 – 4.21 (1H, dd, $J=5.6$, 14.7 Hz), 3.11 – 3.05 (1H, dt, $J=5.6$, 11.1 Hz), 2.42 – 2.37 (3H, m), 2.34 – 2.31 (1H, d, $J=13.9$ Hz), 1.74 – 0.69 (48H, m); LCMS, 100% pure $R_t = 4.70$; m/z (relative intensity) 722 ($[M+H]^+$ 100%).

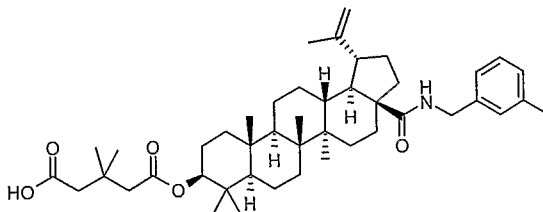
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-3-methoxybenzylamine amide.



[00289] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 3-methoxybenzylamine, followed by **method E** deprotection. ¹H NMR (400 MHz, CDCl₃); δ ppm 7.08 – 7.06 (1H, m), 6.71– 6.69 (1H, d, $J=7.8$ Hz), 6.66 – 6.63 (2H, m), 5.73 – 5.70 (1H, t, $J=5.8$ Hz), 4.58 (1H, s), 4.44 (1H, s), 4.36 – 4.28 (3H, m), 3.64 (3H, s), 3.02 – 2.99 (1H, dt, $J=5.6$, 11.1 Hz), 2.34 – 2.33 (1H, m), 2.31 – 2.28 (1H, d, $J=13.9$ Hz), 2.30 (2H, s), 2.25 – 2.22

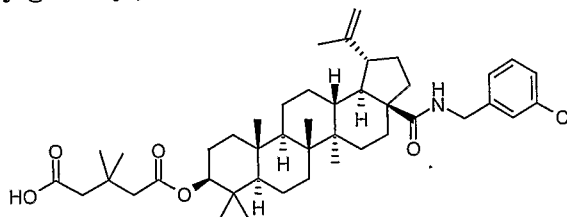
(1H, d, $J=13.9$ Hz), 1.63 – 0.75 (47H, m); LCMS, 100% pure, $R_t = 4.56$; m/z (relative intensity) 719 ($[M+H]^+$ 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-3-methylbenzylamine amide.



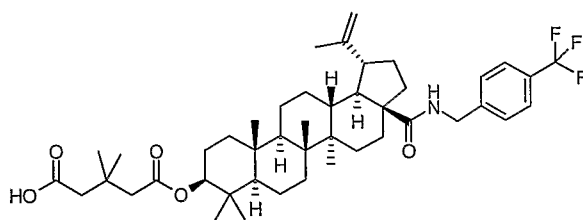
[00290] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 3-methylbenzylamine, followed by **method E** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 7.16 – 7.12 (1H, d, $J=7.5$ Hz), 7.02 – 6.99 (3H, m), 5.81 – 5.78 (1H, t, $J=5.6$ Hz), 4.67 (1H, m), 4.52 (1H, m), 4.44 – 4.41 (1H, dd, $J=5.4, 10.6$ Hz), 4.38 – 4.36 (1H, d, $J=5.8$ Hz), 4.27 – 4.22 (1H, dd, $J=5.5, 14.6$ Hz), 3.13 – 3.07 (1H, dt, $J=4.3, 11.2$ Hz), 2.45 – 2.40 (1H, m), 2.40 – 2.37 (1H, d, $J=14.0$ Hz), 2.39 (2H, s), 2.34 – 2.31 (1H, d, $J=14.0$ Hz), 2.27 (3H, s), 1.96 – 1.82 (2H, m), 1.72 – 0.68 (45H, m); LCMS, 100% pure, $R_t = 4.68$; m/z (relative intensity) 703 ($[M+H]^+$ 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-3-chlorobenzylamine amide.



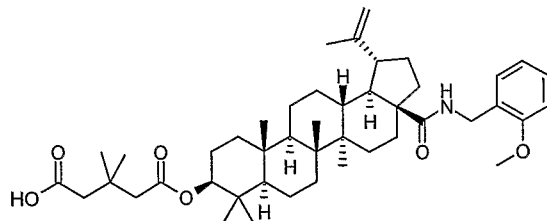
[00291] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 3-chlorobenzylamine, followed by **method E** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 7.19 – 7.16 (3H, m), 7.12 – 7.09 (1H, m), 5.92 – 5.88 (1H, t, $J=5.9$ Hz), 4.67 (1H, m), 4.52 (1H, m), 4.44 – 4.38 (2H, m), 4.26 – 4.21 (1H, dd, $J=5.8, 15.0$ Hz), 3.11 – 3.05 (1H, dt, $J=4.4, 11.2$ Hz), 2.42 – 2.35 (1H, m), 2.40 – 2.38 (1H, d, $J=14.1$ Hz), 2.39 (2H, s), 2.34 – 2.31 (1H, d, $J=14.1$ Hz), 1.91 – 1.83 (2H, m), 1.72 – 0.61 (45H, m); LCMS, 98% pure, $R_t = 4.70$; m/z (relative intensity) 723 ($[M+H]^+$ 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-4-(trifluoromethyl) benzylamine amide.



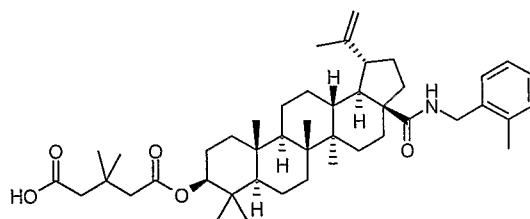
[00292] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 4-trifluoromethylbenzylamine, followed by **method E** deprotection. ¹H NMR (400 MHz, CDCl₃); δ ppm 7.51 -7.48 (2H, d, *J*=8.2 Hz), 7.33 - 7.32 (2H, d, *J*=8.2 Hz), 5.97 - 5.95 (1H, t, *J*=5.9 Hz), 4.75 (1H, m), 4.60 (1H, m), 4.50 - 4.40 (2H, m), 4.35 - 4.30 (1H, dd, *J*=5.8, 15.1 Hz), 3.10 - 3.04 (1H, dt, *J*=4.4, 11.2 Hz), 2.42 - 2.35 (1H, m), 2.42 - 2.37 (1H, d, *J*=13.9 Hz), 2.39 (2H, s), 2.35 - 2.31 (1H, d, *J*=13.9 Hz), 1.90 - 1.84 (2H, m), 1.72 - 0.68 (45H, m); LCMS, 100% pure, *R*_t = 4.70; *m/z* (relative intensity) 757 ([*M*+*H*⁺]100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-2-methoxybenzylamine amide.



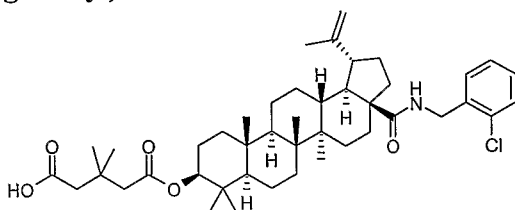
[00293] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2-methoxybenzylamine, followed by **method E** deprotection. ¹H NMR (400 MHz, CDCl₃); δ ppm 7.30 -7.24 (2H, m), 6.92 - 6.88 (1H, dt, *J*=0.9, 7.4 Hz), 6.88 - 6.86 (1H, d, *J*=8.1Hz), 6.21 - 6.18 (1H, t, *J*=5.8 Hz), 4.72 (1H, m), 4.58 (1H, m), 4.53 - 4.45 (2H, m), 4.43 - 4.38 (1H, dd, *J*=6.0, 14.5 Hz), 3.85 (3H, s), 3.12 - 3.05 (1H, dt, *J*=4.5, 11.3 Hz), 2.49 - 2.41 (2H, s), 2.47 - 2.44 (1H, d, *J*=13.8 Hz), 2.40 - 2.37 (1H, d, *J*=13.8 Hz), 2.35 - 2.32 (1H, m), 1.95 - 1.91 (2H, m), 1.76 - 0.66 (45H, m); LCMS, 100% pure, *R*_t = 4.65; *m/z* (relative intensity) 719 ([*M*+*H*⁺]95%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-2-methylbenzylamine amide.



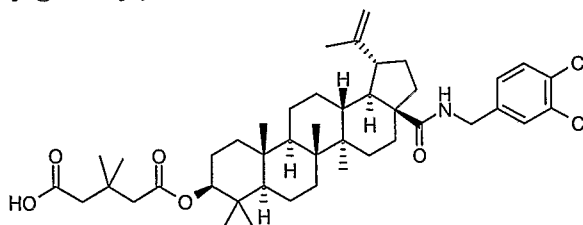
[00294] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2-methylbenzylamine, followed by **method E** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 7.26 -7.14 (4H, m), 5.67 (1H, t, $J=5.3$ Hz), 4.75 (1H, m), 4.60 (1H, m), 4.54 – 4.37 (3H, m), 3.23 – 3.12 (1H, dt, $J=4.5$, 11.3 Hz), 2.57 - 2.37 (5H, m), 2.33 (3H, s), 2.06 – 1.84 (2H, m), 1.76 – 0.66 (45H, m); LCMS, 100% pure, R_f = 4.68; m/z (relative intensity) 703 ($[\text{M}+\text{H}^+]$ 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-2-chlorobenzylamine amide.



[00295] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2-chlorobenzylamine, followed by **method E** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 7.47 -7.41 (1H, m), 7.39 – 7.33 (1H, m), 7.26 – 7.19 (2H, m), 6.16 (1H, t, $J=6.0$ Hz), 4.73 (1H, m), 4.59 (1H, m), 4.58 – 4.39 (3H, m), 3.18 – 3.08 (1H, dt, $J=4.5$, 11.3 Hz), 2.52 - 2.30 (5H, m), 2.00 – 1.86 (2H, m), 1.83 – 0.62 (45H, m); LCMS, 100% pure, R_f = 4.72; m/z (relative intensity) 723 ($[\text{M}+\text{H}^+]$ 100%).

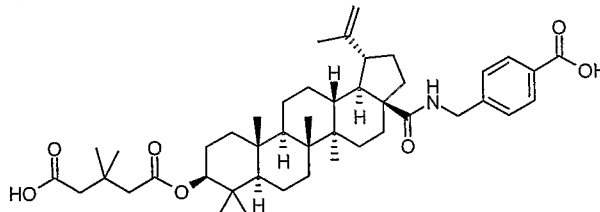
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-3,4-dichlorobenzylamine amide.



[00296] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 3,4-dichlorobenzylamine, followed by **method E** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 7.43 -7.35 (2H, m), 7.14 (1H, dd, $J=2.0$, 8.2 Hz), 6.00 (1H, t, $J=6.0$ Hz), 4.75

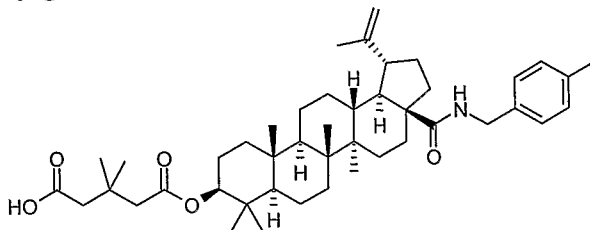
(1H, m), 4.61 (1H, m), 4.55 – 4.41 (2H, m), 4.28 (1H, dd, $J=5.9, 15.4$ Hz), 3.20 – 3.08 (1H, dt, $J=4.5, 11.2$ Hz), 2.53 – 2.36 (5H, m), 2.01 – 1.87 (2H, m), 1.76 – 0.66 (45H, m); LCMS, 94% pure, $R_t=4.79$; m/z (relative intensity) 757 ($[M+H^+]$ 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-4-carboxybenzylamine amide.



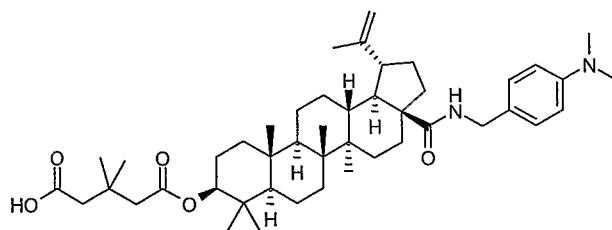
[00297] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with methyl 4-aminomethylbenzoate, followed by **method E** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 8.05 (2H, d, $J=8.4$ Hz), 7.39 (2H, d, $J=8.4$ Hz), 6.09 (1H, t, $J=6.0$ Hz), 4.75 (1H, m), 4.67 (1H, dd, $J=6.4, 15.2$ Hz), 4.61 (1H, m), 4.54 – 4.46 (1H, m), 4.34 (1H, dd, $J=5.3, 15.2$ Hz), 3.21 – 3.12 (1H, dt, $J=4.5, 11.3$ Hz), 2.52 – 2.37 (5H, m), 2.04 – 1.90 (2H, m), 1.84 – 0.71 (46H, m); LCMS, 92% pure, $R_t = 4.28$; m/z (relative intensity) 733 ($[M+H^+]$ 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-4-methylbenzylamine amide.



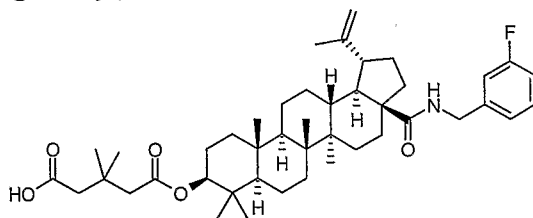
[00298] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 4-methylbenzylamine, followed by **method E** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 7.17 -7.15 (2H, d, $J=8.1$ Hz), 7.14 -7.12 (2H, d, $J=8.1$ Hz), 5.84 (1H, t, $J=5.6$ Hz), 4.74 (1H, m), 4.59 (1H, m), 4.51 – 4.41 (2H, m), 4.35 – 4.30 (1H, dd, $J=5.5, 14.5$ Hz), 3.20 – 3.14 (1H, dt, $J=4.5, 11.3$ Hz), 2.51 – 2.37 (5H, s), 2.33 (3H, s), 2.00 – 1.88 (2H, m), 1.77 – 0.76 (45H, m); LCMS, 100% pure, $R_t = 4.67$; m/z (relative intensity) 703 ($[M+H^+]$ 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-4-(dimethylamino) benzylamine amide.



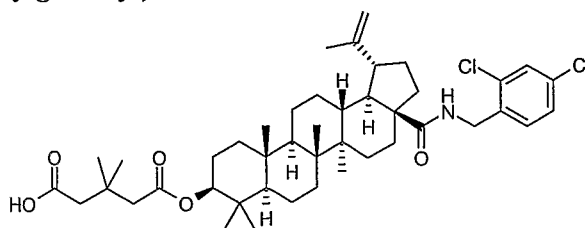
[00299] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 4-(*N,N*-dimethylamino)benzyl amine, followed by **method E** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 7.17 -7.15 (2H, d, $J=8.6$ Hz), 6.77 -6.65 (2H, d, $J=8.6$ Hz), 5.79 (1H, t, $J=5.1$ Hz), 4.74 (1H, m), 4.59 (1H, m), 4.50 - 4.46 (1H, dd, $J=5.5$, 10.2 Hz), 4.39 - 4.34 (1H, dd, $J=5.4$, 14.4 Hz), 4.31 - 4.26 (1H, dd, $J=5.4$, 14.4 Hz), 3.20 - 3.14 (1H, dt, $J=4.6$, 11.4 Hz), 2.95 (6H, s), 2.52 - 2.37 (5H, m), 2.04 - 1.87 (2H, m), 1.77 - 0.75 (45H, m); LCMS, 99% pure, $R_t = 3.92$; m/z (relative intensity) 732 ($[\text{M}+\text{H}^+]$ 100%).

3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-3-fluorobenzylamine amide.



[00300] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 3-fluorobenzylamine, followed by **method E** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 7.30 -7.25 (1H, m), 7.07 - 7.05 (1H, d, $J=7.6$ Hz), 6.99 - 6.92 (2H, m), 6.02 (1H, t, $J=5.8$ Hz), 4.74 (1H, m), 4.59 (1H, m), 4.50 - 4.45 (2H, m), 4.36 - 4.31 (1H, dd, $J=5.8$, 15.0 Hz), 3.18 - 3.11 (1H, dt, $J=4.5$, 11.4 Hz), 2.49 - 2.37 (5H, m), 1.99 - 1.91 (2H, m), 1.79 - 0.75 (45H, m); LCMS, 100% pure, $R_t = 4.59$; m/z (relative intensity) 707 ($[\text{M}+\text{H}^+]$ 100%).

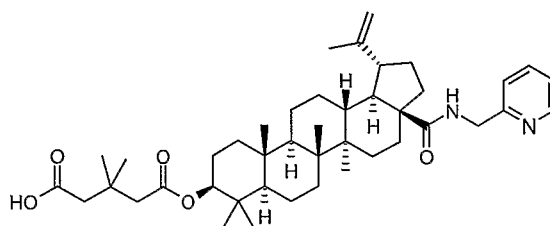
3-*O*-(3',3'-Dimethylglutaryl)betulinic acid *N*-2,4-dichlorobenzylamine amide.



[00301] The compound was synthesized from 3-*O*-(5'-methoxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with 2,4-

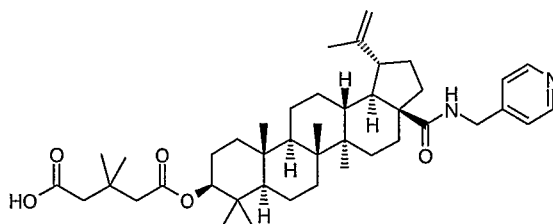
dichlorobenzylamine, followed by **method E** deprotection. ^1H NMR (400 MHz, CDCl_3); δ ppm 7.39 - 7.37 (2H, m), 7.21 - 7.19 (1H, dd, $J=2.1, 8.2$ Hz), 6.15 (1H, t, $J=6.1$ Hz), 4.72 (1H, m), 4.58 (1H, m), 4.52 - 4.46 (2H, m), 4.40 - 4.34 (1H, dd, $J=5.9, 14.5$ Hz), 3.10 (1H, dt, $J=4.6, 11.4$ Hz), 2.47 - 2.30 (5H, m), 1.94 - 1.90 (2H, m), 1.77 - 0.75 (45H, m); LCMS, 100% pure, $R_t = 4.81$; m/z (relative intensity) 758 ($[\text{M}+\text{H}^+]$ 100%).

3-O-(3',3'-Dimethylglutaryl)betulinic acid *N*-(2-pyridylmethyl) amide potassium salt



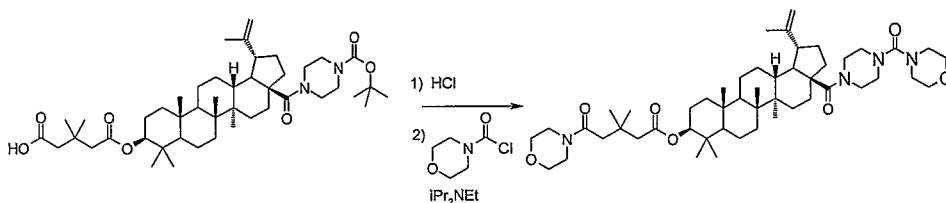
[00302] The compound was synthesized from 3-*O*-acetylbetulinic acid chloride applying **method D** with (2-pyridinylmethyl)amine, followed by **method G** deprotection and **method H** side chain introduction. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.47 (1H, d, $J=4.9$ Hz), 7.79 (1H, td, $J=7.7, 1.7$ Hz), 7.37 (1H, d, $J=7.8$ Hz), 7.26 - 7.33 (1H, m), 4.70 (1H, d, $J=2.0$ Hz), 4.58 (1H, s), 4.34 - 4.53 (3H, m), 3.08 (1H, td, $J=10.8, 4.4$ Hz), 2.36 - 2.58 (3H, m), 2.16 - 2.26 (3H, m), 1.82 - 1.96 (2H, m), 0.77 - 1.77 (45H, m); LCMS, 100% pure, $R_t = 3.95$ min.

3-O-(3',3'-Dimethylglutaryl)betulinic acid *N*-(4-pyridylmethyl) amide potassium salt



[00303] The compound was synthesized from 3-*O*-acetylbetulinic acid chloride applying **method D** with (4-pyridinylmethyl)amine, followed by **method G** deprotection and **method H** side chain introduction. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.36 (2H, d, $J=5.9$ Hz), 7.27 (2H, d, $J=5.9$ Hz), 4.61 (1H, s), 4.49 (1H, s), 4.19 - 4.38 (3H, m), 2.98 (1H, td, $J=10.8, 4.4$ Hz), 2.28 - 2.49 (3H, m), 2.06 - 2.17 (3H, m), 1.70 - 1.85 (3H, m), 0.63 - 1.68 (44H, m).

3-*O*-(3',3'-Dimethyl-5'-(4-morpholinyl)-5'-oxopentanoyl)betulinic acid 1-[4-(4-morpholinylcarbonyl)piperazinyl] amide.

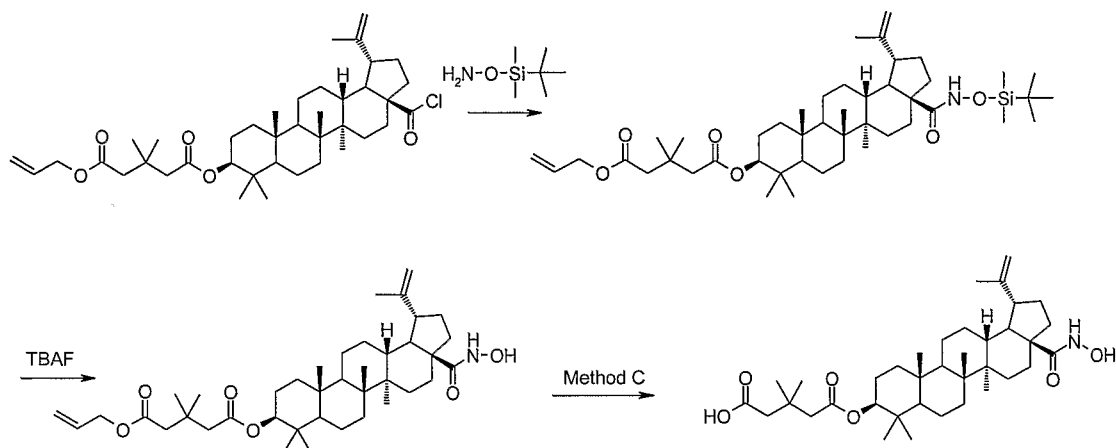


[00304] 4M HCl in dioxane (0.23 mL, 0.47 mmol) was added to a solution of 3-*O*-(3',3'-dimethylglutaryl)betulinic acid 1-[4-(*tert*-butoxycarbonyl)piperazinyl] amide (36 mg, 47 μ mol) in dichloromethane (3 mL) and the reaction mixture was stirred at rt for 3 days. The solvents were removed *in vacuo* to give the HCl salt (34 mg, quantitative) as a white solid which was used as such in the next step.

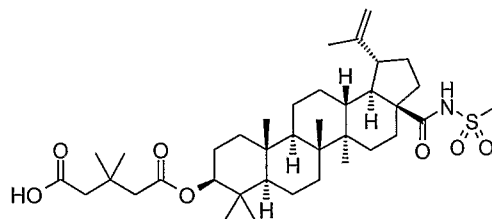
[00305] 4-Morpholinecarbonyl chloride (22 mg, 17 μ l, 0.14 mmol) was added to a solution of HCl salt (34 mg, 47 μ mol) and DIPEA (31 mg, 42 μ l, 0.24 mmol) in dichloromethane (1 mL) at rt. The reaction mixture was stirred at rt overnight then, diluted in EtOAc and washed with 2M HCl (aq). The organic phase was dried (Na₂SO₄) and concentrated *in vacuo* to give the desired title compound (10 mg, 25%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.70 - 2.15 (46H, m), 2.36 - 2.58 (4H, m), 2.91 (2H, d, *J*=45.30 Hz), 3.14 - 3.37 (9H, m), 3.41 - 3.81 (16H, m), 4.37 - 4.51 (1H, m), 4.58 (1H, s), 4.72 (1H, d, *J*=1.9 Hz); LCMS, 97% pure; *R*_f= 4.05; *m/z* (relative intensity) 871 ([M+Na]⁺, 100%).

3-O-(3',3'-Dimethylglutaryl)betulinic acid *N*-hydroxy amide.

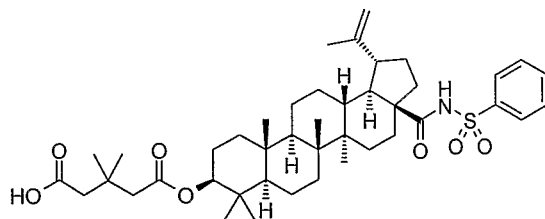
SCHEME 12



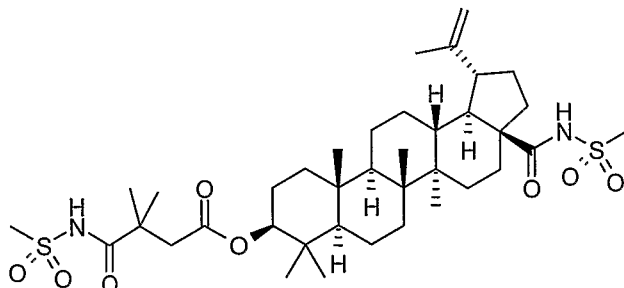
[00306] 3-O-(3',3'-Dimethylglutaryl)betulinic acid *N*-hydroxy amide can be prepared in three steps from 3-O-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride as shown in scheme 12. Coupling of the acid chloride with the silyl ether of hydroxylamine followed by desilylation with tetrabutylammonium fluoride and deallylation using **method C** yields the *N*-hydroxy amide analogue.

3-O-(3',3'-Dimethylglutaryl)betulinic acid *N*-methylsulfonyl amide.

[00307] The compound was synthesized from 3-O-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with methanesulfonamide, followed by **method C** deprotection. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.66 - 1.68 (45H, m), 1.75 - 1.89 (2H, m), 2.07 - 2.19 (2H, m), 2.33 (1H, d), 2.36 - 2.44 (3H, m), 2.92 (1H, dt), 3.60 (3H, s), 4.42 (1H, dd), 4.53 (1H, s), 4.66 (1H, d, $J=2.2$ Hz).

3-O-(3',3'-Dimethylglutaryl)betulinic acid N-phenylsulfonyl amide.

[00308] The compound was synthesized 3-O-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid chloride applying **method D** with benzenesulfonamide followed by **method C** deprotection. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.51 – 2.29 (47H, m), 2.37 - 2.53 (5 H, m), 2.90 (1H, td $J=10.7$, 4.4 Hz), 4.48 (1H, dd, $J=5.9$, 11.5 Hz), 4.55 (1H, s), 4.66 (1H, d, $J=1.7$ Hz), 7.52-7.58 (2H, m), 7.65 (1H, td, $J=6.6$, 1.2 Hz), 8.08-8.04 (2H, m), 8.47 (1H, s).

3-O-(4'-(Methylsulfonylamino)-4-oxo-3',3'-dimethylbutanoyl)betulinic acid N-methylsulfonyl amide.

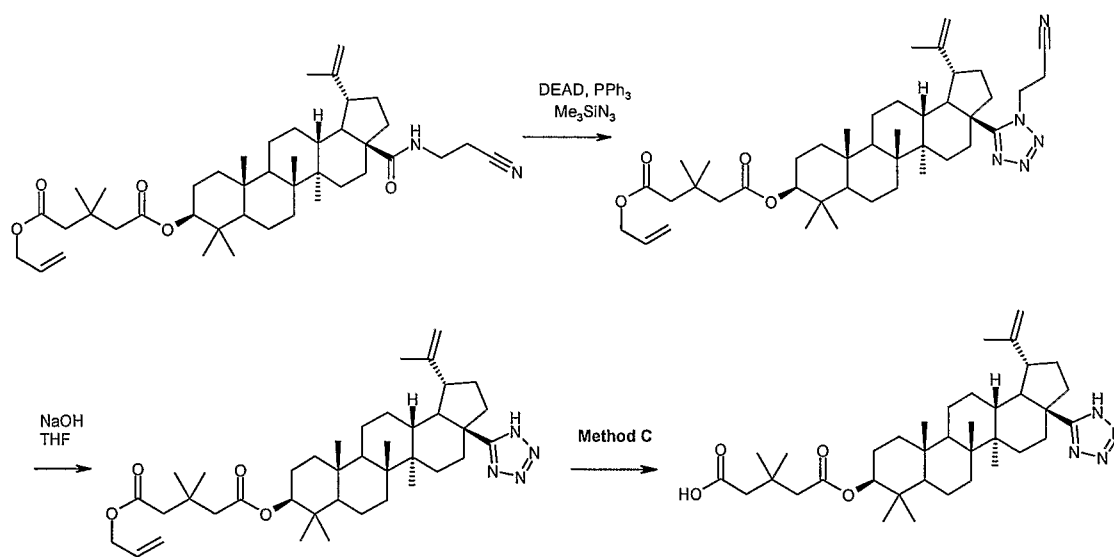
[00309] 3-O-(3',3'-dimethylsuccinyl)betulinic acid was activated as the bis-acid chloride with oxalyl chloride and reacted with an excess of methanesulfonamide. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.53 - 2.02 (47H, m), 2.34 (1H, d, $J=2.9$ Hz), 2.55 (1H, d), 2.64 (1H, d), 2.97 (1H, dt, $J=4.4$ Hz), 3.12 - 3.34 (6H, m), 4.46 (1H, dd, $J=11.2$, 5.4 Hz), 4.55 (1H, s), 4.66 (1H, s), 8.29 (1H, s), 9.31 (1H, s).

EXAMPLE 5

C-28 Heterocyclic Derivatives

[00310] Tetrazole compounds can be prepared in three steps from 3-*O*-(3',3'-dimethylglutaryl)betulinic acid 2-cyanoethylamide as shown in Scheme 13.

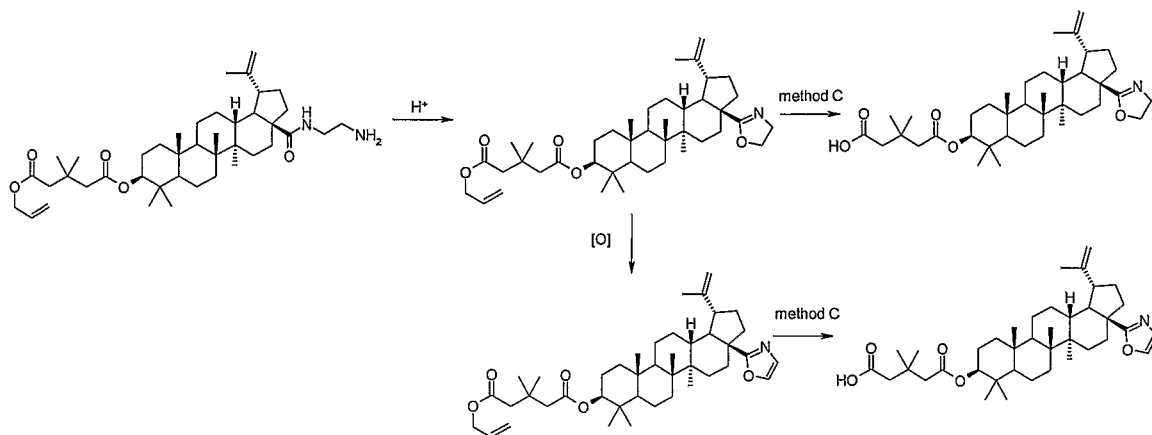
SCHEME 13



[00311] The tetrazole ring can be obtained by reaction of the activated amide with azidotrimethylsilane. Subsequent removal of the 2-cyanoethyl protecting group under basic conditions, followed by deallylation using **method C** affords the desired compound.

[00312] Both oxazoline and oxazole compounds can be prepared in three steps from 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulinic acid 2-aminoethyl amide TFA salt as shown in Scheme 14.

SCHEME 14



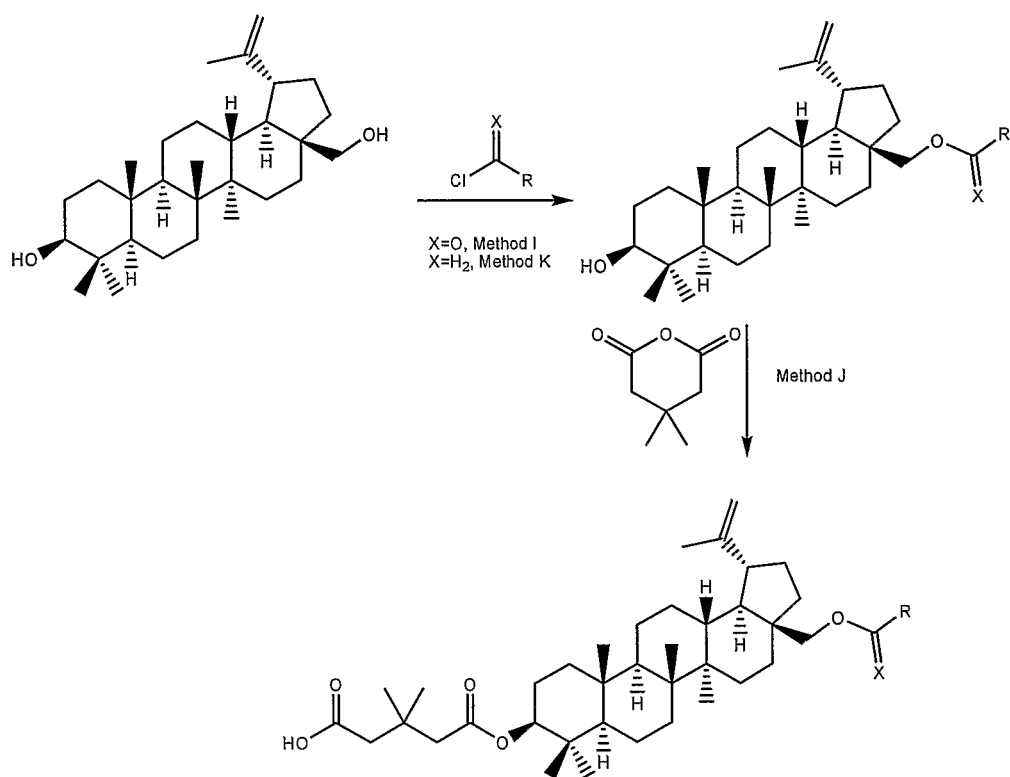
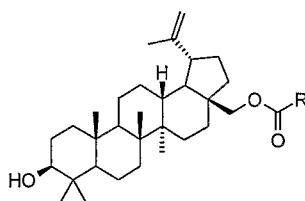
[00313] Acid mediated cyclization of the amine salt affords the oxazoline. Further aromatization with manganese(IV) oxide yields the corresponding oxazole derivative. Both compounds can be deallylated using **method C**.

EXAMPLE 6

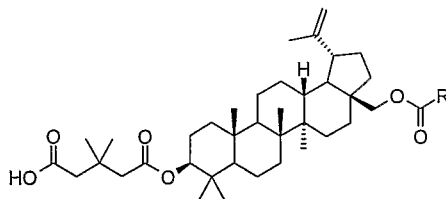
Synthesis of Betulin C-28 *O*-Acyl Derivatives

[00314] Betulin C-28 *O*-acyls were prepared in two steps from betulin as shown in Scheme 15.

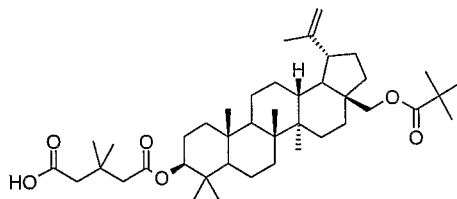
SCHEME 15

**Method I: Ester formation method.**

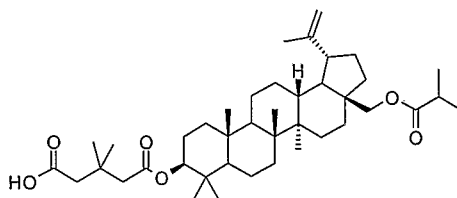
[00315] Betulin 28-*O*-acyl compounds were prepared by adding the desired acid chloride or anhydride (2 equivalents) and DMAP (0.5 equivalents) at 0°C to a solution of betulin (1 equivalent) in dry pyridine. The reaction was stirred at 115°C overnight. The reaction mixture was diluted in EtOAc, washed successively with 1M HCl aqueous solution (3X), water and dried over MgSO₄. The combined organic layers were concentrated to dryness *in vacuo*. Flash column chromatography on silica gel (heptane:EtOAc) provided the desired compound.

Method J: 3',3'-Dimethylglutaric anhydride addition method.

[00316] 3-*O*-(3',3'-Dimethylglutaryl)betulin 28-*O*-acyl compounds were prepared by adding 3,3-dimethylglutaric anhydride (10 equivalents) and DMAP (1 equivalent) to a solution of the desired betulin ester (1 equivalent) in dry pyridine, in presence of activated 4 Å molecular sieves. The reaction was stirred at 115 °C overnight, diluted in EtOAc, washed successively with 1M HCl aqueous solution (2X), water and dried over MgSO₄. The combined organic layers were concentrated to dryness *in vacuo*. Flash column chromatography on silica gel (heptane:EtOAc) provided the desired compound.

3-*O*-(3',3'-Dimethylglutaryl)-28-*O*-(pivaloyl)betulin.

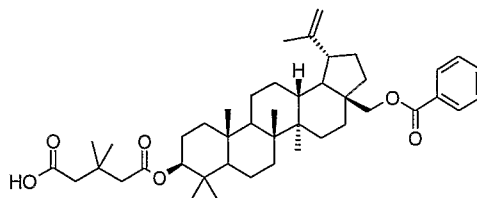
[00317] The compound was synthesized applying **method I** with pivaloyl chloride followed by **method J** glutaric side chain introduction: ¹H NMR (400 MHz, Acetone-d₆) δ ppm 4.62 (1H, d, *J*=2.6 Hz), 4.45 - 4.49 (1H, m), 4.29 - 4.37 (1H, m), 4.23 (1H, dd, *J*=11.2, 1.6 Hz), 3.71 (1H, d, *J*=11.3 Hz), 2.23 - 2.49 (6H, m), 0.66 - 1.97 (56H, m); LCMS, 94% pure; *R*_f= 4.66; *m/z* (relative intensity) 692 ([M+Na]⁺, 100%).

3-*O*-(3',3'-Dimethylglutaryl)-28-*O*-(isobutyryl)betulin.

[00318] The compound was synthesized applying **method I** with isobutyryl chloride followed by **method J** glutaric side chain introduction: ¹H NMR (400 MHz, Acetone-d₆) δ ppm 4.62 (1H, d, *J*=2.2 Hz), 4.47 (1H, s), 4.14 - 4.39 (2H, m), 3.72 (1H, d, *J*=11.0 Hz),

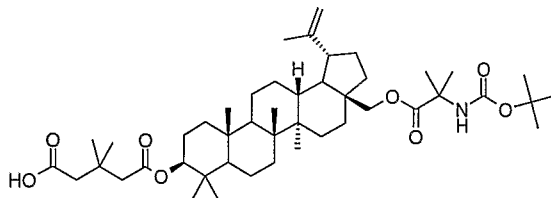
2.20 - 2.54 (6H, m), 1.79 - 2.01 (5H, m), 0.61 - 1.80 (49H, m); LCMS 93% pure; R_f = 4.56; m/z (relative intensity) 677 ($[M+Na]^+$, 100%).

3-O-(3',3'-Dimethylglutaryl)-28-O-(benzoyl)betulin.



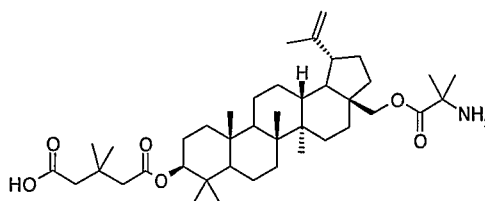
[00319] The compound was synthesized applying **method I** with benzoyl chloride followed by **method J** glutaric side chain introduction: 1H NMR (400 MHz, Acetone- d_6) δ ppm 7.92 (2H, d, J =7.3 Hz), 7.26 - 7.64 (3H, m), 4.18 - 4.79 (4H, m), 3.75 - 4.13 (1H, m), 2.13 - 2.88 (16H, m), 0.36 - 2.13 (37H, m); LCMS, 100% pure; R_f = 5.42; m/z (relative intensity) 752 ($[M+Na^+ + \text{Acetonitrile}]^+$, 100%).

3-O-(3',3'-Dimethylglutaryl)-28-O-((2-*tert*-butoxycarbonylamino)-isobutyryl)betulin.



[00320] The compound can be synthesized applying **method I** with 2-(*tert*-butoxycarbonylamino)isobutyryl chloride followed by **method J** glutaric side chain introduction.

3-O-(3',3'-Dimethylglutaryl)-28-O-(2-aminoisobutyryl)betulin.

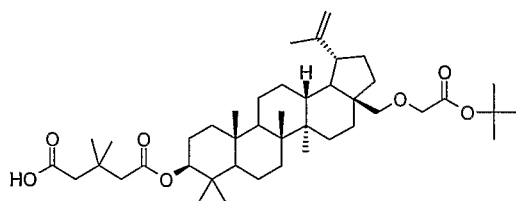


[00321] 3-O-(3',3'-Dimethylglutaryl)-28-O-((2-*tert*-butoxycarbonylamino)-isobutyryl)betulin can be deprotected using **method F**.

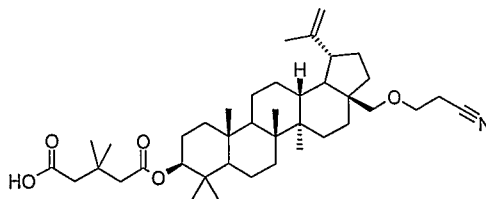
EXAMPLE 7

Synthesis of Betulin C-28 *O*-Ether Compounds**Method K: Synthetic route to C-28 ethers.**

[00322] Betulin C-28 ether compounds can be prepared by adding the desired electrophile (2 equivalents) (e.g. alkyl halide or Michael acceptor) to a solution of betulin (1 equivalent) and DMAP (1.1 equivalents) in DMF. The reaction mixture is heated to reflux. The combined organic layers are concentrated to dryness *in vacuo* and the resulting solid is purified by flash column chromatography on silica gel (hexane:EtOAc) to provide the desired ether.

3-*O*-(3',3'-Dimethylglutaryl)-28-*O*-(2-*tert*-butoxycarbonylmethyl)betulin.

[00323] The compound is synthesized by applying **method K** with *tert*-butyl chloroacetate followed by **method J** glutaric side chain introduction.

3-*O*-(3',3'-Dimethylglutaryl)-28-*O*-(2-cyanoethyl)betulin.

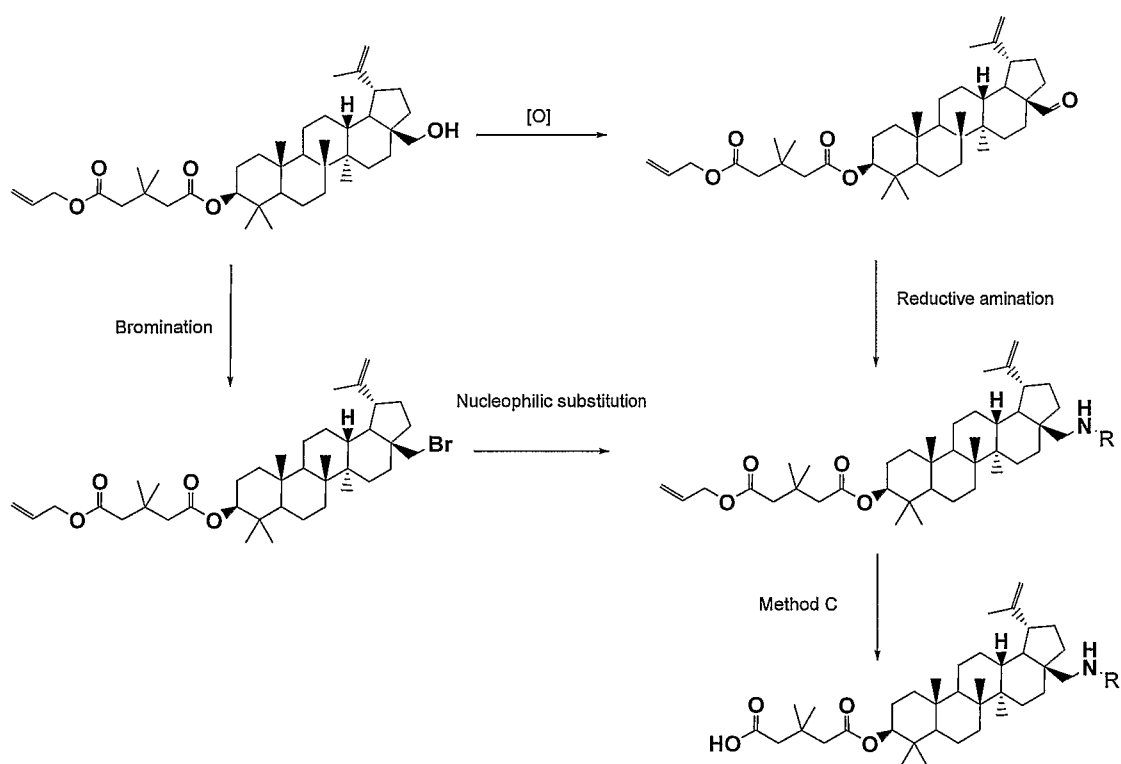
[00324] The compound can be synthesized applying **method K** with acrylonitrile followed by **method J** glutaric side chain introduction.

EXAMPLE 8

Synthesis of C-28 Amines (28-Aminolup-20(29)-enes) from Betulin

[00325] The C-28 amines can be synthesized starting from either betulin or betulinic acid. A method for synthesis of C-28 amines from betulin is shown in Scheme 16.

SCHEME 16



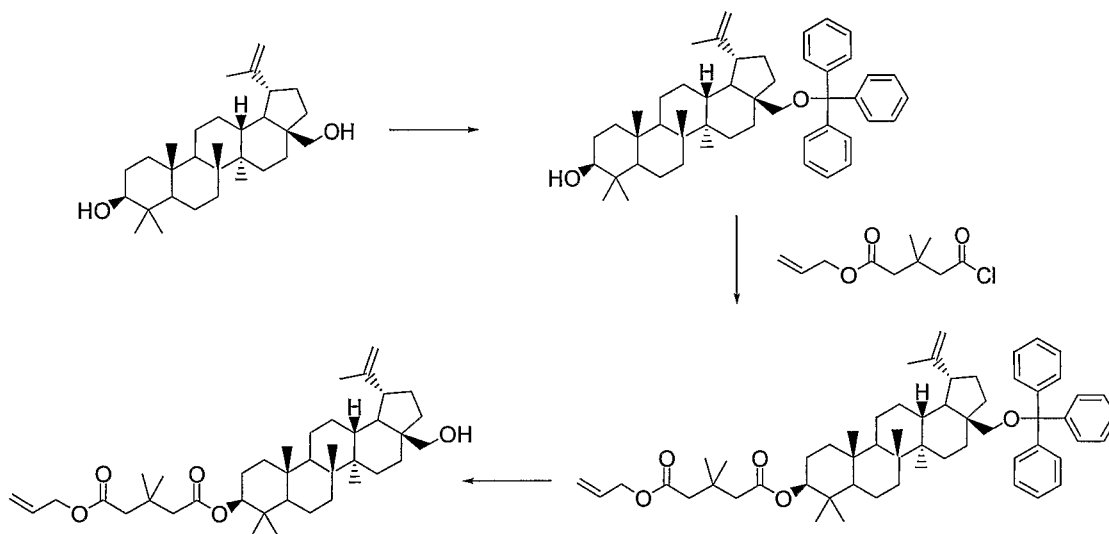
[00326] C-28-Aminolup-20(29)-enes can be prepared from 3-O-(5'-allyloxy-3',3'-dimethylglutaryl)betulin, either via oxidation of the hydroxy group in the C-28 position to the corresponding aldehyde followed by reductive amination, or via conversion of the same hydroxyl group to an alkyl bromide, followed by displacement with a selection of amines.

[00327] 3-O-(5'-Allyloxy-3',3'-dimethylglutaryl)betulin starting material was prepared either via protection of the C-28 hydroxy of betulin with trityl ether, followed by coupling to 5-allyloxy-3,3-dimethylglutaryl chloride and removal of the trityl group (Scheme 17) or by silyl protection of the C-28 hydroxy followed by coupling with allyl 3,3-dimethylglutaryl chloride and desilylation (Scheme 18).

A. Preparation of allyl protected 3-*O*-(3',3'-dimethylglutaryl)betulin: via trityl ether.

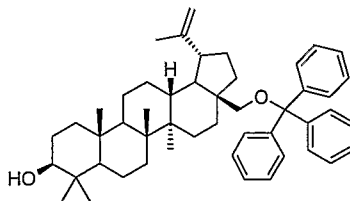
[00328] 3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)betulin was synthesized in three steps from betulin as shown in Scheme 17.

SCHEME 17



[00329] Betulin was selectively trityl protected at the C-28 hydroxy position, then coupled to allyl 3,3-dimethylglutaryl chloride. Treatment with PPTS afforded 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulin.

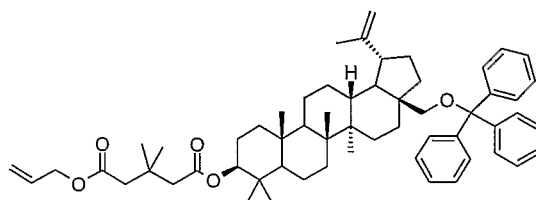
28-*O*-(Trityl)betulin.



[00330] Trityl chloride (2.85 g, 10.0 mmol) and DMAP (0.97 g, 7.7 mmol) were added to a suspension of betulin (3.1 g, 7.0 mmol) in DMF (20 mL). The reaction mixture was heated to reflux for 5.5 hours. The reaction mixture was diluted in EtOAc (200 mL), washed six times with water and dried over Na₂SO₄. The combined organic layers were concentrated to dryness *in vacuo* and the resulting solid was purified by flash column

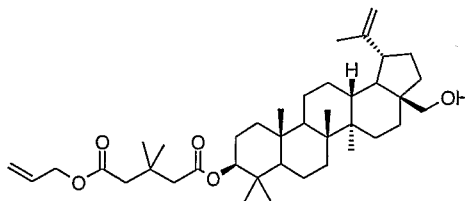
chromatography on silica gel (EtOAc 0 to 20% in Heptane) to provide the desired trityl ether as a white solid (2.0 g, 42%): ^1H NMR (400 MHz, Acetone- d_6) δ ppm 7.81 (3H, s), 7.29 - 7.47 (6H, m), 7.04 - 7.28 (6H, m), 4.34 - 4.48 (2H, m), 3.10 (1H, d, $J=8.8$ Hz), 2.96 (1H, dd, $J=10.2, 5.5$ Hz), 2.82 (1H, d, $J=8.8$ Hz), 2.01 - 2.16 (3H, m), 1.87 - 1.94 (2H, m), 0.41 - 1.68 (38H, m).

3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)-28-*O*-(trityl)betulin.



[00331] Betulin 28-*O*-trityl ether (2.0 g, 2.92 mmol) was added to a solution of allyl 3,3'-dimethylglutaryl chloride (0.66 g, 3.06 mmol) and -DIPEA (1.04 mL, 6.0 mmol) in dry dichloromethane (20 mL) at 0°C. The reaction mixture was stirred at 40°C overnight, diluted in dichloromethane (50 mL), washed three times with 1M Na_2CO_3 , water and dried over MgSO_4 . The combined organic layers were concentrated to dryness *in vacuo*. Flash column chromatography on silica gel (Heptane 95%:EtOAc 5%) provided the desired compound (1.0 g, 39%) as a pale oil: ^1H NMR (400 MHz, Acetone- d_6) δ ppm 7.32 - 7.51 (6H, m, $J=7.0$ Hz), 7.03 - 7.31 (9H, m), 5.72 - 5.91 (1H, m), 4.99 - 5.27 (2H, m), 4.22 - 4.51 (5H, m), 3.10 (1H, d, $J=9.5$ Hz), 2.82 (1H, d, $J=9.1$ Hz), 2.18 - 2.43 (5H, m), 2.00 - 2.16 (3H, m), 0.27 - 2.00 (45H, m); LCMS, 100% pure; $R_f=5.30$; m/z (relative intensity) 890 ($[\text{M}+\text{Na}]^+$, 100%).

3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)betulin.

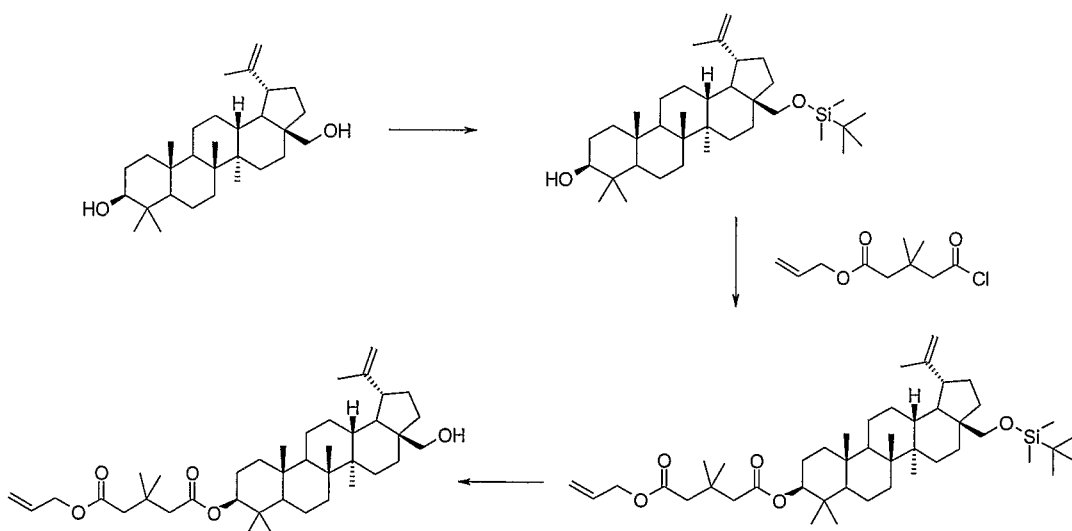


[00332] 3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)betulin 28-*O*-trityl ether (0.98 g, 1.11 mmol) and PPTS (1.53 g, 6.62 mmol) were refluxed overnight in a 2: 1 mixture EtOH/dichloromethane (18 mL). The reaction mixture was concentrated *in vacuo* and the residue partitioned between water and EtOAc. The organic phase was washed twice with

water, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel (EtOAc 0 to 20% in Heptane) provided the desired compound (0.518 g, 75%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ ppm 5.82 - 6.00 (1H, m), 5.17 - 5.38 (2H, m), 4.68 (1 H, d, $J=2.4$ Hz), 4.52 - 4.61 (3H, m), 4.42 - 4.50 (1H, m), 3.80 (1H, d, $J=10.3$ Hz), 3.33 (1H, d, $J=10.8$ Hz), 0.57 - 2.56 (53H, m).

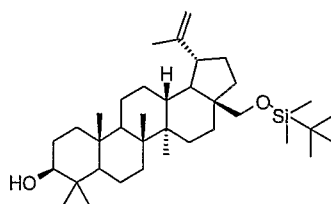
B. Preparation of allyl protected 3-*O*-(3',3'-dimethylglutaryl)betulin: -- via *tert*-butyldimethylsilyl ether.

SCHEME 18



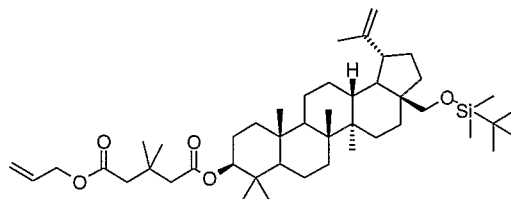
[00333] 3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)betulin was synthesized in three steps from betulin as shown in Scheme 18. Betulin was selectively silyl protected at the C-28 alcohol position, then coupled to allyl 3,3-dimethylglutaryl chloride. Desilylation using tetrabutylammonium fluoride afforded 3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)betulin.

28-*O*-(*tert*-Butyldimethylsilyl)betulin.



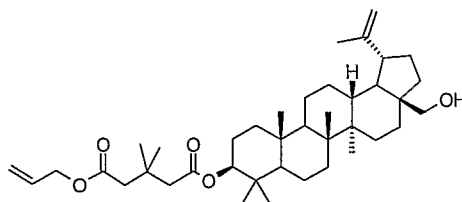
[00334] A solution of *tert*-butyldimethylsilyl chloride (0.79 g, 4.8 mmol) in dry DMF (10 mL) was added to a suspension of betulin (2.0 g, 4.4 mmol) and imidazole (0.4 g, 5.8 mmol) in DMF (20 mL) at 0°C. The reaction mixture was heated at 60°C overnight (became clear solution above 45°C). The reaction mixture was diluted in EtOAc (300 mL), washed three times with saturated NaHCO₃, four times with water, and dried over Na₂SO₄. The combined organic layers were concentrated to dryness *in vacuo* and the resulting solid was purified by flash column chromatography on silica gel (EtOAc 0 to 30% in Heptane) to give the desired TBDMS ether as a white solid (1.8 g, 71%). TLC (30% EtOAc:Heptane) R_f = 0.58, ¹H NMR (400 MHz, CDCl₃) δ ppm 4.63 (1H, d, J =2.4 Hz), 4.53 (1H, s), 3.63 (1H, d, J =9.8 Hz), 3.10 - 3.25 (2H, m), 2.30 - 2.42 (1H, m), 1.80 - 1.96 (4H, m), 0.58 - 1.72 (56H, m).

3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)-28-*O*-(*tert*-butyldimethylsilyl) betulin.



[00335] 28-*O*-(*tert*-Butyldimethylsilyl)betulin ether (1.8 g, 3.2 mmol) was added at 0 °C to a solution of allyl 3,3-dimethylglutaryl chloride (0.98 g, 4.4 mmol) in dry dichloromethane (10 mL) and DIPEA (1.5 mL, 9.0 mmol). The reaction mixture was stirred at 40°C overnight. The reaction was concentrated to dryness *in vacuo* and the crude solid was purified by flash column chromatography on silica gel (heptane 95%:EtOAc 5%) to give the desired compound (0.58 g, 25%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm -0.06 - 0.06 (6H, m), 0.66 - 1.70 (54H, m), 1.73 - 1.99 (3H, m), 2.26 - 2.50 (5H, m), 3.21 (1H, d, J =9.8 Hz), 3.63 (1H, d, J =8.8 Hz), 4.33 - 4.48 (1H, m), 4.49 - 4.68 (4H, m), 5.19 (1H, d, J =11.7 Hz), 5.28 (1H, d, J =17.1 Hz), 5.72 - 6.01 (1H, m).

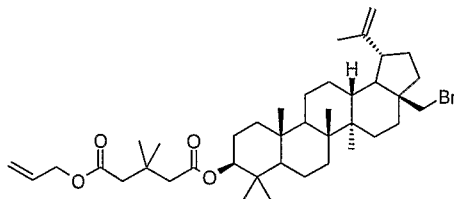
3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)betulin.



[00336] 3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)betulin 28-*O*-TBDMS ether (0.578 g, 0.78 mmol) and tetrabutylammonium fluoride (2.1 mL, 1 M in THF, 2.17 mmol) were stirred overnight in THF (2 mL). The reaction mixture was diluted in EtOAc, and. washed twice with water, dried over Na₂SO₄ and concentrated *in vacuo*. Flash column chromatography on silica gel (EtOAc 0 to 10% in heptane) provided the desired compound (0.402 g, 82%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.71 - 2.04 (49H, m), 2.28 - 2.55 (5H, m), 3.33 (1H, dd, *J*=10.5, 4.2 Hz), 3.80 (1H, dd, *J*=10.5, 3.7 Hz), 4.41 - 4.51 (1H, m), 4.53 - 4.72 (4H, m), 5.23 (1H, d, *J*=10.3 Hz), 5.32 (1H, d, *J*=17.1 Hz), 5.81 - 6.01 (1 H, m).

C. Amine synthesis via nucleophilic substitution.

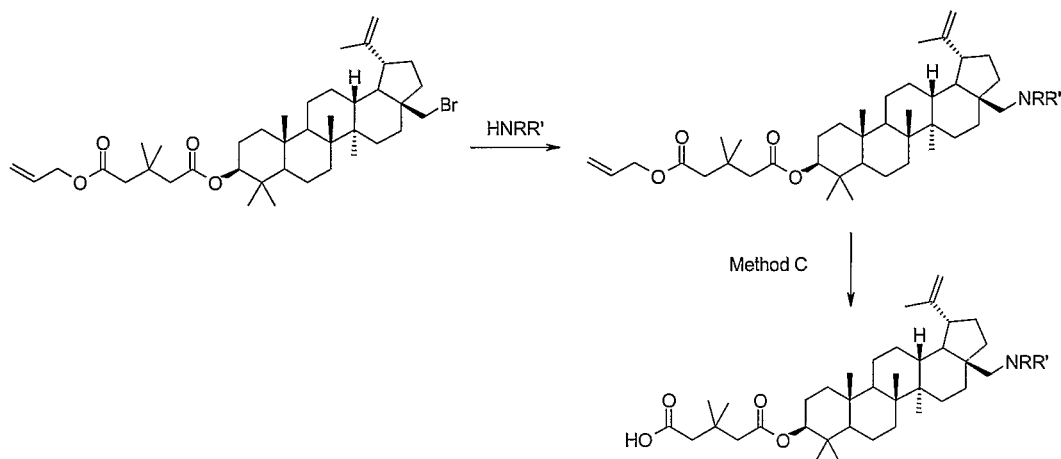
28-Bromo-3-*O*-(5'-allyloxy-3',3'-dimethylglutaryl)lup-20(29)-ene.



[00337] 3-*O*-(5'-Allyloxy-3',3'-dimethylglutaryl)betulin was reacted with triphenylphosphine and carbon tetrabromide to provide the desired halogen derivative.

Method L: Amine introduction via nucleophilic substitution.

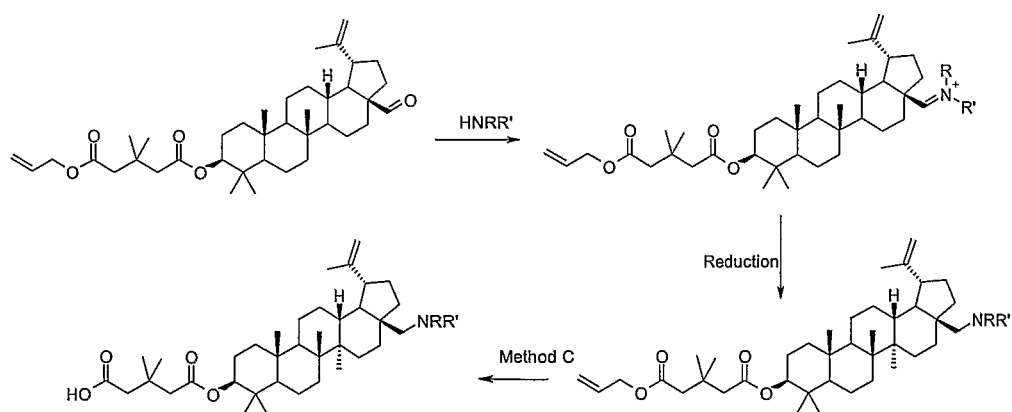
SCHEME 19



[00338] 3-O-(3',3'-Dimethylglutaryl)-28-aminolup-20(29)-enes can be prepared by reacting the desired primary or secondary amine with 28-bromo-3-O-(5'-allyloxy-3',3'-dimethylglutaryl)lupane under standard conditions.

C. Amine synthesis via reductive amination.**Method M: Amine introduction via reductive amination.**

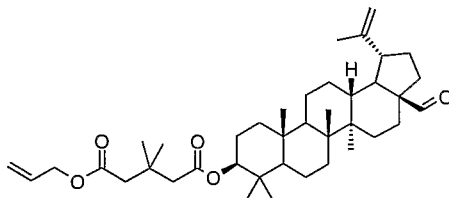
SCHEME 20



[00339] 3-O-(3',3'-Dimethylglutaryl)-28-aminolup-20(29)-enes can be obtained in two steps by reacting the desired primary or secondary amine with 3-O-(5'-allyloxy-3',3'-

dimethylglutaryl)-28-oxolup-20(29)-ene, followed by the reduction of the intermediate imine under standard conditions.

3-O-(5'-Allyloxy-3',3'-dimethylglutaryl)-28-oxolup-20(29)-ene.



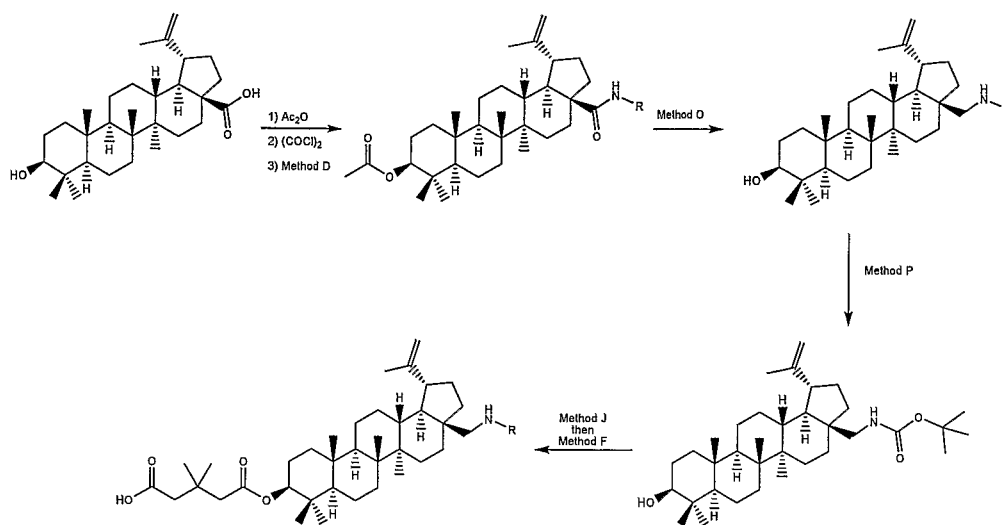
[00340] A solution of 3-O-(5'-allyloxy-3',3'-dimethylglutaryl)betulin (370 mg) in dichloromethane (4 mL) was added to a suspension of Dess-Martin periodinate (290 mg) in dichloromethane (3 mL) and left stirring at rt for three hours. The reaction mixture was washed three times with 1M sodium hydroxide, dried over Na₂SO₄ and concentrated to yield 381 mg of crude 3-O-(5'-allyloxy-3',3'-dimethylglutaryl)-28-oxolup-20(29)-ene. This compound was used without further purification.

EXAMPLE 9

Synthesis of C-28 Amines (28-Aminolup-20(29)-enes) from Betulinic Acid.

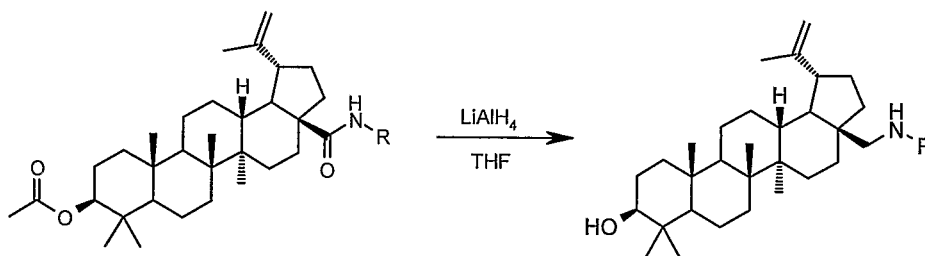
[00341] 3-O-(3',3'-Dimethylglutaryl)-28-aminolup-20(29)-enes can be prepared in six steps from betulinic acid as shown in Scheme 21.

SCHEME 21



[00342] Betulinic acid was converted to the appropriate 3-*O*-acetylbetulinic acid C-28 amide as previously described (Scheme 11). Lithium aluminum hydride (LAH) reduction of the amides to the corresponding amines via **method O** was accompanied by deacetylation. The resulting amino alcohols were selectively *N*-Boc protected using **method P**. Final introduction of the glutaric side chain in the C-3 position using **method J** and then **method F** afforded the 3-*O*-(3',3'-dimethylglutaryl)-28-aminolup-20(29)-enes.

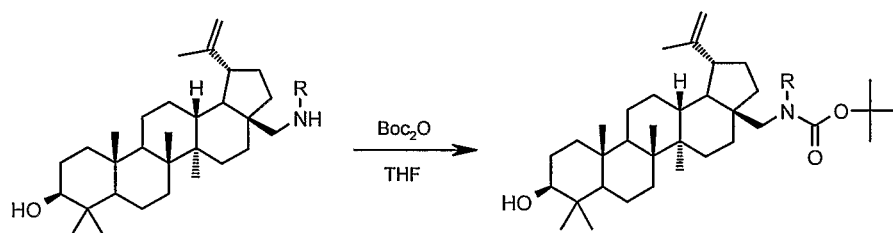
Method O: Reduction of betulinic amides.



[00343] A solution of 3-*O*-(acetyl)betulinic acid amide (1 equivalent) in dry THF was stirred under nitrogen while adding a solution of LAH in THF (1 M in THF, 4 equivalents). The reaction mixture was heated at 45 °C for 16 hours. The reaction was carefully quenched with a solution of K₂CO₃ (1 M) and extracted several times with

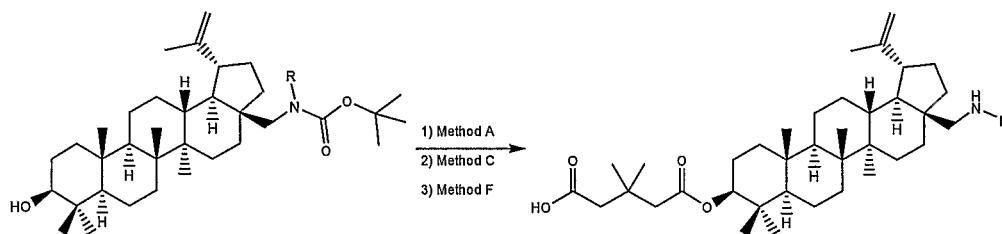
EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to give the desired compound as a white solid which was used without further purification.

Method P: Boc protection of 28-aminolup-20(29)-ene.



[00344] Di-*tert*-butyl dicarbonate (1.1 eq.) was added to a solution of 28-aminolup-20(29)-ene (1 eq.) in dry THF (5 mL) and left stirring at rt for three hours. The reaction mixture was then diluted with methanol and all organic solvents were removed *in vacuo* to yield a crude solid which was used without further purification.

***N*-Alkylated-3-*O*-(3',3'-dimethylglutaryl)-28-aminolup-20(29)-ene derivatives.**



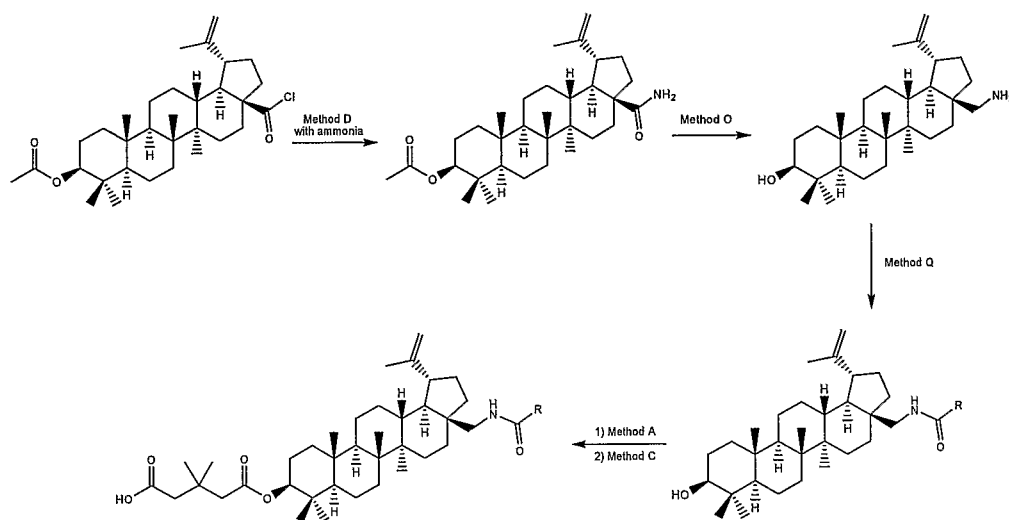
[00345] 3-*O*-(3',3'-Dimethylglutaryl)-28-(*t*-butoxycarbonylamino)lup-20(29)-enes can be prepared applying **method A** (acetylation with allyl 3,3'-dimethylglutaryl chloride) followed by **method C** (de-allylation) and **method F** (Boc deprotection).

EXAMPLE 10

Synthesis of Betulin C-28 Reverse Amides (28-Acylaminolup-20(29)-enes)

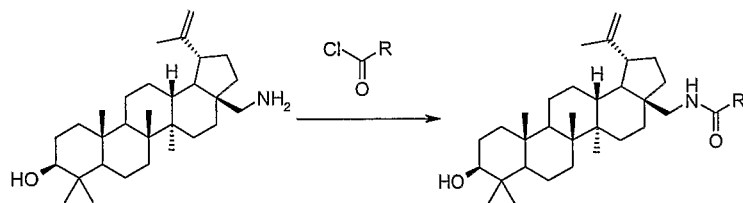
[00346] 3-*O*-(3',3'-Dimethylglutaryl)-28-acylaminolup-20(29)-enes can be prepared in four steps from 3-*O*-(acetyl)betulinic acid as shown in Scheme 22.

SCHEME 22

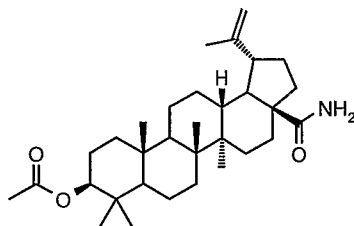


[00347] 3-*O*-Acetylbetulinic acid was converted into the C-28 primary amide using **method D**. Reduction to the amino alcohol using **method O** was followed by selective *N*-acylation using **method Q**. Finally the glutaric side chain can be introduced using **method A** followed by **method C** to yield the desired reverse amide.

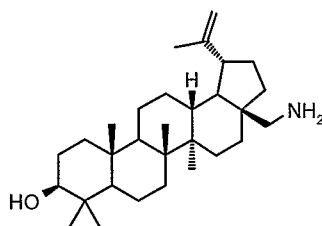
Method Q: Amide coupling.



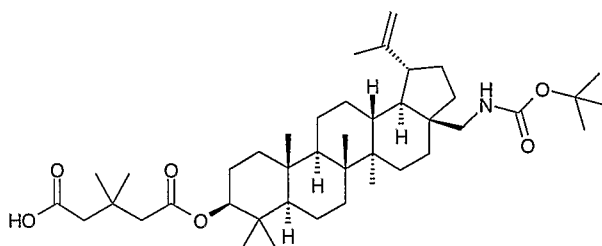
[00348] A solution of the desired acid chloride (2 equivalents) in dichloromethane was added to a solution of 28-aminolup-20(29)-ene (1 equivalent) and DIPEA in dry dichloromethane and the reaction stirred at rt for three hours. Methanol was added and the mixture diluted with dichloromethane and washed twice with 1 M HCl. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo* to give the desired crude product, which can be used without further purification.

3-*O*-Acetylbetulinic acid amide.

[00349] The compound was synthesized from 3-*O*-acetylbetulinic acid applying **method D** with 7 M ammonia in methanol. Purification by flash column chromatography gave the desired compound (230 mg, 43 %). R_f 0.4 (EtOAc:Heptane 38:62).

28-Aminolup-20(29)-ene.

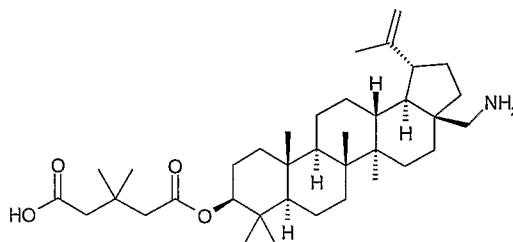
[00350] A solution of LAH in THF (1 M, 2 mL) was added to a solution of 3-*O*-acetylbetulinic acid amide (230 mg, 0.46 mmol) in dry THF (3 mL) and the reaction was stirred at 45 °C for 16 hours. The reaction was carefully quenched with 1 M potassium carbonate, and extracted several times with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give the desired crude 28-aminolup-20(29)-ene (170 mg) which was used without further purification.

***tert*-Butoxycarboxamide *N*-[3-*O*-(3',3'-dimethylglutaryl)lup-20(29)-en-28-yl]**

[00351] 28-Aminolup-20(29)-ene was sequentially *N*-Boc protected using **method P**, acylated with allyl 3,3'-dimethylglutaryl chloride using **method A** and deallylated using

method C. ^1H NMR (400MHz, CDCl_3); δ ppm 4.68 (1H, m), 4.58 (1H, m), 4.52 – 4.47 (1H, dd, $J=4.6, 10.8$ Hz), 4.41 – 4.34 (1H, m), 3.32 – 3.27 (1H, dd, $J=5.4, 13.4$ Hz), 2.97 – 2.92 (1H, dd, $J=6.8, 13.7$ Hz), 2.49– 2.38 (4H, m), 2.07 – 1.97 (1H, m), 1.75 – 0.77 (48H, m); LCMS, 87% pure, $R_t = 5.21$; m/z (relative intensity) 707 ($[\text{M}+\text{Na}^+]$ 55%).

3-*O*-(3',3'-dimethylglutaryl)lup-20(29)-en-28-ylamine

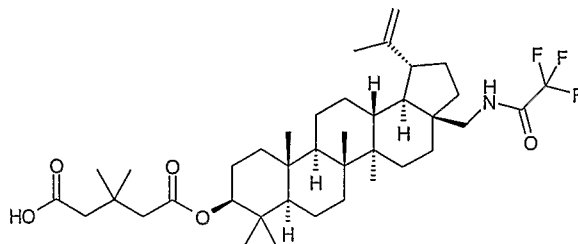


[00352] Trifluoroacetic acid (ca. 10 equivalents) was added to a solution of *tert*-butoxycarboxamide *N*-[3-*O*-(3',3'-dimethylglutaryl)lup-20(29)-en-28-yl] in dichloromethane at 0°C. Cooling was removed and the reaction mixture allowed to warm to rt over 2 hrs. The reaction mixture was concentrated to dryness *in vacuo*, re-diluted in dichloromethane and re-evaporated. Dilution and evaporation was twice repeated. The crude contained two compounds that were separated by flash column chromatography to yield two products:

3-*O*-(3',3'-dimethylglutaryl)lup-20(29)-en-28-ylamine:

[00353] ^1H NMR (250 MHz, CD_3OD); δ ppm 4.66 (1H, m), 4.59 (1H, m), 4.40 – 4.34 (2H, m), 3.08 – 3.02 (1H, m), 2.68 – 2.62 (1H, m), 2.42 – 2.28 (4H, m), 2.04 – 1.85 (1H, m), 1.74 – 0.75 (50H, m); LCMS, 95% pure, $R_t = 4.03$; m/z (relative intensity) 585 ($[\text{M}+\text{H}^+]$ 100%).

Trifluoromethylcarboxamide *N*-[3-*O*-(3',3'-dimethylglutaryl)lup-20(29)-en-28-yl]



[00354] ^1H NMR (250 MHz, CD_3OD); δ ppm 6.15 (1H, br s), 4.71 (1H, m), 4.62 (1H, m), 4.52 – 4.46 (2H, m), 3.67 – 3.59 (1H, dd, $J=6.8, 14.7$ Hz), 3.16 – 3.08 (1H, dd, $J=5.9, 13.6$ Hz), 2.50 – 2.36 (4H, m), 2.10 – 1.93 (1H, m), 1.77 – 0.75 (48H, m); LCMS, 95% pure, $R_t = 4.97$; m/z (relative intensity) 703 ($[\text{M}+\text{Na}^+]$ 100%).

EXAMPLE 11

Pharmacological Activity

[00355] The biological evaluation of HIV-1 inhibition can be carried out as follows according to established protocols (Montefiori, D.C., *et al.*, *Clin. Microbiol.* 26:231-235 (1988); Roehm, N., *et al. J. Immunol. Methods* 142:257-265 (1991)).

[00356] The human T-cell line, MT-2, was maintained in continuous culture with complete medium (RPMI 1640 with 10% fetal calf serum supplemented with L-glutamine at 5% CO_2 and 37°C). Test samples were first dissolved in dimethyl sulfoxide at a concentration of 10 mg/mL to generate master stocks with dilutions made into tissue culture media to generate working stocks. The final drug concentrations used for screening were 25, 2.5, 0.25, and 0.025 $\mu\text{g/mL}$. For agents found to be active, additional dilutions were prepared for subsequent testing so that an accurate EC_{50} value (defined below) could be determined. Test samples were prepared in duplicate (45 μL /well) and to each sample well was added 90 μL of media containing MT-2 cells at 3×10^5 cells/mL and 45 μL of virus inoculum (HIV-1 IIIIB isolate) at a concentration necessary to result in 50% killing of the cell targets at 5 days post-infection (PI). Control wells containing virus and cells only (no drug) and cells only (no virus or drug) were also prepared. A second set of samples were prepared identical to the first and were added to cells under identical conditions without virus (mock infection) for toxicity determinations (IC_{50} defined below). In addition, AZT was also assayed during each experiment as a positive drug control. On day 5 PI, virus-induced cell killing was determined by measuring cell viability using the XTT method (Roehm, N., *et al.*, *supra*). Compound toxicity was determined by XTT using the mock-infected samples. If a test sample had suppressive capability and was not toxic, its effects were reported in the following terms: IC_{50} , the

concentration of test sample which is toxic to 50% of the mock-infected MT-2 cells; EC_{50} , the concentration of the test sample that is able to suppress HIV replication by 50%; and the Therapeutic index (TI) the ratio of the IC_{50} to EC_{50} . The effective (EC_{50}) and inhibitory (IC_{50}) concentrations for anti-HIV activity and cytotoxicity, respectively, were determined (Roehm, N., *et al.*, *supra*).

[00357] The biological evaluation of HIV-1 inhibition for compounds 49, 206, 218, 223, 227, 231, 235, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 291, 293, 297, 301, 309, 311, 315, 319, 321, 325, 329, 333, 337, 341, 345, 349, 353, 357, 361, 365, 369, 373, 377, 381, 409, 413, 429, 437, 441, 445, 449, 453, 457, 461, 465, 469, 473, 477, 481, 485, 493, 501, 505, 509, 672, 674, 676, 687, 689, 693, 697, 701, 705, 709, 717, 721, 725, 805, 821, 825, 829, 833, 837, 841, 845, 849, 853, 913, 1013, 1017, 1065, and 1137 was determined as described above. The anti-HIV activity (EC_{50}) for these compounds ranged from about 0.001 μ M to about 0.30 μ M. The cytotoxicity (IC_{50}) ranged from about 5 μ M to about 100 μ M. All data represented as an average of at least two experiments.

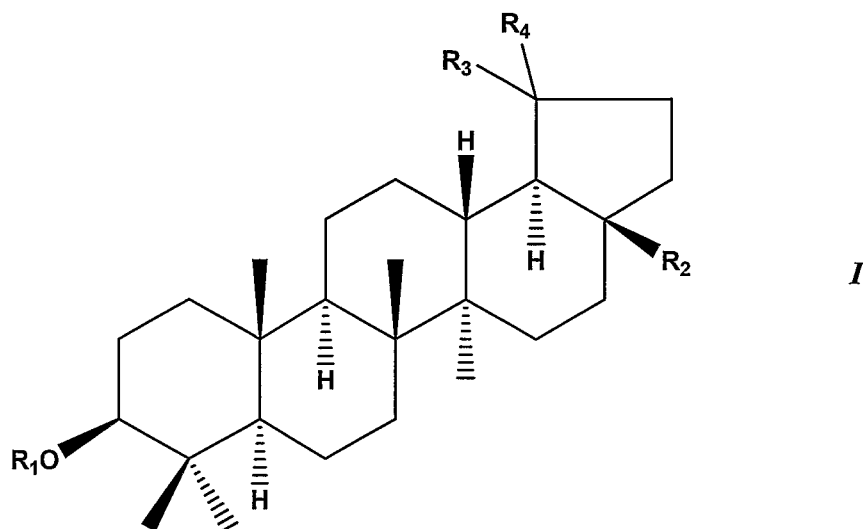
[00358] The following examples are illustrative, but not limiting, of the methods and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

[00359] Those skilled in the art will recognize that while specific embodiments have been illustrated and described, various modifications and changes can be made without departing from the spirit and scope of the invention.

[00360] Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims. All publications, patent applications and patents cited herein are fully incorporated by reference.

WHAT IS CLAIMED IS:

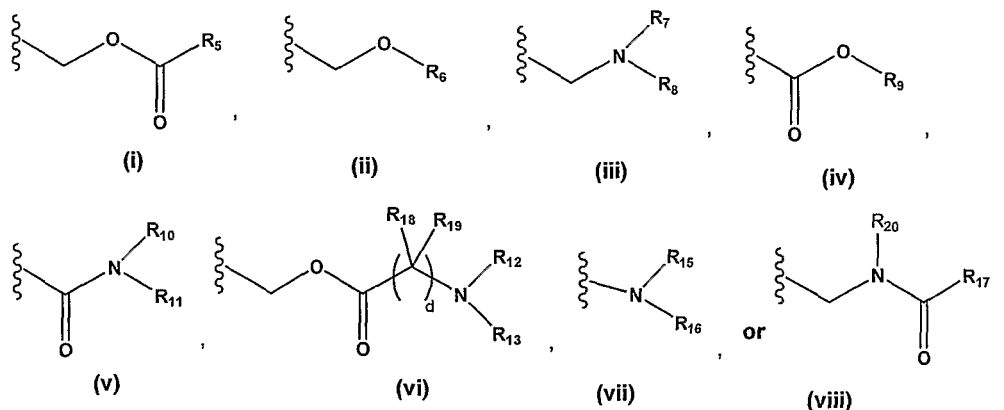
1. A compound of Formula *I*:



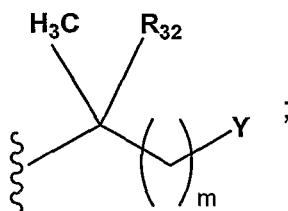
or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R_1 is C_3 - C_{20} alkanoyl, carboxyalkanoyl, carboxyalkenoyl, alkoxycarbonylalkanoyl, alkenyloxycarbonylalkanoyl, cyanoalkanoyl, hydroxyalkanoyl, aminocarbonylalkanoyl, hydroxyaminocarbonylalkanoyl, monoalkylaminocarbonylalkanoyl, dialkylaminocarbonylalkanoyl, heteroarylalkanoyl, heterocyclalkanoyl, heterocycylcarbonylalkanoyl, heteroarylaminocarbonylalkanoyl, heterocyclaminocarbonylalkanoyl, cyanoaminocarbonylalkanoyl, alkylsulfonylaminocarbonylalkanoyl, arylsulfonylaminocarbonylalkanoyl, sulfoaminocarbonylalkanoyl, phosphonoaminocarbonylalkanoyl, phosphono, sulfo, phosphonoalkanoyl, sulfoalkanoyl, alkylsulfonylalkanoyl, or alkylphosphonoalkanoyl;

R_2 is formyl, carboxyalkenyl, heterocyclyl, heteroaryl, $-CH_2SR_{14}$, $-CH_2SOR_{14}$, $-CH_2SO_2R_{14}$,



R_3 is hydrogen, hydroxyl, isopropenyl, isopropyl, 1'-hydroxyisopropyl, 1'-haloisopropyl, 1'-thioisopropyl, 1'-trifluoromethylisopropyl, 2'-hydroxyisopropyl, 2'-haloisopropyl, 2'-thioisopropyl, 2'-trifluoromethylisopropyl, 1'-hydroxyethyl, 1'-(alkoxy)ethyl, 1'-(alkoxyalkoxy)ethyl, 1'-(arylalkoxy)ethyl; 1'-(arylcabonyloxy)ethyl, acetyl, 1'-(hydroxyl)-1'-(hydroxyalkyl)ethyl, (2'-oxo)tetrahydrooxazolyl, 1',2'-epoxyisopropyl, 2'-haloisopropenyl, 2'-hydroxyisopropenyl, 2'-aminoisopropenyl, 2'-thioisopropenyl, 3'-haloisopropenyl, 3'-hydroxyisopropenyl, 3'-aminoisopropenyl, 3'-thioisopropenyl, 1'-alkoxyethyl, 1'-hydroxyiminoethyl, 1'-alkoxyimino, or



wherein Y is ---SR_{33} or $\text{---NR}_{33}\text{R}_{34}$;

R_{32} is hydrogen or hydroxy;

R_{33} and R_{34} are independently hydrogen, alkyl, alkanoyl, arylalkyl, heteroarylalkyl, arylsulfonyl or arylaminocarbonyl; or

R_{33} and R_{34} can be taken together with the nitrogen to which they are attached to form a heterocycle, wherein the heterocycle can optionally include one or more additional nitrogen, sulfur or oxygen atoms;

m is zero to three;

R_4 is hydrogen; or

R_3 and R_4 can be taken together to form oxo, alkylimino, alkoxyimino or benzyloxyimino;

R₅ is C₂-C₂₀ alkyl, alkenyl, alkynyl, carboxy(C₂-C₂₀)alkyl, amino, aminoalkyl, dialkylamino, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, cyanoalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl, sulfo, phosphono, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, alkanoylaminoalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, heterocyclalkylcarbonylalkyl, cycloalkylcarbonylalkyl, heteroarylalkylaminocarbonylalkyl, arylalkylaminocarbonylalkyl, heterocyclalkylaminocarbonylalkyl, carboxyalkylaminocarbonylalkyl, arylsulfonylaminocarbonylalkyl, alkylsulfonylaminocarbonylalkyl, arylphosphonoaminocarbonylalkyl, alkylphosphonoaminocarbonylalkyl, or hydroxyimino(amino)alkyl;

R₆ is hydrogen, phosphono, sulfo, alkyl, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, carboxyalkyl, alkoxycarbonylalkyl, cyanoalkyl; CH₂CONR₇R₈, trialkylsilyl, ethoxyethyl, or tetrahydropyranyl ether;

R₇ and R₈ are independently hydrogen, alkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxyalkyl, alkoxyalkoxyalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclalkyl, aryl, arylalkyl, arylcarbonylaminoalkyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, or cycloalkyl, or R₇ and R₈ can together with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl group, wherein the heterocyclyl or heteroaryl can optionally include one or more additional nitrogen, sulfur or oxygen atoms;

R₉ is hydrogen, phosphono, sulfo, alkyl, alkenyl, trialkylsilyl, cycloalkyl, carboxyalkyl, alkoxycarbonyloxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, cyanoalkyl, phosphonoalkyl, sulfoalkyl, alkylsulfonyl, alkylphosphono, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, heterocyclalkyl, or dialkoxyalkyl;

R₁₀ and R₁₁ are independently hydrogen, alkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, alkoxyalkoxyalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkyl, hydroxyalkoxyalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroarylalkyl, arylalkyl, arylcarbonylaminoalkyl,

alkylsulfonyl, arylsulfonyl, alkylsulfonylaminoalkyl, arylsulfonylaminoalkyl, or cycloalkyl, or alkyl interrupted by one or more oxygen atoms, or R₁₀ and R₁₁ can together with the nitrogen atom to which they are attached form a heterocyclyl group, wherein the heterocyclyl can optionally include one or more additional nitrogen, sulfur or oxygen atoms;

R₁₂ and R₁₃ are independently hydrogen, alkyl, alkenyl, alkylamino, alkynyl, alkoxy, alkoxycarbonyl, alkoxyaminoalkyl, cycloalkyloxy, heterocyclylaminoalkyl, cycloalkyl, cyanoalkyl, cyano, sulfo, phosphono, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, alkoxyalkyl, heteroaryl, heteroarylalkyl, dialkylaminoalkyl, heterocyclylalkyl, or R₁₂ and R₁₃ can together with the nitrogen atom to which they are attached form a heterocyclyl group or a heteroaryl group, wherein the heterocyclyl or heteroaryl can optionally include one or more additional nitrogen, sulfur or oxygen atoms, or R₁₂ and R₁₃ can together with the nitrogen atom to which they are attached form an alkylazo group, and d is one to six;

R₁₄ is hydrogen, alkyl, alkenyl, arylalkyl, carboxyalkyl, carboxyalkenyl, alkoxycarbonylalkyl, alkenyloxycarbonylalkyl, cyanoalkyl, hydroxyalkyl, carboxybenzyl, aminocarbonylalkyl;

R₁₅ and R₁₆ are independently hydrogen, alkyl, alkoxycarbonyl, alkoxyaminoalkyl, cyclo(oxo)alkyl, cycloalkylcarbonyl, heterocyclylaminoalkyl, cycloalkyl, cyanoalkyl, cyano, sulfo, phosphono, sulfoalkyl, phosphonoalkyl, alkylsulfonyl, alkylphosphono, alkoxyalkyl, heterocyclylalkyl, or R₁₅ and R₁₆ can together with the nitrogen atom to which they are attached form a heterocyclyl group, wherein the heterocyclyl can optionally include one or more additional nitrogen, sulfur or oxygen atoms, or R₁₅ and R₁₆ can together with the nitrogen atom to which they are attached form an alkylazo group;

R₁₇ is hydrogen, alkyl, perhaloalkyl, alkoxy, alkenyl, carboxyalkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, alkoxycarbonyl, cyanoalkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, alkanoylaminoalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, heterocyclylcarbonylalkyl, cycloalkylcarbonylalkyl, heteroarylalkylaminocarbonylalkyl, arylalkylaminocarbonylalkyl, heterocyclylalkylaminocarbonylalkyl, carboxyalkylaminocarbonylalkyl, arylsulfonylaminocarbonylalkyl, alkylsulfonylaminocarbonylalkyl, or hydroxyimino(amino)alkyl;

R_{18} and R_{19} are independently hydrogen, methyl or ethyl; d is one to six; and

R_{20} is hydrogen, C_1 - C_6 alkyl, or aryl;

wherein any alkyl, aryl, cycloalkyl, heterocyclyl, or heteroaryl group, or any substituent which includes any of these groups, is optionally substituted;

when R_1 is C_3 - C_{20} alkanoyl, carboxyalkanoyl or alkoxyalkanoyl, and R_3 is isopropenyl, isopropyl, 2'-hydroxyisopropyl, 2'-haloisopropyl, or 2'-thioisopropyl, and R_2 is formula (i), formula (ii) or formula (iv), then R_5 cannot be C_2 - C_{20} alkyl or carboxy(C_2 - C_{20})alkyl, or R_6 cannot be hydrogen or carboxyalkyl, or R_9 cannot be hydrogen;

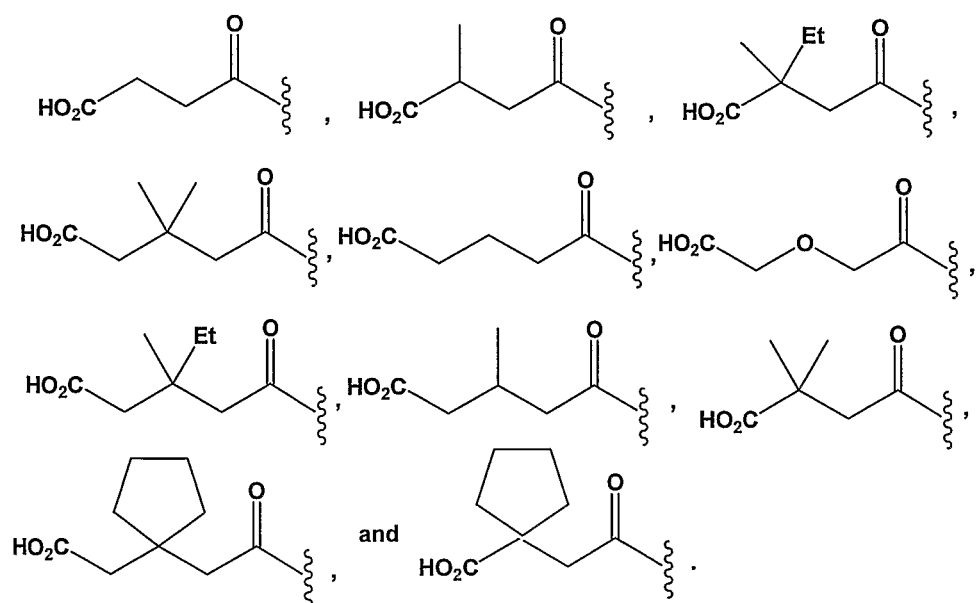
when R_1 is carboxyalkanoyl, and R_3 is isopropenyl, isopropyl, isobutyl, isobutenyl, or 2'-hydroxyisopropyl, and R_2 is formula (ii), formula (iv) or formula (v), then R_6 cannot be alkyl, R_9 cannot be alkyl or carboxyalkyl, and R_{10} and R_{11} cannot be carboxyalkyl;

when R_1 is carboxyalkenoyl, R_2 is formula (ii), and R_3 is isopropenyl, then R_6 cannot be hydrogen; and

when R_1 is 3',3'-dimethylsuccinyl, R_2 is formula (iv), and R_9 is hydrogen, then R_3 cannot be 1'-hydroxyethyl, 1'-(oxo)ethyl or 1'-(alkoxy)ethyl.

2. A compound according to claim 1, wherein R_1 is carboxyalkanoyl.

3. A compound according to claim 2, wherein R_1 is a carboxyalkanoyl selected from the group consisting of



4. A compound according to claim 3, wherein R_1 is a carboxyalkanoyl, wherein said carboxyalkanoyl is succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl, or 3',3'-dimethylglutaryl.
5. A compound according to claim 1, wherein R_1 is alkenyloxycarbonylalkanoyl, wherein said alkenyloxycarbonylalkanoyl is a C_1 - C_4 alkene ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl.
6. A compound according to claim 5, wherein the C_1 - C_4 alkene ester is an allyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl.
7. A compound according to claim 1, wherein R_1 is alkoxycarbonylalkanoyl, wherein said alkoxycarbonylalkanoyl is a C_1 - C_4 alkyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl.
8. A compound according to claim 7, wherein the C_1 - C_4 alkyl ester is an ethyl or propyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl.
9. A compound according to claim 1, wherein R_1 is alkanoyl, wherein said alkanoyl is *tert*-butylcarbonyl or isopropylcarbonyl.
10. A compound according to claim 1, wherein R_1 is carboxyalkanoyl, wherein said carboxyalkanoyl is 2',2'-dimethylmalonyl, 2',3'-dihydroxysuccinyl, 2',2',3',3'-tetramethylsuccinyl, 3'-methylsuccinyl, or 2',2'-dimethylsuccinyl.
11. A compound according to claim 1, wherein R_1 is carboxyalkenoyl, wherein said carboxyalkenoyl is alk-2-enoyl.
12. A compound according to claim 1, wherein R_1 is cyanoalkanoyl, wherein said cyanoalkanoyl is 4'-cyanopropanoyl or 4'-cyanobutanoyl.
13. A compound according to claim 1, wherein R_1 is hydroxyalkanoyl, wherein said hydroxyalkanoyl is 3',3'-dimethyl-4'-hydroxybutanoyl.

14. A compound according to claim 1, wherein R_1 is aminocarbonylalkanoyl, wherein said aminocarbonylalkanoyl is 4'-amino-3',3'-dimethylsuccinyl or 4'-aminosuccinyl.
15. A compound according to claim 1, wherein R_1 is alkylsulfonylaminocarbonylalkanoyl, wherein said alkylsulfonylaminocarbonylalkanoyl is 4'-methylsulfonylamino-3',3'-dimethylsuccinyl.
16. A compound according to claim 1, wherein R_1 is arylsulfonylaminocarbonylalkanoyl, wherein said arylsulfonylaminocarbonylalkanoyl is 4'-phenylsulfonylamino-3',3'-dimethylsuccinyl.
17. A compound according to claim 1, wherein R_1 is heterocycloalkanoyl, wherein said heteroarylalkanoyl is tetrazolylalkanoyl.
18. A compound according to claim 1, wherein R_1 is phosphonoalkyl, wherein said phosphonoalkyl is C_1 - C_6 phosphonoalkyl.
19. A compound according to claim 1, wherein R_1 is sulfoalkyl, wherein said sulfoalkyl is C_1 - C_6 sulfoalkyl.
20. A compound of claim 1, wherein R_2 is heterocyclyl, and said heterocyclyl is selected from the group consisting of oxazolyl, morpholinyl, piperidinyl, piperazinyl, dihydropyrrolyl, piperidinyl, and dihydrofuranyl.
21. A compound of any one of claims 1-19, wherein R_2 is (i) and R_5 is alkyl, wherein said alkyl is selected from the group consisting of C_1 - C_6 alkyl.
22. A compound of any one of claims 1-19, wherein R_2 is (i) and R_5 is alkenyl, wherein said alkenyl is selected from the group consisting of propen-2-yl, buten-2-yl, and penten-2-yl.
23. A compound of any one of claims 1-19, wherein R_2 is (i) and R_5 is C_2 - C_{10} carboxyalkyl, wherein said C_2 - C_{10} carboxyalkyl is 2'-carboxy-2',2'-dimethylethyl or 3'-carboxy-3',3'-dimethylpropyl.

24. A compound of any one of claims 1-19, wherein R₂ is (i) and R₅ is heterocyclyl, or heterocyclylalkyl.
25. A compound of claim 24, wherein said heterocyclyl is tetrazolyl, morpholinyl, pyridinyl, imidazolyl, isoxazolyl, or furanyl.
26. A compound of claim 24, wherein said heterocycloalkyl is a heterocyclo(C₁-C₆)alkyl.
27. A compound of claim 1, wherein R₂ is (ii) and R₆ is cycloalkyl or heterocycloalkyl.
28. A compound of claim 1, wherein R₂ is (ii) and R₆ is methylpyridinyl or cycloocten-2-yl.
29. A compound of claim 1, wherein R₂ is (ii) and R₆ is carboxyalkyl.
30. A compound of claim 1, wherein R₂ is (ii) and R₆ is alkoxycarbonylalkyl.
31. A compound of claim 1, wherein R₂ is (ii) and R₆ is cyanoalkyl.
32. A compound of claim 1, wherein R₂ is (iii) and R₇ and R₈ are independently alkoxyalkylamine or hydrogen.
33. A compound of claim 1, wherein R₂ is (iii) and R₇ and R₈ together with the nitrogen atom to which they are attached form a heterocyclyl group, wherein the heterocyclyl group can optionally include one or more additional nitrogen, sulfur or oxygen groups.
34. A compound of claim 33, wherein said heterocyclyl group is pyrrolyl, morpholinyl, or piperazinyl.
35. A compound of any one of claims 1-19, wherein R₂ is (v) and R₁₀ and R₁₁ are both hydrogen.
36. A compound of any one of claims 1-19, wherein R₂ is (v) and R₁₀ and R₁₁ are independently alkyl, aminoalkyl, aminoalkoxyalkyl, alkoxycarbonylamino, alkoxycarbonylalkyl, cyanoalkyl, alkylsulfonyl, alkoxyalkyl, cycloalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, alkylcarbonylaminoalkyl, alkoxyalkoxyalkyl, or dialkylaminoalkyl.

37. The compound of claim 36, wherein R_2 is (v), one of R_{10} and R_{11} is hydrogen, and one of R_{10} and R_{11} is alkyl, wherein the alkyl group is selected from methyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl, propyl, ethyl, isopropyl, (R)-2-[2,3-dihydroxypropyl], (S)-2-[2,3-dihydroxypropyl], (S)-2-[1-hydroxy-4-methylpentyl], (R)-2-[1-hydroxy-4-methylpentyl], or (S)-1-carboxy-3-methylbutyl.
38. The compound of claim 36, wherein R_2 is (v), one of R_{10} and R_{11} is hydrogen, and one of R_{10} and R_{11} is aminoalkyl, wherein the aminoalkyl is 2-(1-amino-2-methylpropyl).
39. The compound of claim 36, wherein R_2 is (v), one of R_{10} and R_{11} is hydrogen, and one of R_{10} and R_{11} is alkoxyalkyl, wherein the alkoxyalkyl group is 2-methoxyethyl or 2-hydroxyethoxyethyl.
40. The compound of claim 36, wherein R_2 is (v), one of R_{10} and R_{11} is hydrogen, and one of R_{10} and R_{11} is alkoxycarbonylaminoalkyl, wherein the alkoxycarbonylaminoalkyl group is 2-(*tert*-butoxycarbonylamino)ethyl.
41. The compound of claim 36, wherein R_2 is (v), one of R_{10} and R_{11} is hydrogen, and one of R_{10} and R_{11} is dialkylaminoalkyl, wherein the dialkylaminoalkyl group is 2-*N,N*-dimethylaminoethyl, 2-*N,N*-dimethylaminopropyl, (1R, 3R)-3-*N,N*-dimethylaminocyclopentyl, or (1S, 3S)-3-*N,N*-dimethylaminocyclopentyl.
42. A compound of any one of claims 1-19, wherein R_2 is (v) and one of R_{10} and R_{11} is hydrogen, and one of R_{10} and R_{11} is cycloalkyl, heterocyclyl, aryl, arylalkyl, arylcarbonylaminoalkyl, arylsulfonyl, heterocyclylheterocyclylalkyl, heterocyclylarylalkyl, arylaminoalkyl, aminocycloalkyl, or heterocycloalkyl.
43. The compound of claim 42, wherein R_2 is (v), one of R_{10} and R_{11} is hydrogen, and one of R_{10} and R_{11} is cycloalkyl, wherein the cycloalkyl group is cyclopropyl.
44. The compound of claim 42, wherein R_2 is (v), one of R_{10} and R_{11} is hydrogen, and one of R_{10} and R_{11} is heterocyclyl, wherein the heterocyclyl group is selected from (S)-1-[(*tert*-butoxycarbonyl)pyrrolidinyl], (R)-1-[(*tert*-butoxycarbonyl)pyrrolidinyl], (S)-3-pyrrolidinyl, (R)-3-pyrrolidinyl, (S)-3-(1-methylpyrrolidinyl), (R)-3-(1-

- methypyrrolidinyl), (S)-3-(1-acetylpyrrolidinyl), (R)-3-(1-acetylpyrrolidinyl), (S)-3-(1-methylsulfonylpyrrolidinyl), (R)-3-(1-methylsulfonylpyrrolidinyl), 4-(1-(*tert*-butoxycarbonyl)piperidinyl), 4-piperidinyl, 4-(1-methylpiperidinyl), or 4-[1-(1-hydroxyethyl)piperidinyl)].
45. The compound of claim 42, wherein R₂ is (v), one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is aryl, wherein the aryl group is 4-fluorophenyl, 2-(1,3,4-thiadiazolyl)methyl, or 2,3-dichlorobenzyl, 4-azido-2,3,5,6-tetrafluorobenzyl.
46. The compound of claim 42, wherein R₂ is (v), one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is arylalkyl, wherein the arylalkyl group is selected from 4-fluorobenzyl, 3-fluorobenzyl, 2-fluorobenzyl, 4-chlorobenzyl, 3-chlorobenzyl, 2-chlorobenzyl, 4-methylbenzyl, 3-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 3-methoxybenzyl, 2-methoxybenzyl, 4-*N,N*-dimethylaminobenzyl, 4-trifluoromethylbenzyl, 4-carboxybenzyl, 3,4-dichlorobenzyl, 2,4-dichlorobenzyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-benzyl, 3-trifluoromethylbenzyl, 4-*tert*-butylbenzyl, 4-aminobenzyl, 4-acetamidobenzyl, (R)-1-phenylethyl, (S)-1-phenylethyl, (R)-2-hydroxy-1-phenylethyl, (S)-2-hydroxy-1-phenylethyl, or 2-phenylethyl.
47. The compound of claim 42, wherein R₂ is (v), one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ is heterocycloalkyl, wherein the heterocycloalkyl group is selected from 4-(1-methylimidazolyl)methyl, 3-(5-methylisoxazolyl)methyl, 3-(4-morpholinyl)propyl, 3-(1-imidazolyl)propyl, 2-(4-methylmorpholinyl)methyl, 2-morpholinylmethyl, or 2-(4-*tert*-butoxycarbonyl morpholinyl)methyl.
48. The compound of claim 42, wherein R₂ is (v), one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ heterocyclarylalkyl, wherein the heterocyclarylalkyl group is selected from 4-(4-morpholinyl)benzyl or 4-(4-methylpiperazinyl)benzyl.
49. The compound of claim 42, wherein R₂ is (v), one of R₁₀ and R₁₁ is hydrogen, and one of R₁₀ and R₁₁ heterocyclheterocyclalkyl, wherein the heterocyclheterocyclalkyl group is 3-[6-(4-morpholinyl)pyridinyl]methyl.

50. The compound of claim 42, wherein R_2 is (v), one of R_{10} and R_{11} is hydrogen, and one of R_{10} and R_{11} arylaminoalkyl, wherein the arylaminoalkyl is 2-[(4-azido-2,3,5,6-tetrafluorobenzoyl)amino]ethyl.
51. The compound of claim 42, wherein R_2 is (v), one of R_{10} and R_{11} is hydrogen, and one of R_{10} and R_{11} aminocycloalkyl, wherein the aminocycloalkyl is (1R, 3R)-3-aminocyclopentyl, (1S, 3S)-3-aminocyclopentyl, (1r, 4r)-4-aminocyclohexyl, or (1s, 4s)-4-aminocyclohexyl.
52. The compound of claim 42, wherein R_2 is (v), one of R_{10} and R_{11} is hydrogen, and one of R_{10} and R_{11} dialkylaminocycloalkyl, wherein the dialkylaminocycloalkyl is (1r, 4r)-4-*N,N*-dimethylaminocyclohexyl or (1s, 4s)-4-*N,N*-dimethylaminocyclohexyl.
53. A compound of any one of claims 1-19, wherein R_2 is (v) and R_{10} and R_{11} are taken together to form a heterocyclyl group, wherein said heterocyclyl group can optionally include one or more additional nitrogen, sulfur or oxygen atoms.
54. The compound of any one of claims 1-19, wherein R_2 is (v) and R_{10} and R_{11} are taken together to form one of 4-(*tert*-butoxycarbonyl)piperazinyl, morpholinyl, piperidinyl, piperazinyl,
4-(4-morpholinylcarbonyl)piperazinyl, 4-methylpiperazinyl,
4-ethylpiperazinyl, 4-isopropylpiperazinyl,
4-(cyclopropylmethyl)piperazinyl, 4-benzylpiperazinyl,
4-[3-(5-methylisoxazolyl)methyl]piperazinyl,
4-(4-pyridinylmethyl)piperazinyl, 4-acetyl piperazinyl,
4-(isopropylaminocarbonyl)piperazinyl,
4-(methylsulfonyl)piperazinyl, 4-cyclopropylpiperazinyl,
4-(2-methoxyethylaminocarbonyl)piperazinyl,
4-(2-hydroxyethyl)piperazinyl, 4-(2-methoxyethyl)piperazinyl,
4-(3-dimethylaminopropyl)piperazinyl, 4-(aminocarbonyl)piperazinyl, 4-(aminosulfonyl)piperazinyl, 3-oxopiperazinyl,
4-methyl-3-oxopiperazinyl, 4-(hydroxyethyl)-3-oxopiperazinyl,

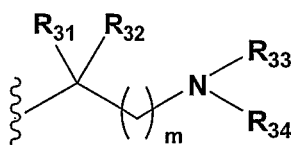
4-(2-hydroxybenzoyl)piperazinyl,
4-[3-(1,2,4-oxadiazolyl)methyl]piperazinyl,
4-[4-(dimethylaminosulfonyl)benzyl]piperazinyl,
4-[1-(1,2,3,4-tetrahydronaphthyl)]piperazinyl,
4-[4-(acetamidobenzyl)]piperazinyl,
(1S, 4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptanyl,
(1R, 4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptanyl,
(1S, 4S)-2,5-diazabicyclo[2.2.1]heptanyl,
(1R, 4R)-2,5-diazabicyclo[2.2.1]heptanyl,
(1S, 4S)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl,
(1R, 4R)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanyl,
4-(4-azido-2,3,5,6-tetrafluorobenzyl)piperazinyl, pyrrolidinyl,
(R,S)-3-hydroxypyrrolidinyl, (R)- 3-hydroxypyrrolidinyl,
(S)- 3-hydroxypyrrolidinyl,
(R)-3-(*tert*-butoxycarbonylamino)pyrrolidinyl,
(S)-3-(*tert*-butoxycarbonylamino)pyrrolidinyl,
(R)- 3-aminopyrrolidinyl, (S)- 3-aminopyrrolidinyl,
(R)- 2-(hydroxymethyl)pyrrolidinyl,
(S)- 2-(hydroxymethyl)pyrrolidinyl,
(S)- 2-(hydroxymethyl)pyrrolidinyl,
(S)- 2-(hydroxymethyl)pyrrolidinyl,
(S)- 2-(hydroxymethyl)pyrrolidinyl,
(R)- 3-*N*-methylaminopyrrolidinyl, (S)- 3-*N*-methylaminopyrrolidinyl,
(R)- 3-*N,N*-dimethylaminopyrrolidinyl,
(S)- 3-*N,N*-dimethylaminopyrrolidinyl,
(R)- 3-*N,N*-diethylaminopyrrolidinyl,
(S)- 3-*N,N*-diethylaminopyrrolidinyl, (R)- 3-*N*-ethylaminopyrrolidinyl,
(S)- 3-*N*-ethylaminopyrrolidinyl, (R)- 3-(4-morpholinyl)pyrrolidinyl,
(S)- 3-(4-morpholinyl)pyrrolidinyl, (R)- 3-(1-pyrrolidinyl)pyrrolidinyl,
(S)- 3-(1-pyrrolidinyl)pyrrolidinyl, 4-aminopiperidinyl,
4-oxopiperidinyl, 4-hydroxypiperidinyl, 4-*N,N*-diaminopiperidinyl,

4-(4-morpholinyl)piperidinyl, 4-acetamidopiperidinyl,
4-(methylsulfonamide)piperidinyl, (R)- 3-acetamidopyrrolidinyl,
(S)- 3-acetamidopyrrolidinyl,
(R)- 3-(cyclopropanecarboxamido)pyrrolidinyl,
(S)- 3-(cyclopropanecarboxamido)pyrrolidinyl,
(R)- 3-(2-hydroxyacetamido)pyrrolidinyl,
(S)- 3-(2-hydroxyacetamido)pyrrolidinyl,
(R)- 3-(methylsulfonamido)pyrrolidinyl,
(S)- 3-(methylsulfonamido)pyrrolidinyl,
(R)- 2-(aminomethyl)pyrrolidinyl, (S)- 2-(aminomethyl)pyrrolidinyl,
(R)- 2-(*N,N*-dimethylaminomethyl)pyrrolidinyl,
(S)- 2-(*N,N*-dimethylaminomethyl)pyrrolidinyl,
(R)- 2-(acetamidomethyl)pyrrolidinyl,
(S)- 2-(acetamidomethyl)pyrrolidinyl,
(R)- 2-(methylsulfonamidomethyl)pyrrolidinyl,
(S)- 2-(methylsulfonamidomethyl)pyrrolidinyl,
(R)- 2-(*N,N*-diethylaminomethyl)pyrrolidinyl,
(S)- 2-(*N,N*-diethylaminomethyl)pyrrolidinyl,
(R)- 2-(4-morpholinylmethyl)pyrrolidinyl,
(S)- 2-(4-morpholinylmethyl)pyrrolidinyl,
2,6-dimethylmorpholinyl, 1,4-oxazepanyl, thiomorpholinyl,
thiomorpholinyl 1-oxide, or thiomorpholinyl 1,1-dioxide.

55. A compound of claim 1, wherein R₂ is (vi) and R₁₂ and R₁₃ are hydrogen.
56. A compound of claim 1, wherein R₂ is (vi) and one of R₁₂ and R₁₃ are hydrogen and one of R₁₂ and R₁₃ is alkylamino, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, cycloalkyl, cycloalkyloxy, heteroaryl, heteroarylalkyl, dialkylaminoalkyl, or cyanoalkyl.
57. A compound of claim 1, wherein R₂ is (vi) and R₁₂ and R₁₃ can together with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl, wherein the

heterocyclyl or heteroaryl group can optionally include one or more additional nitrogen, sulfur or oxygen atoms.

58. A compound according to claim 1, wherein R_3 is hydroxyl, isopropenyl, isopropyl, 1'-hydroxyisopropyl, 1'-haloisopropyl, 1'-thioisopropyl, 1'-trifluoromethylisopropyl, 2'-hydroxyisopropyl, 2'-haloisopropyl, 2'-thioisopropyl, 2'-trifluoromethylisopropyl, 1'-hydroxyethyl, 1'-(alkoxy)ethyl, 1'-(alkoxyalkoxy)ethyl, 1'-(arylalkoxy)ethyl; 1'-(arylcarbonyloxy)ethyl, acetyl, 1'-(hydroxyl)-1'-(hydroxyalkyl)ethyl, (2'-oxo)tetrahydrooxazolyl, or 1',2'-epoxyisopropyl.
59. A compound according to claim 1, wherein R_4 is hydrogen, R_3 is



R_{31} is hydrogen, R_{32} is methyl, R_{33} and R_{34} are independently hydrogen, alkyl, alkanoyl, arylalkyl, heteroarylalkyl, arylsulfonyl or arylaminocarbonyl; or R_{33} and R_{34} can be taken together with the nitrogen to which they are attached to form heterocyclyl, wherein the heterocyclyl can optionally include one or more additional nitrogen, sulfur or oxygen atoms; and m is zero to three.

60. A compound according to claim 1, wherein R_2 is (i), and R_3 is isopropenyl.
61. A compound according to claim 1, wherein R_2 is (ii), and R_3 is isopropenyl.
62. A compound according to claim 1, wherein R_2 is (iii), and R_3 is isopropenyl.
63. A compound according to claim 1, wherein R_2 is (iv), and R_3 is isopropenyl.
64. A compound according to claim 1, wherein R_2 is (v), and R_3 is isopropenyl.
65. A compound according to claim 1, wherein

R₁ is succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl, or an alkyl or allyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl;

R₂ is (i), (ii) or (iv); and

R₃ is isopropenyl.

66. A compound according to claim 56, wherein R₂ is (i), and R₅ is a heteroarylalkyl.

67. A compound according to claim 56, wherein R₂ is (ii), and R₆ is a heteroaryl.

68. A compound according to claim 56, wherein R₂ is (iv), and R₉ is cyanoalkyl.

69. A compound according to claim 1, wherein

R₁ is succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl, or an alkyl or allyl ester of succinyl, glutaryl, 3'-methylglutaryl, 3'-methylsuccinyl, 3',3'-dimethylsuccinyl or 3',3'-dimethylglutaryl;

R₂ is (iii), (v) or (vi); and

R₃ is isopropenyl.

70. A compound according to claim 69, wherein R₂ is (iii), and R₇ and R₈ taken together with the nitrogen to which they are attached to form a heterocycloalkyl or heteroaryl.

71. A compound according to claim 69, wherein R₂ is (v), and R₁₀ and R₁₁ taken together with the nitrogen to which they are attached to form a heterocycloalkyl or heteroaryl.

72. A compound according to claim 69, wherein R₂ is (vi), and R₁₂ and R₁₃ taken together with the nitrogen to which they are attached to form a heterocycloalkyl or heteroaryl.

73. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier.

74. A pharmaceutical composition according to claim 73, further comprising an antiviral agent or an immunostimulating agent.

75. A pharmaceutical composition according to claim 74, wherein said antiviral agent is selected from the group consisting of one or more of zidovudine, lamivudine, zalcitabine, stavudine, didanosine, tenofovir, abacavir, nevirapine, delavirdine, emtricitabine, efavirenz, saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, amprenavir, fosamprenavir, tipranavir, atazanavir, enfuvirtide, hydroxyurea, interleukin-2, gamma globulin, amantadine, guanidine hydroxybenzimidazole, interferon- α , interferon- β , interferon- γ , a thiosemicarbazone, methisazone, rifampin, ribavirin, a pyrimidine analog, a purine analog, foscarnet, phosphonoacetic acid, acyclovir, a dideoxynucleoside, and ganciclovir.
76. A method of synthesizing a compound of Formula I wherein R_2 is formula (v), comprising
- (a) forming a monoprotected di-carboxylic acid derivative;
 - (b) activating the non-protected carboxyl group of the di-carboxylic acid to form an acid halide;
 - (c) reacting the acid halide of step (b) with betulinic acid to form the R_1 group at the C-3 position;
 - (d) activating the C-28 position of the compound of (c) to form an acid halide;
 - (e) attaching the desired amine at C-28; and
 - (f) deprotecting the protected R_1 carboxyl group of (a).
77. A method of synthesizing a compound of Formula I wherein R_2 is formula (v), comprising:
- (a) protecting a C-3 alcohol of betulinic acid;
 - (b) activating the C-3 protected betulinic acid at the C-28 carbon to form a C-3 protected, C-28 activated betulinic acid;
 - (c) the resulting compound of (b) reacting the C-3 protected, C-28 activated betulinic acid with an appropriated amine;
 - (d) deprotecting the the resulting compound of step (c) at its C-3 position and (e) adding an R_1 ester group at C-3.

78. A method for inhibiting a retroviral infection in cells or tissue of an animal comprising administering an effective retroviral inhibiting amount of a pharmaceutical composition according to claim 57.
79. A method according to claim 78, wherein said retroviral infection does not respond to other therapies.
80. A method for inhibiting a retroviral infection in cells or tissue of an animal comprising administering an effective retroviral inhibiting amount of a pharmaceutical composition according to claim 75.
81. A method according to claim 80, wherein said retroviral infection does not respond to other therapies.
82. The method according to claim 65, wherein said composition is administered to provide said compound in an amount ranging from about 0.1 mg/kg to about 100 mg/kg body weight.
83. The method according to claim 74, wherein said composition is administered to provide said compound in an amount ranging from about 1 mg/kg to about 50 mg/kg body weight.
84. The method according to claim 75, wherein said animal is a human.
85. A method of inhibiting a retroviral infection by contacting a cell with a compound of claim 1.
86. A method of preventing transmission of HIV infection from an HIV infected pregnant woman to a fetus, comprising administering to said woman and/or said fetus a retroviral inhibiting effective amount of a compound of claim 1 during pregnancy or immediately prior to, at, or subsequent to birth.
87. A method of preventing transmission of HIV infection during sexual intercourse, comprising applying a retroviral inhibiting effective amount of one or more compounds of claim 1 to vaginal or other mucosa prior to sexual intercourse.