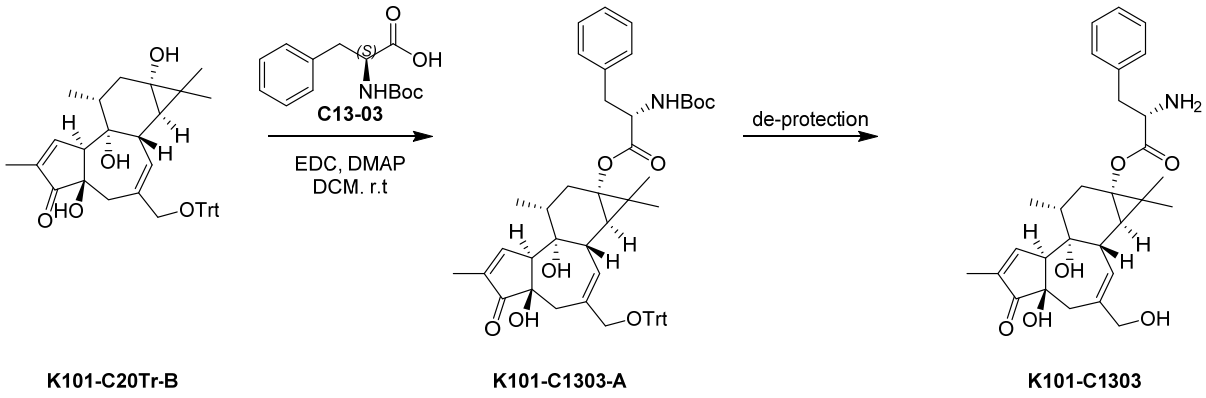
(eluting with: PE/EtOAc=2/1) to give **K101-C1302-A** (34.00 mg, 42.45 μmol, 53.72% yield, 98.736% purity) as a white solid.

[0388] Preparation of compound **K101-C1302**. To a solution of **K101-C1302-A** (28.00 mg, 35.40 μmol, 1.00 eq) in MeOH (1.00 mL) was added $HClO_4$ (464.95 mg, 4.63 mmol, 280.09 uL, 130.73 eq). The mixture was stirred at 0°C for 0.5 hour to give a yellow solution. LC-MS showed the reaction was complete. The reaction mixture was combined with a second preparation of the compound and purified by prep-HPLC (column: Waters XSELECT C18 150 x 30mm x 5um; mobile phase: [A: water (0.1%TFA)-B: B: ACN]; B%: 33%-63%, 10 min) to give **K101-C1302** (10.60 mg, 18.56 μmol, 52.42% yield, 96.032% purity) as a white solid.

[0389] LC-MS (m/z): 571.3 $[M+Na]^+$

[0390] ^1H NMR (400MHz, CD_3OD) δ 7.58-7.52 (m, 2H), 7.43-7.41 (m, 2H), 5.55 (s, 1H), 3.95-3.87 (m, 2H), 3.29-2.99 (m, 4H), 2.72-2.68 (m, 2H), 2.47-2.37 (m, 2H), 2.05-1.96 (m, 2H), 1.72 (s, 3H), 1.43-1.40 (m, 1H), 1.01 (s, 6H), 0.85-0.83 (m, 3H), 0.75-0.73 (m, 3H).

Example 5: Synthesis Scheme of K101-C1303



[0391] Preparation of Compound **K101-C1303-A**: To a solution of **K101-C20Tr-B** (30.00 mg, 50.78 μmol, 1.00 eq) in DCM (2.00 mL) were added (2S)-2-(tert-butoxycarbonylamino)-3-phenyl-propanoic acid (C13-03) (26.95 mg, 101.57 μmol, 2.00 eq), DMAP (24.82 mg, 203.13 μmol, 4.00 eq) and EDC (19.47 mg, 101.57 μmol, 2.00 eq). The mixture was stirred at 20°C for 48 hours to give a yellow solution. LC-MS and TLC (eluting with: PE/EtOAc=2/1) showed the reaction was complete. The reaction mixture was quenched with saturated $NaHCO_3$ (5 mL) and extracted with DCM (10 mL*3). The organic layers were dried over Na_2SO_4 and concentrated to give the crude product. The crude product was purified by prep-TLC (eluting with: PE/EtOAc=2/1) to give **K101-C1303-A** (30.00 mg, 34.85 μmol, 68.63% yield, 97.349% purity) as a white solid.

[0392] ^1H NMR (400MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.37-7.35 (m, 5H), 7.24-7.22 (m, 8H), 7.17-7.12 (m, 7H), 5.54 (s, 1H), 5.04 (m, 1H), 4.87-4.85 (m, 1H), 4.49 (m, 1H), 3.18 (s, 1H), 3.02 (m, 1H), 2.83

CLAIMS

What is claimed is:

1. Use of a PKC activating compound in the manufacture of a medicament for stimulating an immune response in a subject in need thereof.

2. The use of claim 1, wherein the immune response is against a cancer or cancer antigen, a precancerous lesion or growth, or a benign tumor in a subject in need thereof.

3. The use of claim 2,

wherein the compound is to be administered locally to a first cancer locus or mass or site, a first precancerous lesion or growth, or a first locus or mass of benign tumor; or

wherein the compound is to be administered locally to the first cancer locus or mass or site intratumorally or the first precancerous lesion or growth, or the first locus or mass of benign tumor.

4. The use of claim 3, wherein the first cancer locus or mass or site or first precancerous lesion or growth is skin cancer or a first precancerous cutaneous lesion, wherein the compound is to be administered locally by topical administration, preferably wherein the first precancerous lesion or growth is actinic keratosis.

5. The use of any one of claims 2-4, further wherein one or more additional doses of an effective amount of the PKC activator are to be administered to further stimulate the immunological response to the cancer or cancer antigen or precancerous lesion or growth,

preferably wherein the one or more additional doses is to at least a second cancer locus or mass or site different from site of the first cancer locus or mass or site.

6. The use of any one of claims 2-5,

wherein the administered effective amount is sufficient to induce necrosis of the cancer, or

wherein the administered effective amount is effective to induce regression in a non-target cancer locus or mass or a satellite cancer locus or mass; or

wherein the administered effective amount produces immune memory against the cancer or cancer antigen.

7. The use of any one of claims 2-6, wherein the cancer or cancer antigen is an immunogenic cancer or cancer antigen, preferably wherein the cancer is secondary cancer or metastatic cancer.

8. The use of any one of claims 2-7, further wherein an effective amount of one or more of a second immune stimulating or immune enhancing therapeutic agent is to be administered, preferably wherein the second immune stimulating agent is an immune checkpoint inhibitor.

9. The use of claim 8,

wherein the immune checkpoint inhibitor is an anti-CTLA4, anti-PD-1 or anti-PD-L1 antibody, or

wherein the immune stimulating or immune enhancing agent is an immune stimulating or immune enhancing cytokine, preferably wherein the cytokine is IFN-α, IL-2, IL-10, IL-12, IL-15, IL-21, IFN-γ, TNF-α, or GM-CSF.

10. The use of any one of claims 2-9, wherein for stimulating the immune response against a cancer, the PKC activating compound is to be administered in combination with a second cancer therapeutic agent or second cancer therapy.

11. The use of claim 10,

wherein the second cancer therapeutic agent or a second cancer therapy is a second cancer chemotherapeutic agent or radiation,

wherein the second cancer therapeutic agent or second cancer therapy is chimeric antigen receptor T-cell (CAR-T or CART) or a chimeric antigen receptor NK-cell (CAR-NK) therapy appropriate for the cancer.

12. The use of any one of claims 2-11,

wherein the cancer is a metastatic cancer; or

wherein the cancer is selected from adenocarcinoma, adrenocortical cancer, anal cancer, angiosarcoma, biliary cancer, bladder cancer, bone cancer (e.g., osteosarcoma), brain cancer (e.g., gliomas, astrocytoma, neuroblastoma, etc.), breast cancer, cervical cancer, colon cancer, cutaneous lymphoma, endometrial cancer, esophageal cancer, fibrosarcoma, fibroxanthoma, head and neck cancer, hematologic cancer (e.g., leukemia and lymphoma), intestinal cancer (small intestine), liver cancer, lung cancer (e.g., bronchial cancer, small cell lung cancer, non-small cell lung cancer, etc.), mast cell tumor, oral cancer, ovarian cancer, pancreatic cancer, renal cancer, prostate cancer, salivary gland cancer, skin cancer (e.g., basal cell carcinoma, melanoma, squamous cell carcinoma), stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, sarcoma, and soft tissue carcinomas;

wherein the cancer is a hematologic cancer, preferably wherein the hematologic cancer is selected from acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), lymphoma (e.g., Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Burkitt's lymphoma), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), Hairy Cell chronic myelogenous leukemia (CML), and multiple myeloma; or

wherein the cancer is a leukemia selected from acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), Hairy Cell chronic myelogenous leukemia (CML), and multiple myeloma; or

wherein the cancer is a lymphoma selected from Hodgkin's lymphoma, Non-Hodgkin's lymphoma, and Burkitt's lymphoma.

13. The use of claim 2, wherein the immune response is for treatment of a benign tumor,

preferably wherein the benign tumor is adenoma, fibroma, lipoma, myoma, neuroma, papilloma, or osteochondro sarcoma; or

preferably wherein the benign tumor is basal cell carcinoma or neurofibroma, dermatofibroma, epidermoid cyst, or angioma.

14. The use of claim 1, wherein the immune response is for treatment of a wound in a subject in need thereof,

preferably wherein the treatment of a wound is to promote wound healing and/or for treating or preventing an infection of the wound,

more preferably wherein the infection of the wound is a persistent infection of the wound.

15. The use of claim 14,

wherein the promoting wound healing increases the rate of wound healing; or

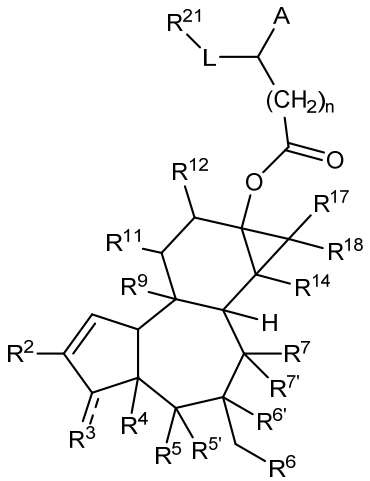
wherein the promoting wound healing reduces scarring of wound tissue, preferably wherein the scarring is keloid or hypertrophic scar.

16. The use of any one of claims 14-15,

wherein the compound is to be administered locally to the wound, or

wherein the compound is to be administered topically to the wound.

17. The use of any one of claims 1-16, wherein the PKC activating compound is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

A is -OH, –C(O)OR^{1}, or -NR^{13}R$^{13'}$;

R^{1} is H or a M+ counterion;

R^{2} is a C$_1$-C$_4$alkyl;

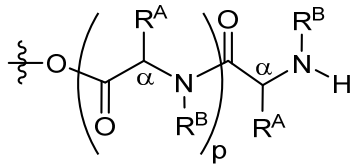
R^{3} is O double bonded to the ring carbon when (- - -) is a bond, or -OR^{a}; wherein R^{a} is H or -C(O)R^{a1}, wherein R^{a1} is C$_1$-C$_6$alkyl, C$_2$-C$_6$alkenyl, C$_0$-C$_6$alkylaryl, or C$_0$-C$_6$alkylheteroaryl;

R^{4} and R^{5} are each independently H or -OR^{b}, wherein R^{b} is H, C$_1$-C$_6$alkyl, C$_2$-C$_6$alkenyl, C$_0$-C$_6$alkylaryl, or C$_0$-C$_6$alkylheteroaryl;

R$^{5'}$ and R$^{6'}$ are each independently H or OH, or R$^{5'}$ and R$^{6'}$ form a bond or are bonded to a common O atom to form an epoxide ring as permitted by valency;

R^{6} is OH, halo, -OP(O)(OR$^{b'}$)$_2$, or -OC(O)R^{c}, wherein each R$^{b'}$ is independently H, C$_1$-C$_6$alkyl, C$_2$-C$_6$alkenyl, C$_0$-C$_6$alkylaryl, or C$_0$-C$_6$alkylheteroaryl; R^{c} is -C$_1$-C$_6$alkyl, -C$_1$-C$_6$alkyl-(NR^{c1})$_2$ or -C$_1$-C$_6$alkylC(O)OR^{k}; R^{c1} is H, C$_1$-C$_6$alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^{6} is



wherein,

each occurrence of R^{A} is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^{A} is same or different;

each occurrence of R^{B} is independently H, or R^{B} together with the adjacent R^{A} and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^{B} is same or different; and

p is 0, 1, or 2;

R$^{6'}$ is H or OH, R$^{7'}$ is H, or R$^{6'}$ and R$^{7'}$ form a bond or are bonded to a common O atom to form an epoxide ring, as permitted by valency;

R^{7} is H or OH;

R^{9} is OR^{e}, wherein R^{e} is H, C$_1$-C$_6$alkyl, or aryl;

R^{11} is C$_1$-C$_4$alkyl;

R^{12} is H, -OH, –OC(O)R^{f}, wherein R^{f} is C$_1$-C$_{12}$alkyl, C$_2$-C$_{12}$alkenyl, -C$_0$-C$_{12}$aliphatic-C$_3$-C$_7$cycloalkyl, -C$_0$-C$_{12}$aliphatic-heterocycloalkyl, -C$_0$-C$_{12}$aliphatic-aryl, or -C$_0$-C$_{12}$aliphatic-heteroaryl;

R^{13} and R$^{13'}$ are each independently H or C$_1$-C$_4$alkyl;

R^{14} is H or OR^{g}; wherein R^{g} is H or C$_1$-C$_6$alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is absent, C_1-C_{12}alkylene, or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with C_1-C_4alkyl;

R^{21} is H, -$S(O)_2R^j$, -SR^j, -$N(R^j)_2$, -$Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –$C(O)OR^k$, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1, and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl, or when an N atom is present an N-protecting group;

each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

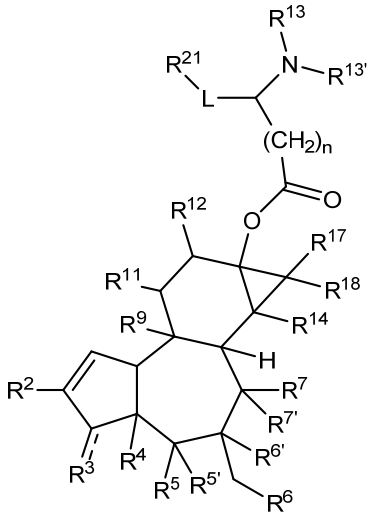
R^k is H or M^+ counterion;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

n is 0 or 1.

18. The use of claim 17, wherein A is –OH, or wherein A is –$C(O)OR^1$, wherein R^1 is H or a M^+ counterion.

19. The use of claim 17, wherein the compound is a compound of formula (II):



(II)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

R^2 is a C_1-C_4alkyl;

R^3 is O double bonded to the ring carbon when (- - -) is a bond, or –OR^a; wherein R^a is H or –

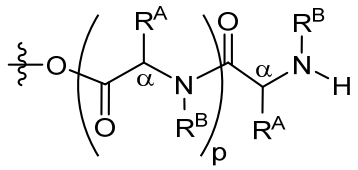
$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^4 and R^5 are each independently H or $–OR^b$, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

$R^{5'}$ and $R^{6'}$ are each independently H or OH, or $R^{5'}$ and $R^{6'}$ form a bond or are bonded to a common O atom to form an epoxide ring as permitted by valency;

R^6 is OH, halo, $-OP(O)(OR^{b'})_2$, or $–OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;R^c is $–C_1$-C_6alkyl, $-C_1$-C_6alkyl-$(NR^{c1})_2$ or $–C_1$-C_6alkyl$C(O)OR^k$, R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with the adjacent R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

$R^{6'}$ is H or OH, $R^{7'}$ is H, or $R^{6'}$ and $R^{7'}$ form a bond or are bonded to a common O atom to form an epoxide ring, as permitted by valency;

R^7 is H or OH;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{12} is H, -OH, $–OC(O)R^f$, wherein R^f is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, $-C_0$-C_{12}aliphatic-C_3-C_7cycloalkyl, $-C_0$-C_{12}aliphatic-heterocycloalkyl, $-C_0$-C_{12}aliphatic-aryl, or $–C_0$-C_{12}aliphatic-heteroaryl;

R^{13} and $R^{13'}$ are each independently H or C_1-C_4alkyl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is absent, C_1-C_{12}alkylene, or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with C_1-C_4alkyl;

R^{21} is H, $-S(O)_2R^j$, $-SR^j$, $-N(R^j)_2$, $-Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or $–C(O)OR^k$, wherein the C_3-

C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1, and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl, or when an N atom is present an N-protecting group;

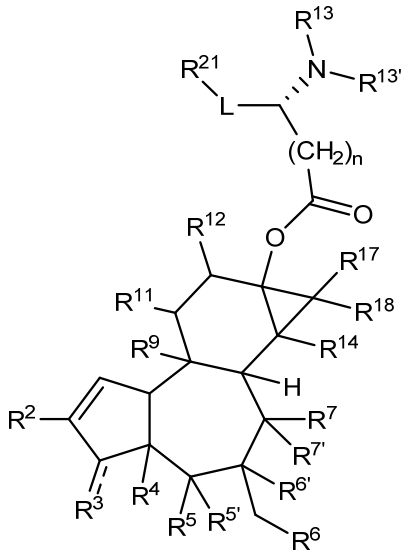
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

R^k is H or M^+ counterion;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

n is 0 or 1; or

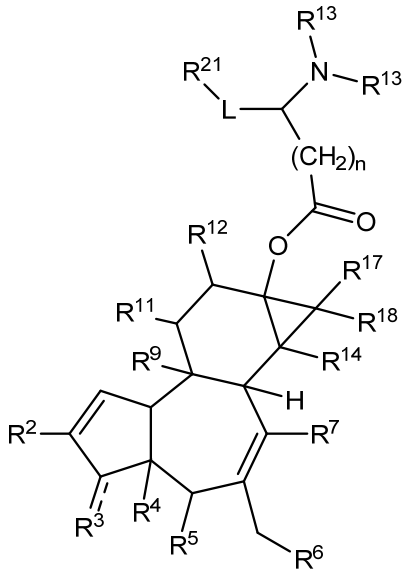
wherein the compound is a compound of formula (II'):



(II')

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof; or

wherein the compound is a compound of formula (IIa):



(IIa)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

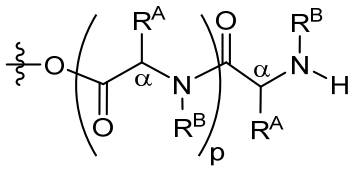
R^2 is a C_1-C_4alkyl;

R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^4 and R^5 are each independently H or -OR^b, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^6 is OH, halo, -$OP(O)(OR^{b'})_2$, or -$OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$ or -C_1-C_6alkyl$C(O)OR^k$; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with the adjacent R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

R^7 is H or OH;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{12} is H, -OH, –OC(O)R^f, wherein R^f is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, -C_0-C_{12}aliphatic-C_3-C_7cycloalkyl, -C_0-C_{12}aliphatic-heterocycloalkyl, -C_0-C_{12}aliphatic-aryl, or -C_0-C_{12}aliphatic-heteroaryl;

R^{13} and $R^{13'}$ are each independently H or C_1-C_4alkyl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is absent, C_1-C_{12}alkylene, or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with C_1-C_4alkyl;

R^{21} is H, -$S(O)_2R^j$, -SR^j, -$N(R^j)_2$, -$Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –C(O)OR^k, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1, and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl, or when an N atom is present an N-protecting group;

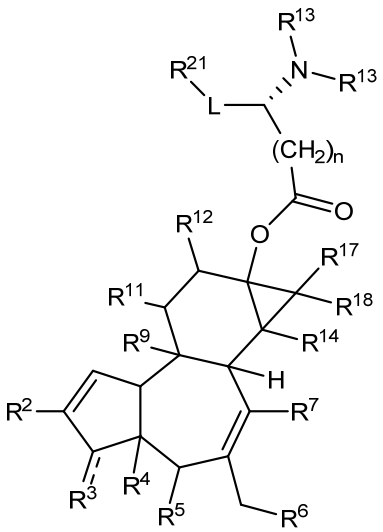
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

R^k is H or M^+ counterion;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

n is 0 or 1; or

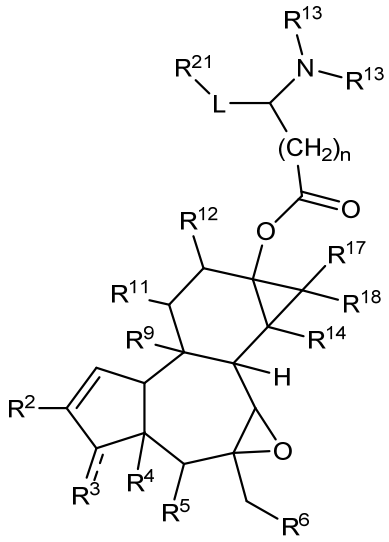
wherein the compound is a compound of formula (IIa'):



(IIa')

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof; or

wherein the compound is a compound of formula (IIb):



(IIb)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

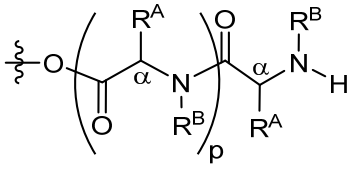
R^2 is a C_1-C_4alkyl;

R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^4 and R^5 are each independently H or -OR^b, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^6 is OH, halo, -$OP(O)(OR^{b'})_2$, or -$OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$ or -C_1-C_6alkyl$C(O)OR^k$; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with the adjacent R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino

acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{12} is H, -OH, $–OC(O)R^f$, wherein R^f is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, -C_0-C_{12}aliphatic-C_3-C_7cycloalkyl, -C_0-C_{12}aliphatic-heterocycloalkyl, -C_0-C_{12}aliphatic-aryl, or -C_0-C_{12}aliphatic-heteroaryl;

R^{13} and $R^{13'}$ are each independently H or C_1-C_4alkyl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is absent, C_1-C_{12}alkylene, or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with C_1-C_4alkyl;

R^{21} is H, -$S(O)_2R^j$, -SR^j, -$N(R^j)_2$, -$Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or $–C(O)OR^k$, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1, and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl, or when an N atom is present an N-protecting group;

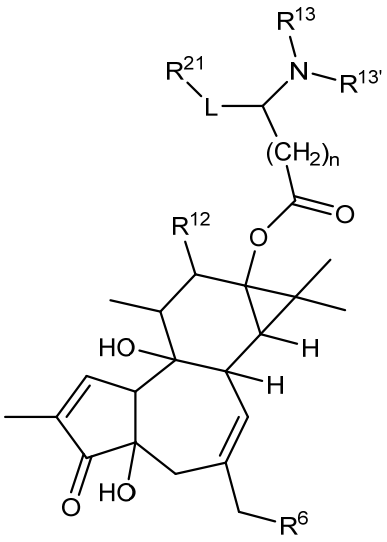
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

R^k is H or M^+ counterion;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

n is 0 or 1; or

wherein the compound is a compound of formula (IIc):



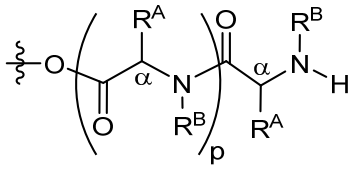
(IIc)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

R^6 is OH, halo, -OP(O)($OR^{b'}$)$_2$, or -OC(O)R^c, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-(NR^{c1})$_2$ or -C_1-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with the adjacent R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

R^{12} is H, -OH, –OC(O)R^f, wherein R^f is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, -C_0-C_{12}aliphatic-C_3-C_7cycloalkyl, -C_0-C_{12}aliphatic-heterocycloalkyl, -C_0-C_{12}aliphatic-aryl, or -C_0-C_{12}aliphatic-heteroaryl;

R^{13} and $R^{13'}$ are each independently H or C_1-C_4alkyl;

L is absent, C_1-C_{12}alkylene, or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with C_1-C_4alkyl;

R^{21} is H, -S(O)$_2R^j$, -SR^j, -N(R^j)$_2$, -Si(R^j)$_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –C(O)OR^k, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1, and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl, or when an N atom is present an N-protecting group;

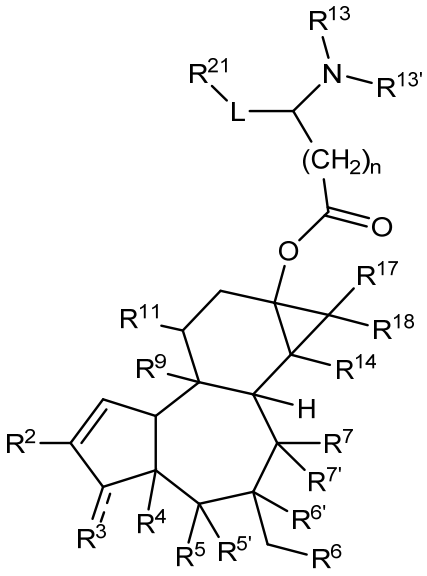
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC$_3$-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

R^k is H or M^+ counterion;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

n is 0 or 1.

20. The use of claim 19, wherein the compound is a compound of formula (III):



(III)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

R^2 is a C_1-C_4alkyl;

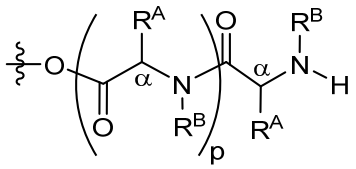
R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^4 and R^5 are each independently H or -OR^b, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

$R^{5'}$ and $R^{6'}$ are each independently H or OH, or $R^{5'}$ and $R^{6'}$ form a bond or are bonded to a common O atom to form an epoxide ring as permitted by valency;

R^6 is OH, halo, -$OP(O)(OR^{b'})_2$, or -$OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$ or -C_1-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with the adjacent R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino

acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

$R^{6'}$ is H or OH, $R^{7'}$ is H, or $R^{6'}$ and $R^{7'}$ form a bond or are bonded to a common O atom to form an epoxide ring, as permitted by valency;

R^7 is H or OH;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{13} and $R^{13'}$ are each independently H or C_1-C_4alkyl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is absent, C_1-C_{12}alkylene, or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with C_1-C_4alkyl;

R^{21} is H, $-S(O)_2R^j$, $-SR^j$, $-N(R^j)_2$, $-Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or $-C(O)OR^k$, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1, and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl, or when an N atom is present an N-protecting group;

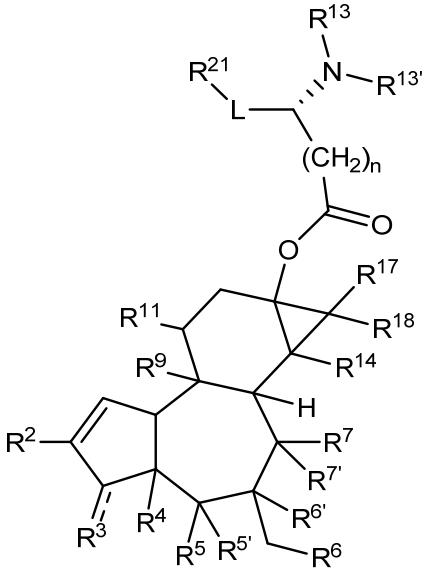
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

R^k is H or M^+ counterion;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

n is 0 or 1; or

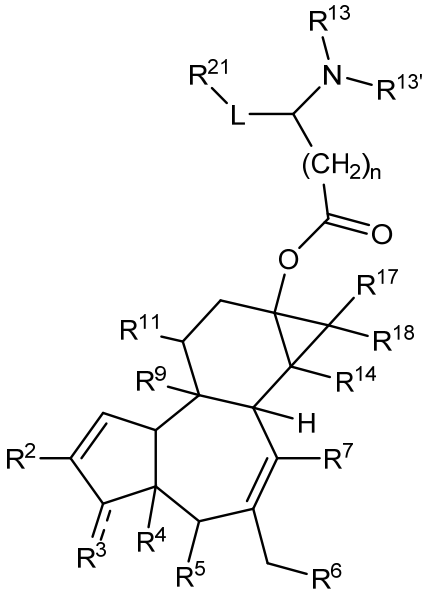
wherein the compound is a compound of formula (III'):



(III')

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof; or

wherein the compound is a compound of formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

R^2 is a C_1-C_4alkyl;

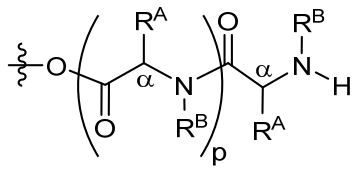
R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^4 and R^5 are each independently H or -OR^b, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^6 is OH, halo, -$OP(O)(OR^{b'})_2$, or -$OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$

or -C_1-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with the adjacent R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

R^7 is H or OH;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{13} and $R^{13'}$ are each independently H or C_1-C_4alkyl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is absent, C_1-C_{12}alkylene, or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with C_1-C_4alkyl;

R^{21} is H, -$S(O)_2R^j$, -SR^j, -$N(R^j)_2$, -$Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –C(O)OR^k, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1, and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl, or when an N atom is present an N-protecting group;

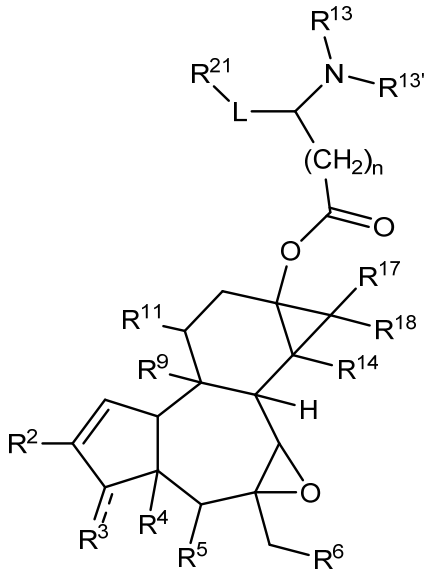
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

R^k is H or M^+ counterion;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

n is 0 or 1; or

wherein the compound is a compound of formula (IIIb):



(IIIb)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

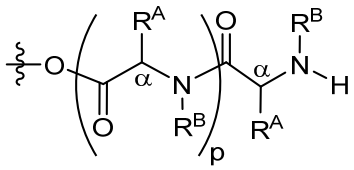
R^2 is a C_1-C_4alkyl;

R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^4 and R^5 are each independently H or -OR^b, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^6 is OH, halo, -$OP(O)(OR^{b'})_2$, or -$OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$ or -C_1-C_6alkyl$C(O)OR^k$; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with the adjacent R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{13} and $R^{13'}$ are each independently H or C_1-C_4alkyl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is absent, C_1-C_{12}alkylene, or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with C_1-C_4alkyl;

R^{21} is H, $-S(O)_2R^j$, $-SR^j$, $-N(R^j)_2$, $-Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or $-C(O)OR^k$, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1, and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl, or when an N atom is present an N-protecting group;

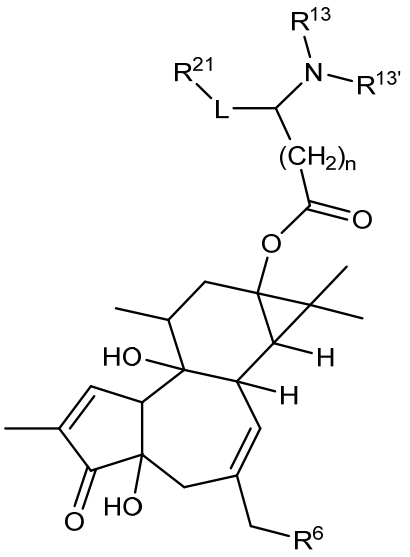
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

R^k is H or M^+ counterion;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

n is 0 or 1; or

wherein the compound is a compound of formula (IIIc):



(IIIc)

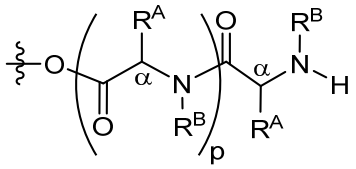
or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

R^6 is OH, halo, $-OP(O)(OR^{b'})_2$, or $-OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-

C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$ or -C_1-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with the adjacent R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

R^{13} and $R^{13'}$ are each independently H or C_1-C_4alkyl;

L is absent, C_1-C_{12}alkylene, or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with C_1-C_4alkyl;

R^{21} is H, -$S(O)_2R^j$, -SR^j, -$N(R^j)_2$, -$Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –C(O)OR^k, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1, and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl, or when an N atom is present an N-protecting group;

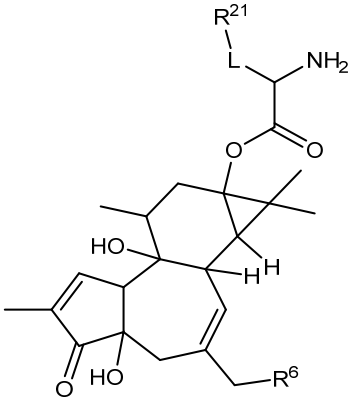
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

R^k is H or M^+ counterion;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

n is 0 or 1; or

wherein the compound is a compound of formula (IIIe):



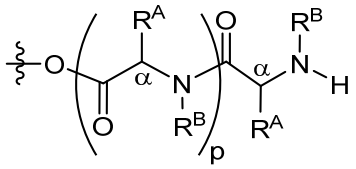
(IIIe)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

R^6 is OH, halo, -OP(O)($OR^{b'}$)$_2$, or -OC(O)R^c, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-(NR^{c1})$_2$ or -C_1-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with the adjacent R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

L is absent, C_1-C_{12}alkylene, or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with C_1-C_4alkyl;

R^{21} is H, -S(O)$_2R^j$, -SR^j, -N(R^j)$_2$, -Si(R^j)$_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –C(O)OR^k, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1, and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl, or when an N atom is present an N-protecting group;

each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl,

heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

R^k is H or M^+ counterion; and

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl.

21. The use of any one of claims 17-20,

wherein R^{21} is C_3-C_7cycloalkyl, and wherein the C_3-C_7cycloalkyl is optionally substituted with 1 to 3 of J^1, preferably wherein the C_3-C_7cycloalkyl is selected from the group consisting of cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, wherein the C_3-C_7cycloalkyl is optionally substituted with 1 to 3 of J^1; or

wherein R^{21} is heterocyclyl, wherein the heterocyclyl is optionally substituted with 1 to 3 of J^1, preferably wherein the heterocyclyl is selected from the group consisting of oxiranyl, oxetanyl, azetidynyl, oxazolyl, thiazolidinyl, thiazolyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, 2,3-dihydrofuranyl, dihydropyranyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyridinyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and azapanyl, wherein the heterocyclyl is optionally substituted with 1 to 3 of J^1; or

wherein R^{21} is aryl, wherein the aryl is optionally substituted with 1 to 3 of J^1, preferably wherein

R^{21} is a phenyl or naphthyl, wherein the phenyl or naphthyl is optionally substituted with 1 to 3 of J^1; or

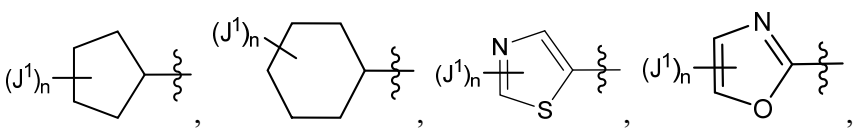
wherein R^{21} is heteroaryl, wherein the heteroaryl is optionally substituted with 1 to 3 of J^1, preferably wherein the heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzoxazolyl, benzothiazolyl, purinyl, benzimidazolyl, indolyl, isoquinolyl, quinoxalinyl, and quinolyl, wherein the heteroaryl is optionally substituted with 1 to 3 of J^1; or

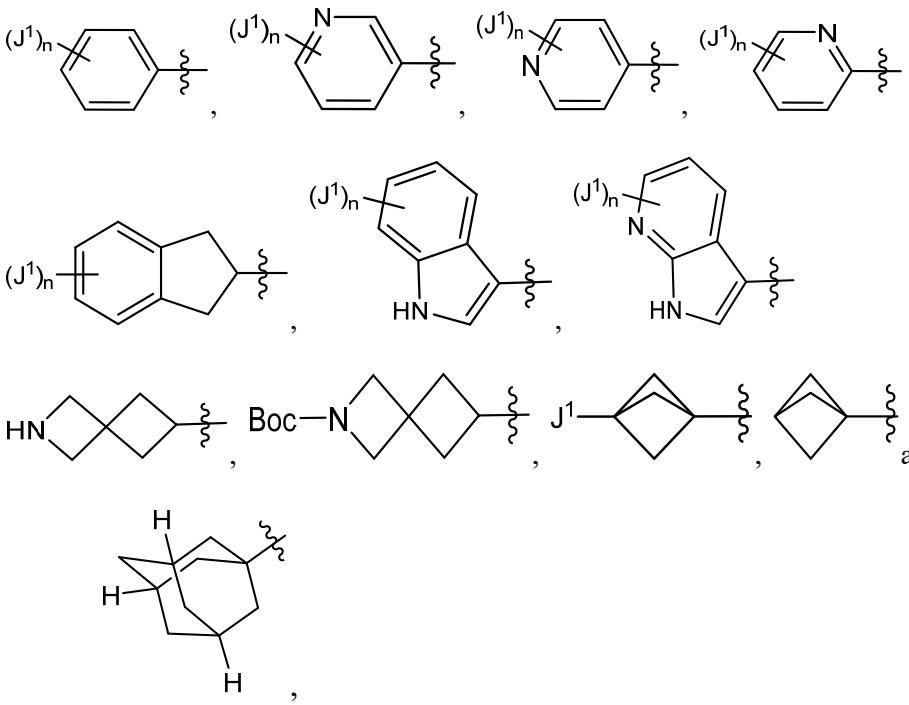
wherein R^{21} is adamantyl, wherein the adamantyl is optionally substituted with OH, halo, or C_1-C_4alkyl; or

wherein R^{21} is spiroC_5-C_{12} cycloalkyl, wherein the spiroC_5-C_{12} cycloalkyl has 0-2 carbon atoms replaced with 0-2 heteroatoms selected from N, O and S, and is optionally substituted with 1 to 3 of J^1, or when an N atom is present an N-protecting group; or

wherein R^{21} is 5 to 12 membered bridged bicyclyl, wherein the bridged bicyclyl has 0-2 carbon atoms replaced with 0-2 heteroatoms selected from N, O or S, and is optionally substituted with 1 to 3 of J^1, or when an N atom is present an N-protecting group; or

wherein R^{21} is selected from:





wherein J^1 is OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl, and n is 0-3.

22. The use of any one of claims 17-21,

wherein L is C_1-C_6alkylene, C_3-C_6alkylene or C_3-C_{12}alkylene; or

wherein L is C_1-C_6alkenylene, C_3-C_6alkenylene or C_3-C_{12}alkenylene.

23. The use of any one of claims 17-22, wherein n is 0.

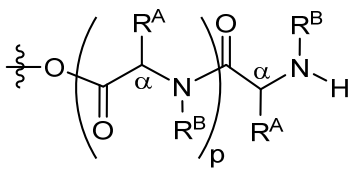
24. The use of any one of claims 17-23,

wherein R^6 is OH; or

wherein R^6 is -OP(O)($OR^{b'}$)$_2$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; or

wherein R^6 is -OC(O)R^c, wherein R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-(NR^{c1})$_2$ or -C_1-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; and R^k is H or a M^+ counterion; or

wherein R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-

natural amino acid, wherein each occurrence of R^A is same or different;

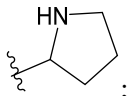
each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2.

25. The use of claim 24,

wherein each R^A is independently hydrogen (glycine), methyl (alanine), propan-2-yl (valine), propan-1-y1 (norvaline), 2-methylpropan-1-y1 (leucine), 1-methylpropan-1-y1 (isoleucine), butan-1-y1 (norleucine), phenyl (2-phenylglycine), benzyl (phenylalanine), p-hydroxybenzyl (tyrosine), indol-3-ylmethyl (tryptophan), imidazol-4-ylmethyl (histidine), hydroxymethyl (serine), 2-hydroxyethyl (homoserine), 1–hydroxyethyl (threonine), mercaptomethyl (cysteine), methylthiomethyl (S-methylcysteine), 2-mercaptoethyl (homocysteine), 2-methylthioethyl (methionine), carbamoylmethyl (asparagine), 2-carbamoylethyl (glutamine), carboxymethyl (aspartic acid), 2-carboxyethyl (glutamic acid), 4-aminobutan-1-y1 (lysine), 4-amino-3-hydroxybutan-1-y1 (hydroxylysine), 3-aminopropan-1-y1 (ornithine), 3-guanidinopropan-1-y1 (arginine), or 3-ureido-propan-1-yl (citrulline);

each R^B is H, or R^B together with the adjacent R_A and the N atom form a prolyl side chain:



; and

p is 0, 1 or 2; or

wherein each R^A is independently methyl (alanine), propan-2-y1 (valine), 2-methylpropan-1-y1 (leucine), imidazol-4-ylmethyl (histidine), hydroxymethyl (serine), 1-hydroxyethyl (threonine), carbamoylmethyl (asparagine), 2-carbamoylethyl (glutamine), 4-aminobutan-1-y1 (lysine), carboxymethyl (aspartic acid), 3-guanidinopropan-1-y1 (arginine), benzyl (phenylalanine), or 4-aminobutan-1-y1 (lysine);

R^B is H; and

p 0, 1, or 2; or

wherein each R^A is independently propan-2-y1 (valine), 2-methylpropan-1-y1 (leucine), carboxymethyl (aspartic acid), benzyl (phenylalanine), or 4-aminobutan-1-y1 (lysine);

each R^B is H; and

p is 0, 1, or 2.

26. The use of claim 25,

wherein p is 0; or

wherein p is 1.

27. The use of claim 25, wherein p is 1;

first of R^A is propan-2-y1 (valine) and second of R^A is propan-2-y1 (valine); and each of R^B is H (dipeptide Val-Val); or

first of R^A is 2-methylpropan-1-y1 (leucine), and second of R^A is 2-methylpropan-1-y1 (leucine); and each of R^B is H (dipeptide Leu-Leu); or

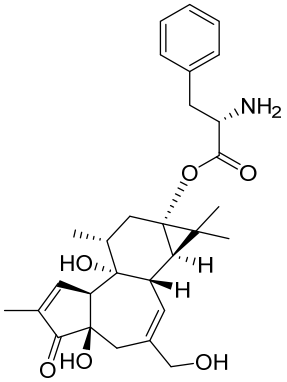
first of R^A is methyl (alanine) and second of R^A is methyl (alanine); and each of R^B is H (dipeptide Ala-Ala); or

first of R^A is 4-aminobutan-1-y1 (lysine); second of R^A is 4-aminobutan-1-y1 (lysine); and each of R^B is H (dipeptide Lys-Lys); or

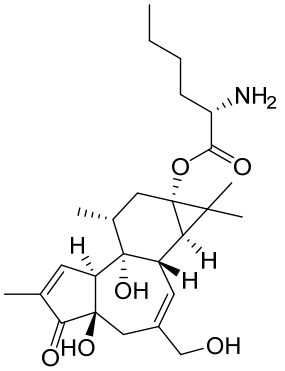
first of R^A is hydrogen; second of R^A is 4-aminobutan-1-y1, and each of R^B is H (dipeptide Gly-Lys).

28. The use of any one of claims 24-27, wherein each of the α-carbon of the amino acid other than glycine is in the L or D configuration.

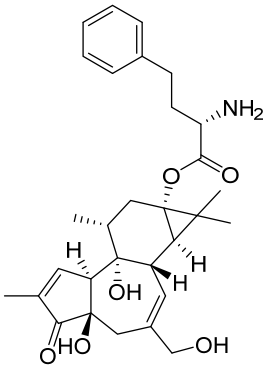
29. The use of claim 17, wherein the compound is selected from the group consisting of the compounds or a pharmaceutical salt thereof listed below:



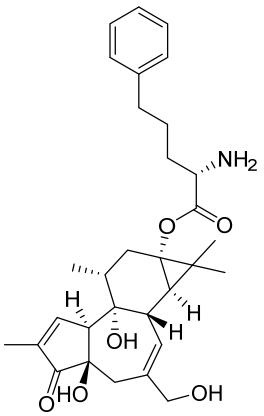
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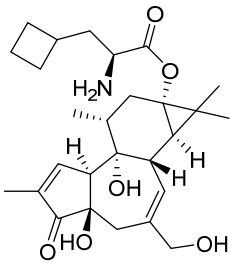
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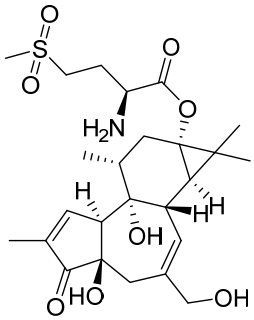
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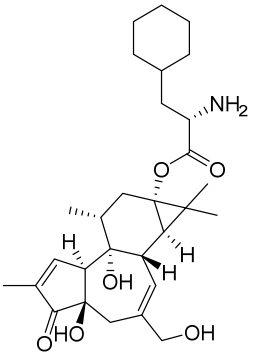
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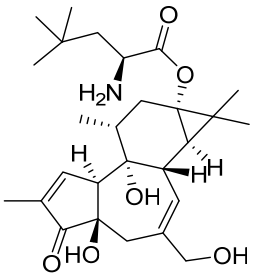
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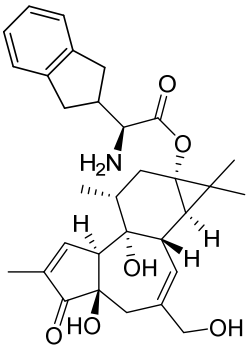
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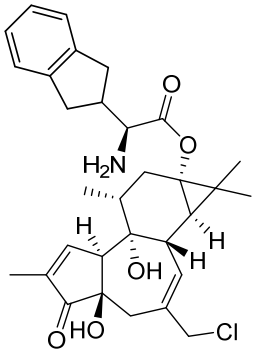
K101-C1327



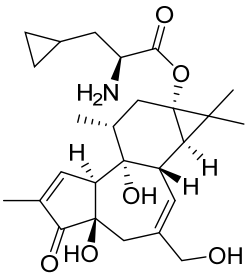
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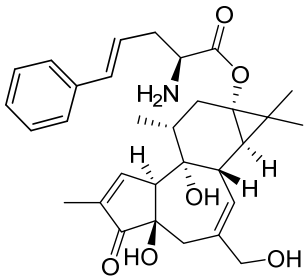
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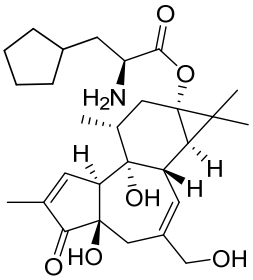
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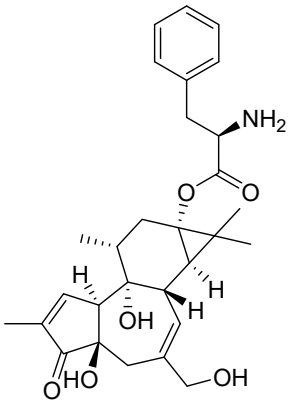
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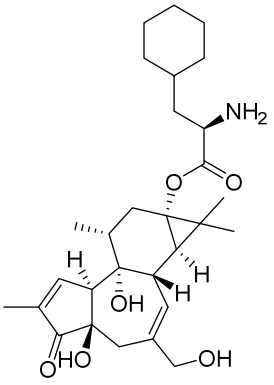
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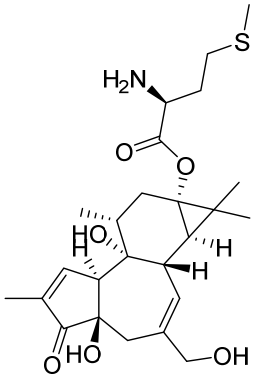
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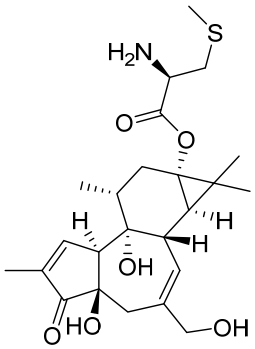
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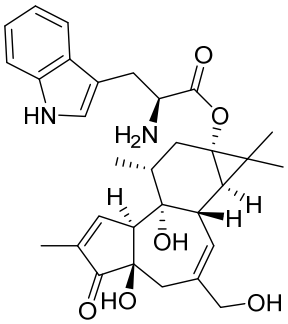
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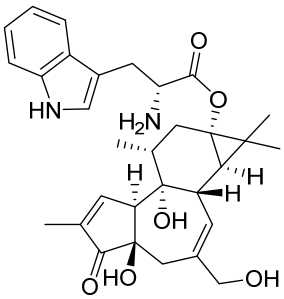
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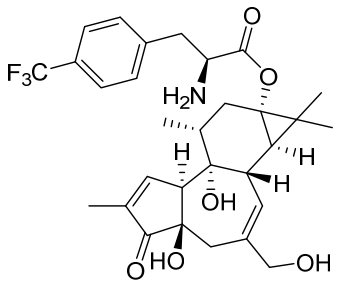
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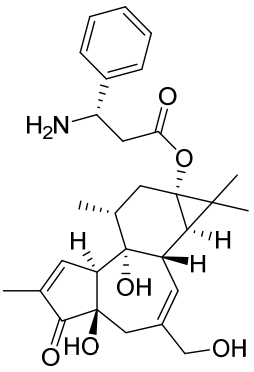
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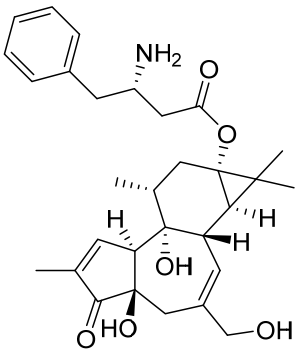
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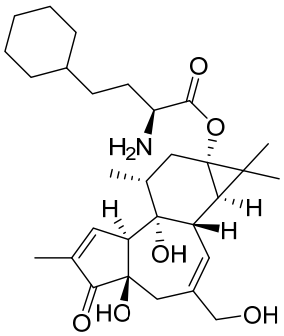
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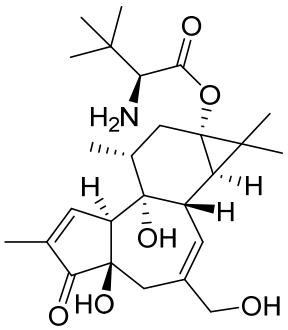
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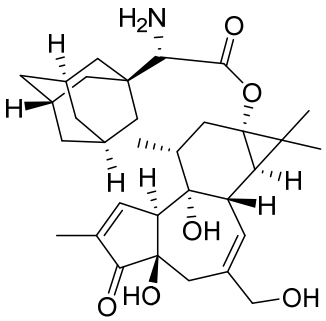
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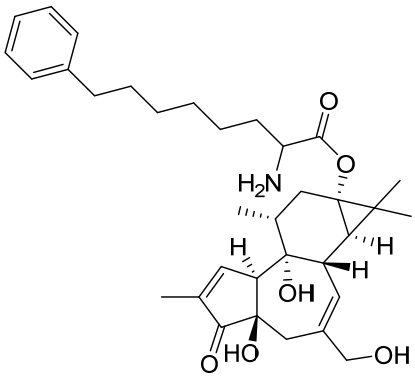
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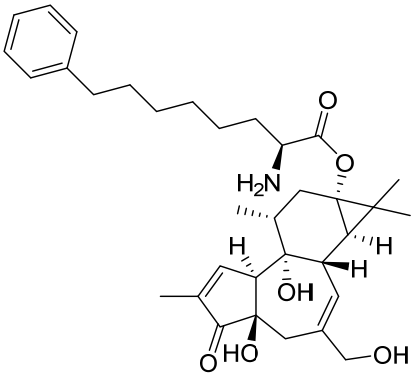
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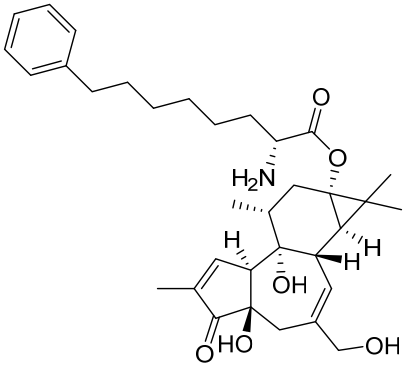
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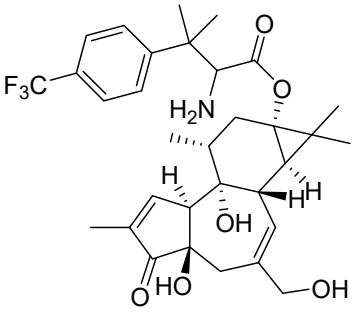
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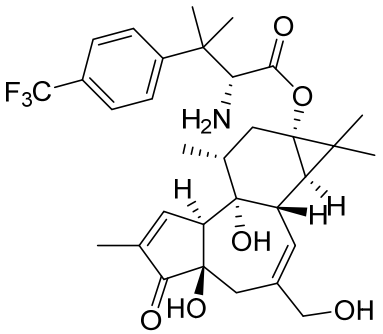
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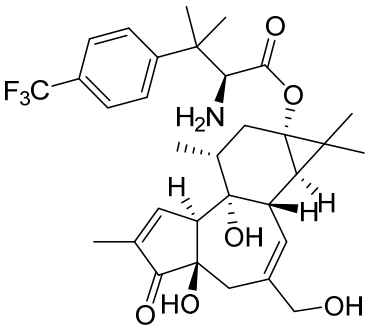
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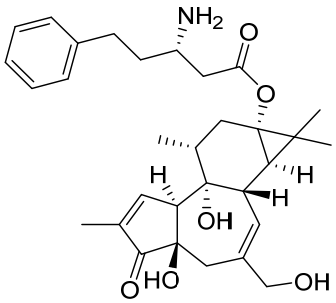
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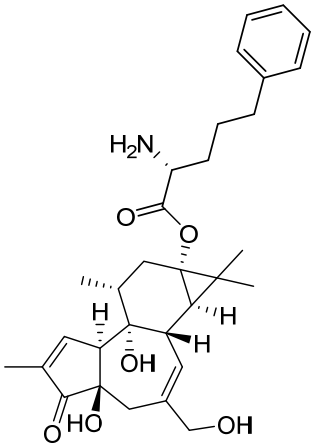
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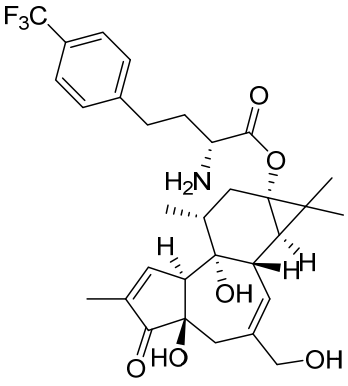
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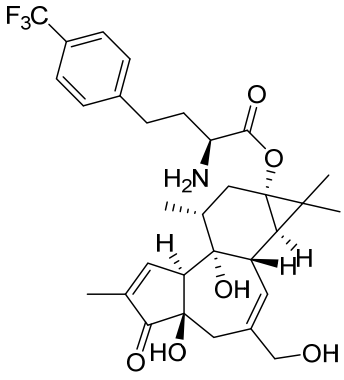
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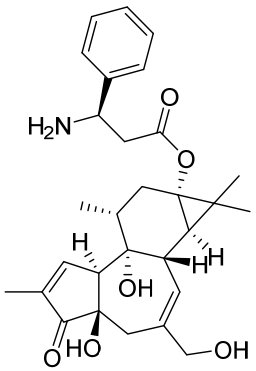
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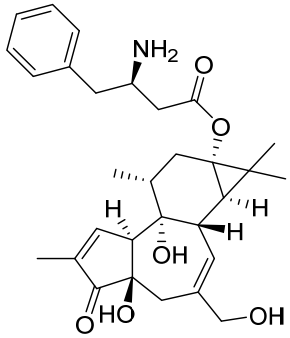
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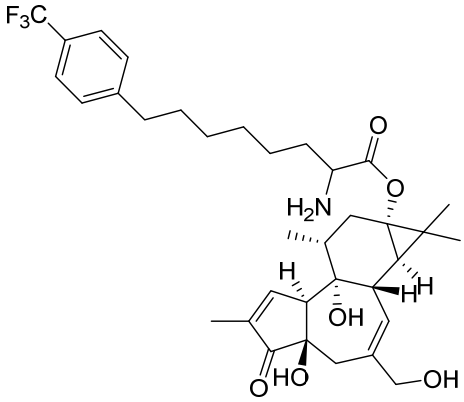
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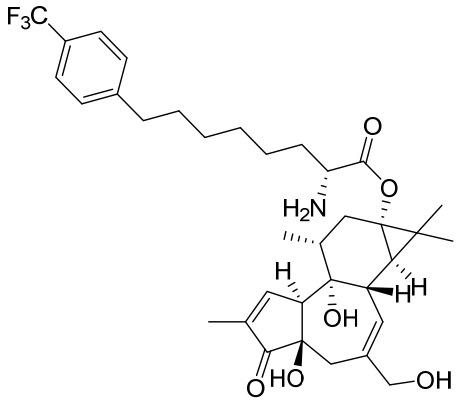
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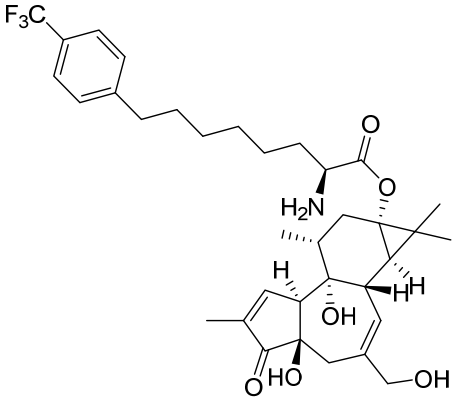
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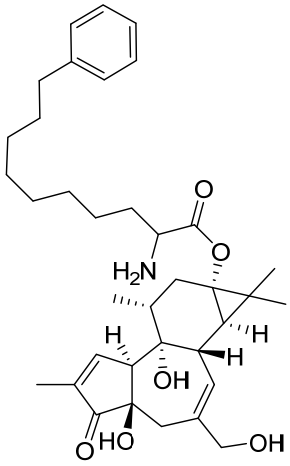
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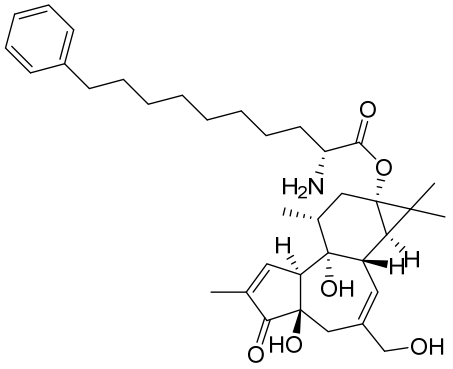
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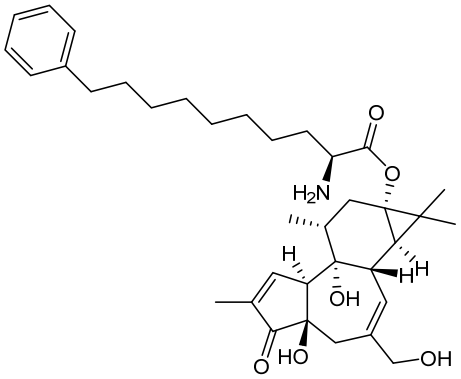
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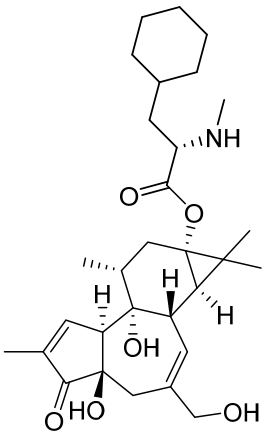
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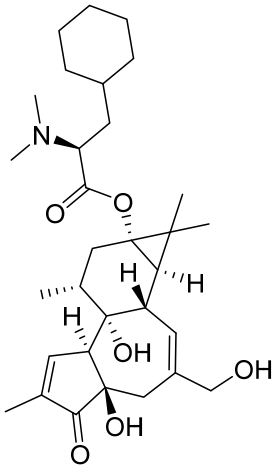
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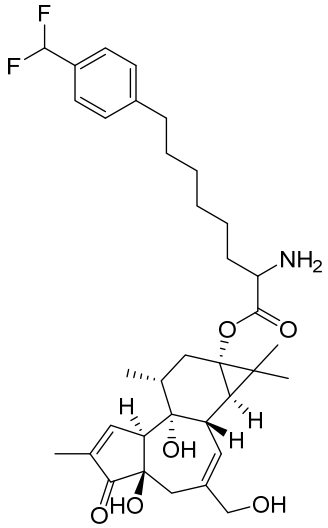
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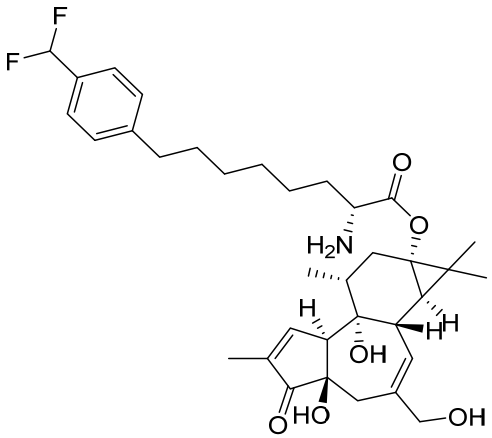
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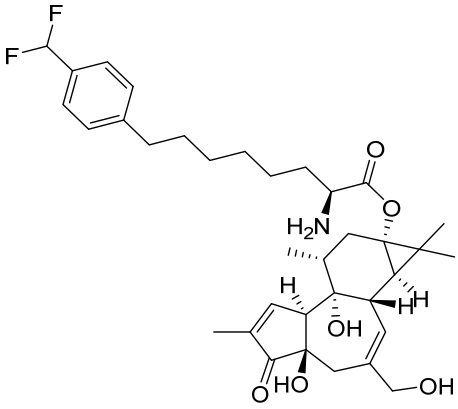
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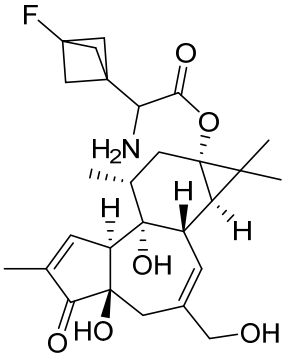
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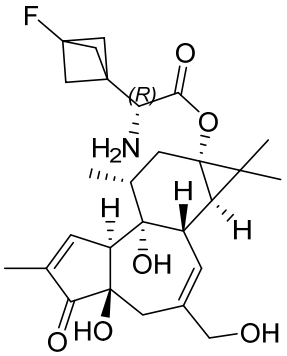
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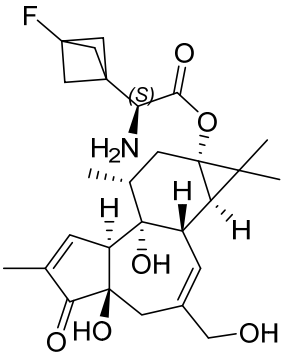
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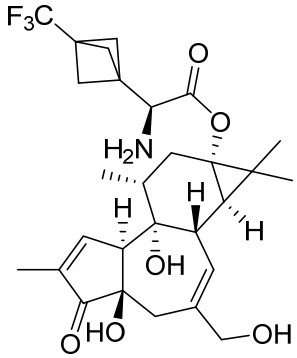
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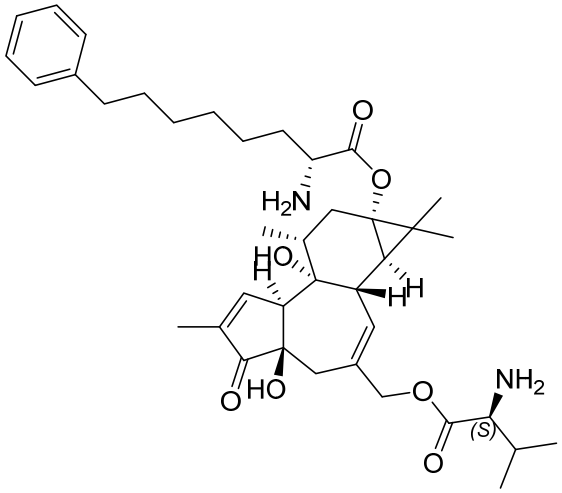
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K101-C137302



K101-C1375



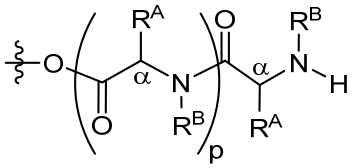
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30. The use claim 29, wherein the substituent on the C20 carbon atom of the compound is replaced with -OP(O)($OR^{b'}$)$_2$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; or

wherein the substituent on the C20 carbon atom of the compound is replaced with -OC(O)R^c, wherein R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-(NR^{c1})$_2$ or -C_1-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; and R^k is H or a M^+ counterion; or

wherein the substituent on the C20 carbon atom of the compound is, where appropropriate, replaced with



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

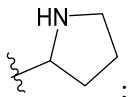
each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2.

31. The use of claim 30, wherein

each R^A is independently hydrogen (glycine), methyl (alanine), propan-2-yl (valine), propan-1-y1 (norvaline), 2-methylpropan-1-y1 (leucine), 1-methylpropan-1-y1 (isoleucine), butan-1-y1 (norleucine), phenyl (2-phenylglycine), benzyl (phenylalanine), p-hydroxybenzyl (tyrosine), indol-3-ylmethyl (tryptophan), imidazol-4-ylmethyl (histidine), hydroxymethyl (serine), 2-hydroxyethyl (homoserine), 1–hydroxyethyl (threonine), mercaptomethyl (cysteine), methylthiomethyl (S-methylcysteine), 2-mercaptoethyl (homocysteine), 2-methylthioethyl (methionine), carbamoylmethyl (asparagine), 2-carbamoylethyl (glutamine), carboxymethyl (aspartic acid), 2-carboxyethyl (glutamic acid), 4-aminobutan-1-y1 (lysine), 4-amino-3-hydroxybutan-1-y1 (hydroxylysine), 3-aminopropan-1-y1 (ornithine), 3-guanidinopropan-1-y1 (arginine), or 3-ureido-propan-1-yl (citrulline);

each R^B is H, or R^B together with the adjacent R_A and the N atom form a prolyl side chain:



; and

p is 0, 1 or 2; or

wherein each R^A is independently methyl (alanine), propan-2-y1 (valine), 2-methylpropan-1-y1 (leucine), imidazol-4-ylmethyl (histidine), hydroxymethyl (serine), 1-hydroxyethyl (threonine), carbamoylmethyl (asparagine), 2-carbamoylethyl (glutamine), 4-aminobutan-1-y1 (lysine), carboxymethyl (aspartic acid), 3-guanidinopropan-1-y1 (arginine), benzyl (phenylalanine), or 4-aminobutan-1-y1 (lysine);

R^B is H; and

p 0, 1, or 2; or

wherein each R^A is independently propan-2-y1 (valine), 2-methylpropan-1-y1 (leucine), carboxymethyl (aspartic acid), benzyl (phenylalanine), or 4-aminobutan-1-y1 (lysine);

each R^B is H; and

p is 0, 1, or 2.

32. The use of claim 84,

wherein p is 0; or

wherein p is 1; or

wherein p is 1;

first of R^A is propan-2-y1 (valine) and second of R^A is propan-2-y1 (valine); and each of R^B is

H (dipeptide Val-Val); or

first of R^A is 2-methylpropan-1-y1 (leucine), and second of R^A is 2-methylpropan-1-y1 (leucine); and each of R^B is H (dipeptide Leu-Leu); or

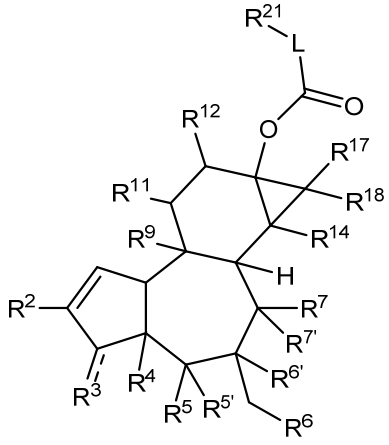
first of R^A is methyl (alanine) and second of R^A is methyl (alanine); and each of R^B is H (dipeptide Ala-Ala); or

first of R^A is 4-aminobutan-1-y1 (lysine); second of R^A is 4-aminobutan-1-y1 (lysine); and each of R^B is H (dipeptide Lys-Lys); or

first of R^A is hydrogen; second of R^A is 4-aminobutan-1-y1, and each of R^B is H (dipeptide Gly-Lys).

33. The use of any one of claims 83-89, wherein each of the α-carbon of the amino acid other than glycine is in the L or D configuration.

34. The use of any one of claims 1-38, wherein the compound is a compound of formula (IV):



(IV)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

R^2 is a C_1-C_4alkyl;

R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

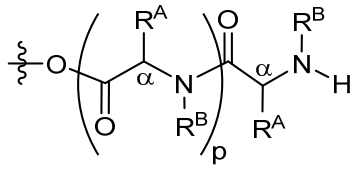
R^4 and R^5 are each independently H or -OR^b, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

$R^{5'}$ and $R^{6'}$ are each independently H or OH, or $R^{5'}$ and $R^{6'}$ form a bond or are bonded to a common O atom to form an epoxide ring as permitted by valency;

R^6 is OH, halo, -$OP(O)(OR^{b'})_2$, or -$OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$ or -C_1-C_6alkyl$C(O)OR^k$; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7

membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

$R^{6'}$ is H or OH, $R^{7'}$ is H, or $R^{6'}$ and $R^{7'}$ form a bond or are bonded to a common O atom to form an epoxide ring, as permitted by valency;

R^7 is H or OH;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{12} is H, -OH, $–OC(O)R^f$, wherein R^f is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, -C_0-C_{12}aliphatic-C_3-C_7cycloalkyl, -C_0-C_{12}aliphatic-heterocycloalkyl, -C_0-C_{12}aliphatic-aryl, or -C_0-C_{12}aliphatic-heteroaryl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is C_0-C_6alkylarylene, C_0-C_6alkylheteroarylene, C_0-C_6alkylC_3-C_7cycloalkylene, C_1-C_{12}alkylene or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with OH or C_1-C_4alkyl; and

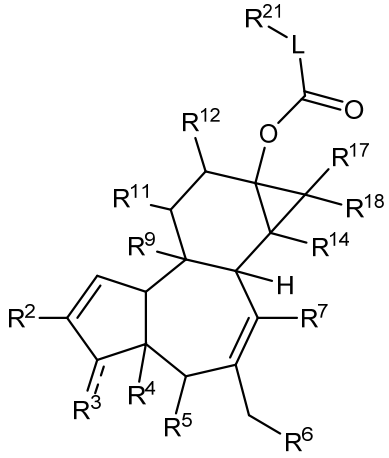
R^{21} is H, -OH, -SH, $-S(O)_2R^j$, $-SR^j$, $-N(R^j)_2$, $-Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or $–C(O)OR^k$, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1; and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl or, when an N atom is present an N-protecting group;

each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

R^k is H or M^+ counterion; or

wherein the compound is a compound of formula (IVa):



(IVa)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

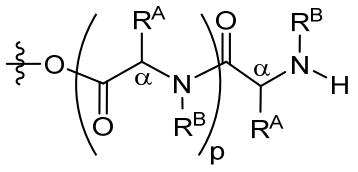
R^2 is a C_1-C_4alkyl;

R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^4 and R^5 are each independently H or -OR^b, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^6 is OH, -$OP(O)(OR^{b'})_2$, halo, or -$OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$ or -C_1-C_6alkyl$C(O)OR^k$; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

R^7 is H or OH;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{12} is H, -OH, –OC(O)R^f, wherein R^f is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, -C_0-C_{12}aliphatic-C_3-C_7cycloalkyl, -C_0-C_{12}aliphatic-heterocycloalkyl, -C_0-C_{12}aliphatic-aryl, or -C_0-C_{12}aliphatic-heteroaryl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is C_0-C_6alkylarylene, C_0-C_6alkylheteroarylene, C_0-C_6alkylC_3-C_7cycloalkylene, C_1-C_{12}alkylene or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with OH or C_1-C_4alkyl; and

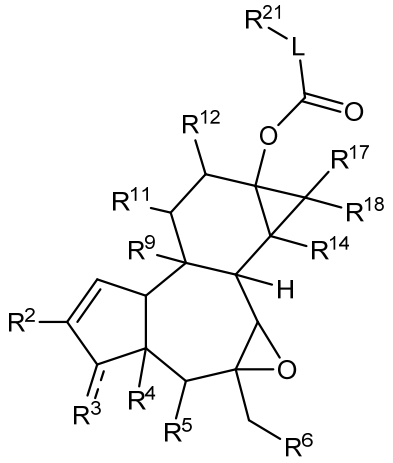
R^{21} is H, -OH, -SH,-S(O)$_2R^j$, -SR^j, -N(R^j)$_2$, -Si(R^j)$_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –C(O)OR^k, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1; and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl or, when an N atom is present an N-protecting group;

each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

R^k is H or M^+ counterion; or

wherein the compound is a compound of formula (IVb)



(IVb)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

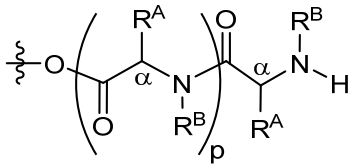
R^2 is a C_1-C_4alkyl;

R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^4 and R^5 are each independently H or -OR^b, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^6 is OH, halo, -$OP(O)(OR^{b'})_2$, or -$OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$ or -C_1-C_6alkyl$C(O)OR^k$; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

R^7 is H or OH;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{12} is H, -OH, –$OC(O)R^f$, wherein R^f is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, -C_0-C_{12}aliphatic-C_3-C_7cycloalkyl, -C_0-C_{12}aliphatic-heterocycloalkyl, -C_0-C_{12}aliphatic-aryl, or -C_0-C_{12}aliphatic-heteroaryl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is C_0-C_6alkylarylene, C_0-C_6alkylheteroarylene, C_0-C_6alkylC_3-C_7cycloalkylene, C_1-C_{12}alkylene or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with OH or C_1-C_4alkyl; and

R^{21} is H, -OH, -SH,-$S(O)_2R^j$, -SR^j, -$N(R^j)_2$, -$Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –$C(O)OR^k$, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1; and wherein optionally 1 to 2 carbon atoms of

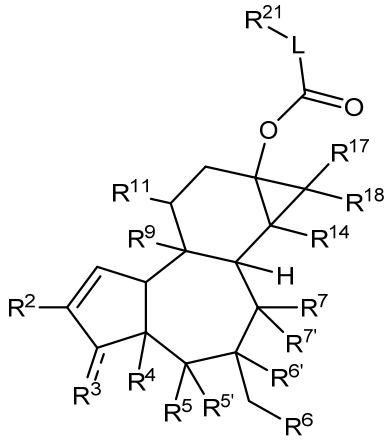
the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl or, when an N atom is present an N-protecting group;

each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

R^k is H or M^+ counterion; or.

35. The use of claim 34, wherein the compound is a compound of formula (V):



(V)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

R^2 is a C_1-C_4alkyl;

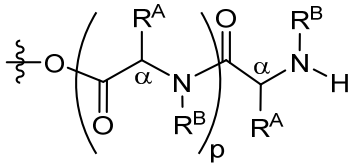
R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^4 and R^5 are each independently H or -OR^b, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

$R^{5'}$ and $R^{6'}$ are each independently H or OH, or $R^{5'}$ and $R^{6'}$ form a bond or are bonded to a common O atom to form an epoxide ring as permitted by valency;

R^6 is OH, halo, -$OP(O)(OR^{b'})_2$, or -$OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$ or -C_1-C_6alkyl$C(O)OR^k$; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

$R^{6'}$ is H or OH, $R^{7'}$ is H, or $R^{6'}$ and $R^{7'}$ form a bond or are bonded to a common O atom to form an epoxide ring, as permitted by valency;

R^7 is H or OH;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is C_0-C_6alkylarylene, C_0-C_6alkylheteroarylene, C_0-C_6alkylC_3-C_7cycloalkylene, C_1-C_{12}alkylene or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with OH or C_1-C_4alkyl; and

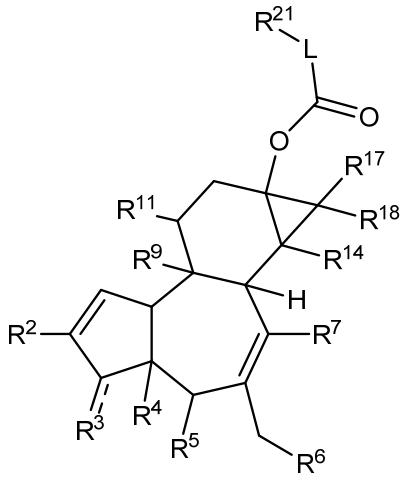
R^{21} is H, -OH, -SH,-$S(O)_2R^j$, -SR^j, -$N(R^j)_2$, -$Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –C(O)OR^k, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1; and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl or, when an N atom is present an N-protecting group;

each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

R^k is H or M^+ counterion; or

wherein the compound is a compound of formula (Va):



(Va)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

or an enantiomer or pharmaceutically acceptable salt thereof;

wherein

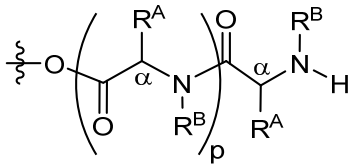
R^2 is a C_1-C_4alkyl;

R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^4 and R^5 are each independently H or -OR^b, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^6 is OH, halo, -$OP(O)(OR^{b'})_2$, or -$OC(O)R^c$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$ or -C_1-C_6alkyl$C(O)OR^k$; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

R^7 is H or OH;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is C_0-C_6alkylarylene, C_0-C_6alkylheteroarylene, C_0-C_6alkylC_3-C_7cycloalkylene, C_1-C_{12}alkylene or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with OH or C_1-C_4alkyl; and

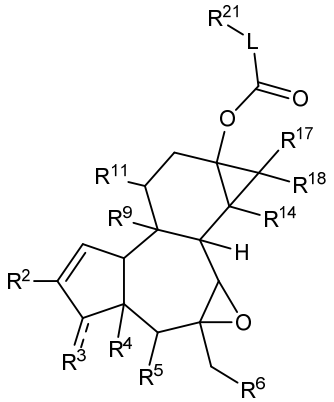
R^{21} is H, -OH, -SH,-$S(O)_2R^j$, -SR^j, -$N(R^j)_2$, -$Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –C(O)OR^k, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1; and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl or, when an N atom is present an N-protecting group;

each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

R^k is H or M^+ counterion;; or

wherein the compound is a compound of formula (Vb):



(Vb)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

R^2 is a C_1-C_4alkyl;

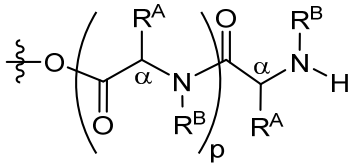
R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -C(O)R^{a1}, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^4 and R^5 are each independently H or -OR^b, wherein R^b is H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-

C_6alkylaryl, or C_0-C_6alkylheteroaryl;

R^6 is OH, halo, -OP(O)($OR^{b'}$)$_2$, or -OC(O)R^c, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-(NR^{c1})$_2$ or -C_1-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

R^9 is OR^e, wherein R^e is H, C_1-C_6alkyl, or aryl;

R^{11} is C_1-C_4alkyl;

R^{14} is H or OR^g; wherein R^g is H or C_1-C_6alkyl;

R^{17} and R^{18} are each independently C_1-C_4alkyl or C_1-C_4alkyl-OR^h, wherein R^h is H or C_1-C_6alkyl;

L is C_0-C_6alkylarylene, C_0-C_6alkylheteroarylene, C_0-C_6alkylC_3-C_7cycloalkylene, C_1-C_{12}alkylene or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with OH or C_1-C_4alkyl; and

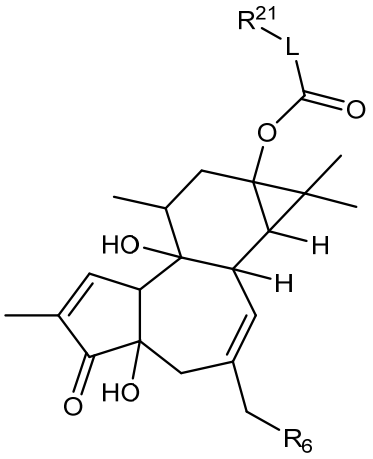
R^{21} is H, -OH, -SH,-$S(O)_2R^j$, -SR^j, -$N(R^j)_2$, -$Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –C(O)OR^k, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1; and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl or, when an N atom is present an N-protecting group;

each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

R^k is H or M^+ counterion; or

wherein the compound is a compound of formula (Vc):



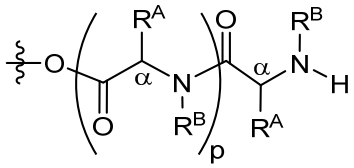
(Vc)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

R^6 is OH, halo, -OP(O)($OR^{b'}$)$_2$, or -OC(O)R^c, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-(NR^{c1})$_2$ or -C_1-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

L is C_0-C_6alkylarylene, C_0-C_6alkylheteroarylene, C_0-C_6alkylC_3-C_7cycloalkylene, C_1-C_{12}alkylene or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with OH or C_1-C_4alkyl; and

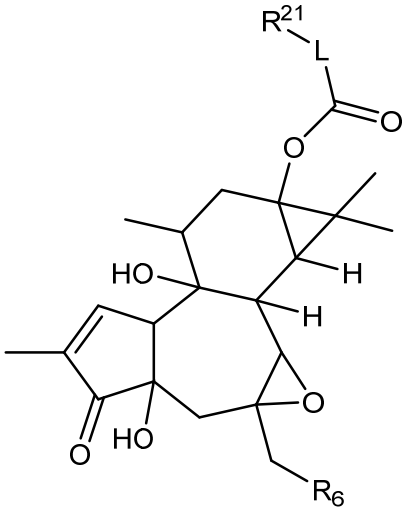
R^{21} is H, -OH, -SH,-S(O)$_2R^j$, -SR^j, -N(R^j)$_2$, -Si(R^j)$_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –C(O)OR^k, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1; and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl or, when an N atom is present an N-protecting group;

each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

R^k is H or M^+ counterion; or

wherein the compound is a compound of formula (Vd):



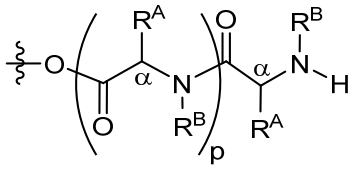
(Vd)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof;

wherein

R^6 is OH, halo, -OP(O)($OR^{b'}$)$_2$, or -OC(O)R^c, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-(NR^{c1})$_2$ or -C_1-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; or

R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

p is 0, 1, or 2;

L is C_0-C_6alkylarylene, C_0-C_6alkylheteroarylene, C_0-C_6alkylC_3-C_7cycloalkylene, C_1-C_{12}alkylene or C_2-C_{12}alkenylene, wherein the C_1-C_{12}alkylene or C_2-C_{12}alkenylene is optionally substituted with OH or C_1-C_4alkyl; and

R^{21} is H, -OH, -SH,-$S(O)_2R^j$, -SR^j, -$N(R^j)_2$, -$Si(R^j)_3$, C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, 5 to 12 membered bridged bicyclyl, adamantyl, or –$C(O)OR^k$, wherein the C_3-C_7cycloalkyl, heterocyclyl, aryl, heteroaryl, spiroC_5-C_{12} cycloalkyl, bridged bicyclyl, or adamantyl is optionally substituted with 1 to 3 of J^1; and wherein optionally 1 to 2 carbon atoms of the spiroC_5-C_{12}cycloalkyl or bridged bicyclyl is replaced with a heteroatom selected from N, O and S, and optionally substituted with C_1-C_4alkyl or, when an N atom is present an N-protecting group;

each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

J^1 is selected from OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl; and

R^k is H or M^+ counterion.

36. The use of any one of claims 34-35,

wherein R^{21} is C_3-C_7cycloalkyl, wherein the C_3-C_7cycloalkyl is optionally substituted with 1 to 3 of J^1, preferably wherein the C_3-C_7cycloalkyl is selected from the group consisting of cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, wherein the C_3-C_7cycloalkyl is optionally substituted with 1 to 3 of J^1; or

wherein R^{21} is heterocyclyl, wherein the heterocyclyl is optionally substituted with 1 to 3 of J^1, preferably wherein the heterocyclyl is selected from the group consisting of oxiranyl, oxetanyl, azetidynyl, oxazolyl, thiazolidinyl, thiazolyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, 2,3-dihydrofuranyl, dihydropyranyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyridinyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and azapanyl, wherein the heterocyclyl is optionally substituted with 1 to 3 of J^1; or

wherein R^{21} is aryl, wherein the aryl is optionally substituted with 1 to 3 of J^1, preferably wherein R^{21} is a phenyl or napthyl, wherein the phenyl or napthyl is optionally substituted with 1 to 3 of J^1; or

wherein R^{21} is heteroaryl, wherein the heteroaryl is optionally substituted with 1 to 3 of J^1; preferably wherein the heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzoxazolyl, benzothiazolyl, purinyl, benzimidazolyl, indolyl, isoquinolyl, quinoxalinyl, and quinolyl, wherein the heteroaryl is optionally substituted with 1 to 3 of J^1; or

wherein R^{21} is adamantyl, wherein the adamantyl is optionally substituted with 1 to 3 of J^1; or

wherein R^{21} is spiroC_5-C_{12} cycloalkyl, wherein the spiroC_5-C_{12} cycloalkyl has 0-2 carbon

atoms replaced with 0-2 heteroatoms selected from N, O and S, and is optionally substituted with 1 to 3 of J^1, or when an N atom is present an N-protecting group; or

wherein R^{21} is 5 to 12 membered bridged bicyclyl, wherein the bridged bicyclyl has 0-2 carbon atoms replaced with 0-2 heteroatoms selected from N, O or S, and is optionally substituted with 1 to 3 of J^1, or when an N atom is present an N-protecting group.

37. The use of any one of claims 34-36,

wherein L is C_1-C_6alkylene, C_3-C_6alkylene or C_3-C_{12}alkyl; or

wherein L is C_1-C_6alkenylene, C_3-C_6alkenylene or C_3-C_{12}alkenylene.

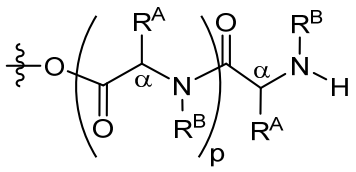
38. The use of any one of claims 34-37,

wherein R^6 is -OH; or

wherein R^6 is $-OP(O)(OR^{b'})_2$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; or

wherein R^6 is $-OC(O)R^c$, wherein R^c is $-C_1$-C_6alkyl, $-C_1$-C_6alkyl-$(NR^{c1})_2$ or $-C_1$-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; and R^k is H or a M^+ counterion; or

wherein: R^6 is



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

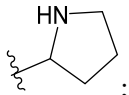
p is 0, 1, or 2.

39. The use of claim 38,

wherein each R^A is independently hydrogen (glycine), methyl (alanine), propan-2-yl (valine), propan-1-y1 (norvaline), 2-methylpropan-1-y1 (leucine), 1-methylpropan-1-y1 (isoleucine), butan-1-y1 (norleucine), phenyl (2-phenylglycine), benzyl (phenylalanine), p-hydroxybenzyl (tyrosine), indol-3-ylmethyl (tryptophan), imidazol-4-ylmethyl (histidine), hydroxymethyl (serine), 2-hydroxyethyl (homoserine), 1–hydroxyethyl (threonine), mercaptomethyl (cysteine), methylthiomethyl (S-

methylcysteine), 2-mercaptoethyl (homocysteine), 2-methylthioethyl (methionine), carbamoylmethyl (asparagine), 2-carbamoylethyl (glutamine), carboxymethyl (aspartic acid), 2-carboxyethyl (glutamic acid), 4-aminobutan-1-y1 (lysine), 4-amino-3-hydroxybutan-1-y1 (hydroxylysine), 3-aminopropan-1-y1 (ornithine), 3-guanidinopropan-1-y1 (arginine), or 3-ureido-propan-1-yl (citrulline);

each R^B is H, or R^B together with the adjacent R_A and the N atom form a prolyl side chain:



; and

p is 0, 1 or 2; or

wherein: each R^A is independently methyl (alanine), propan-2-y1 (valine), 2-methylpropan-1-y1 (leucine), imidazol-4-ylmethyl (histidine), hydroxymethyl (serine), 1-hydroxyethyl (threonine), carbamoylmethyl (asparagine), 2-carbamoylethyl (glutamine), 4-aminobutan-1-y1 (lysine), carboxymethyl (aspartic acid), 3-guanidinopropan-1-y1 (arginine), benzyl (phenylalanine), or 4-aminobutan-1-y1 (lysine);

R^B is H; and

p 0, 1, or 2; or

wherein each R^A is independently propan-2-y1 (valine), 2-methylpropan-1-y1 (leucine), carboxymethyl (aspartic acid), benzyl (phenylalanine), or 4-aminobutan-1-y1 (lysine);

each R^B is H; and

p is 0, 1, or 2.

40. The use of claim 39,

wherein p is 0; or

wherein p is 1; or

wherein p is 1;

first of R^A is propan-2-y1 (valine) and second of R^A is propan-2-y1 (valine); and each of R^B is H (dipeptide Val-Val); or

first of R^A is 2-methylpropan-1-y1 (leucine), and second of R^A is 2-methylpropan-1-y1 (leucine); and each of R^B is H (dipeptide Leu-Leu); or

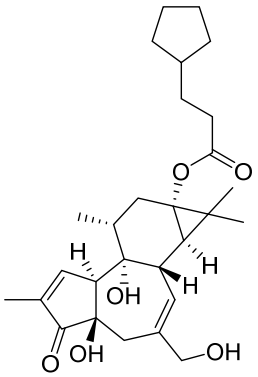
first of R^A is methyl (alanine) and second of R^A is methyl (alanine); and each of R^B is H (dipeptide Ala-Ala); or

first of R^A is 4-aminobutan-1-y1 (lysine); second of R^A is 4-aminobutan-1-y1 (lysine); and each of R^B is H (dipeptide Lys-Lys); or

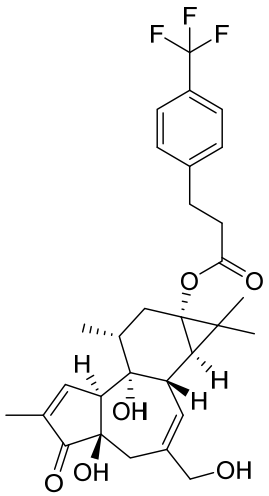
first of R^A is hydrogen; second of R^A is 4-aminobutan-1-y1, and each of R^B is H (dipeptide Gly-Lys).

41. The use of any one of claims 37-40, wherein each of the α-carbon of the amino acid other than glycine is in the L or D configuration.

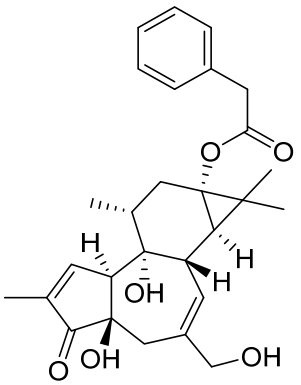
42. The use of claim 34, wherein the compound is selected from the group consisting of the compounds or a pharmaceutical salt thereof listed below:



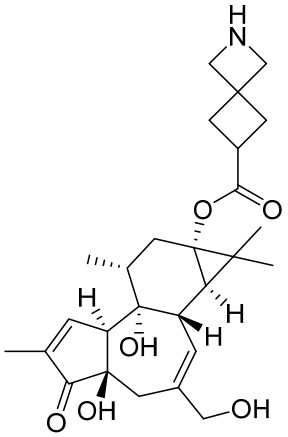
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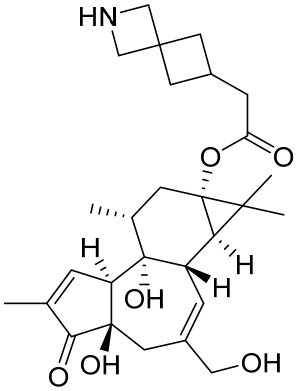
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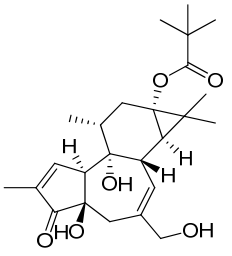
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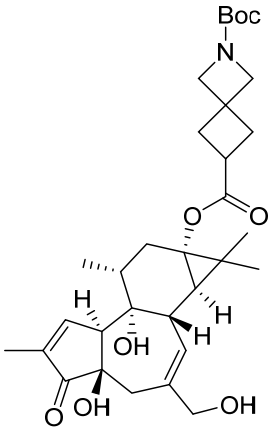
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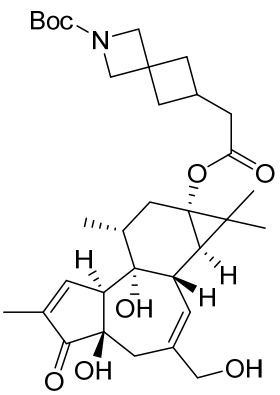
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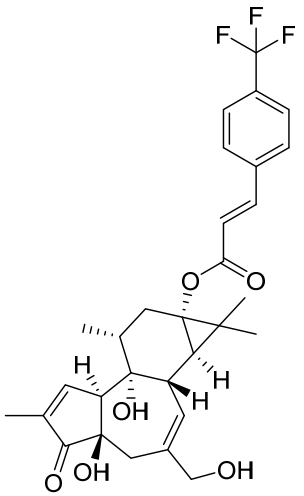
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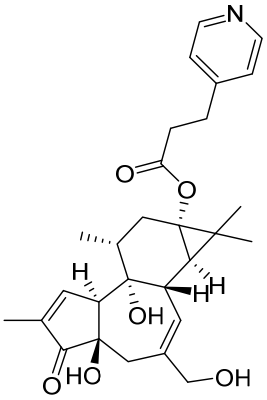
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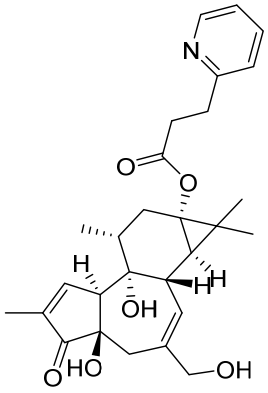
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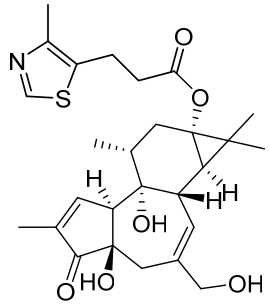
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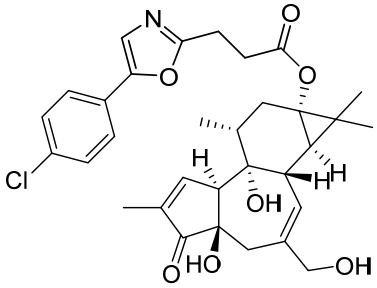
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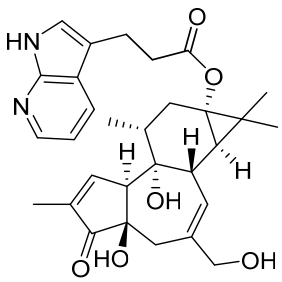
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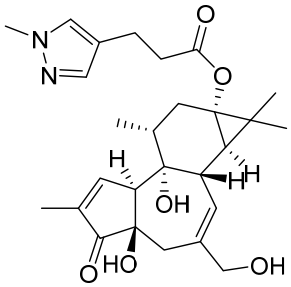
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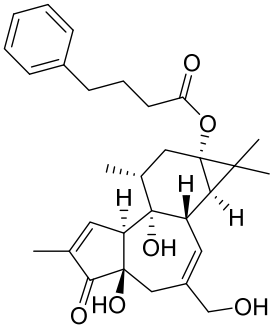
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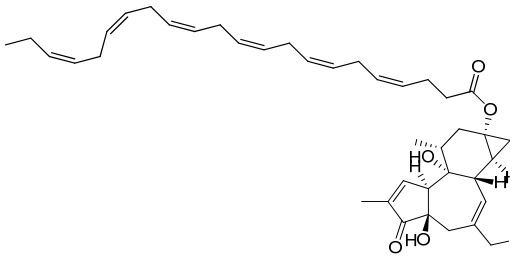
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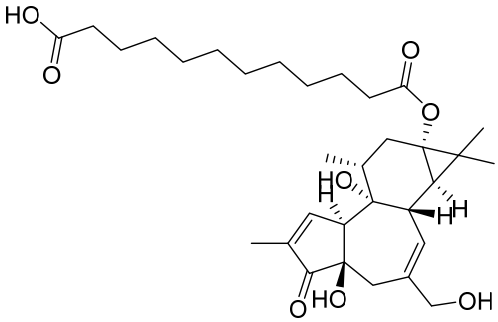
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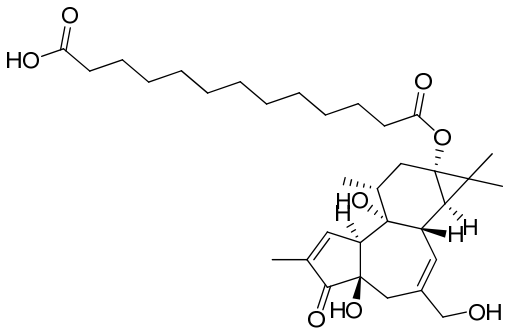
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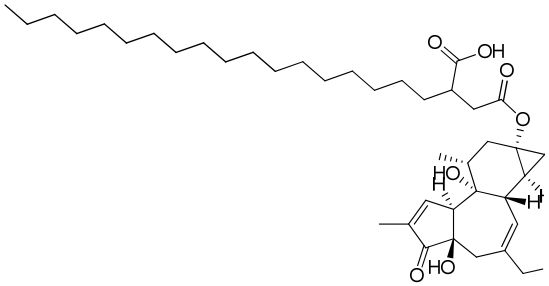
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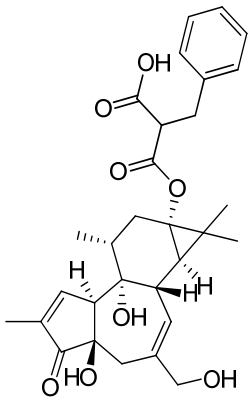
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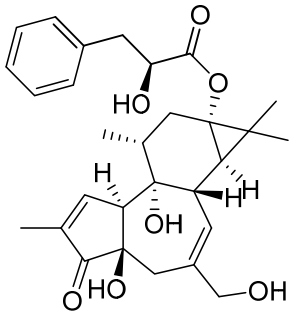
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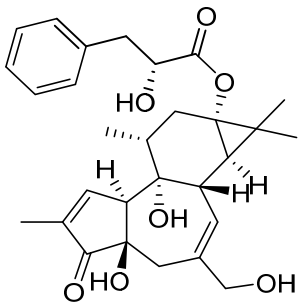
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K101-C1354



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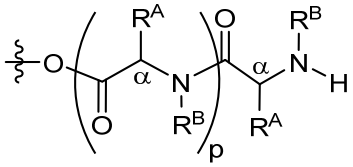
or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

43. The use of claim 42,

wherein the substituent on the C20 carbon atom of the compound is replaced with -$OP(O)(OR^{b'})_2$, wherein each $R^{b'}$ is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl; or

wherein the substituent on the C20 carbon atom of the compound is replaced with -$OC(O)R^c$, wherein R^c is -C_1-C_6alkyl, -C_1-C_6alkyl-$(NR^{c1})_2$ or -C_1-C_6alkylC(O)OR^k; R^{c1} is H, C_1-C_6alkyl, or two R^{c1} together with the N atom form a 5 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O, and S; and R^k is H or a M^+ counterion; or

wherein the substituent on the C20 carbon atom of the compound, where appropriate, is substituted with



wherein,

each occurrence of R^A is independently selected from a side chain of a natural or non-natural amino acid, wherein each occurrence of R^A is same or different;

each occurrence of R^B is independently H, or R^B together with R^A and the N atom to which it is attached form a heterocyclic ring of a natural or non-natural amino acid, wherein each occurrence of R^B is same or different; and

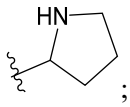
p is 0, 1, or 2.

44. The use of claim 43,

wherein each R^A is independently hydrogen (glycine), methyl (alanine), propan-2-yl (valine), propan-1-y1 (norvaline), 2-methylpropan-1-y1 (leucine), 1-methylpropan-1-y1 (isoleucine), butan-1-y1 (norleucine), phenyl (2-phenylglycine), benzyl (phenylalanine), p-hydroxybenzyl (tyrosine), indol-3-ylmethyl (tryptophan), imidazol-4-ylmethyl (histidine), hydroxymethyl (serine), 2-hydroxyethyl

(homoserine), 1–hydroxyethyl (threonine), mercaptomethyl (cysteine), methylthiomethyl (S-methylcysteine), 2-mercaptoethyl (homocysteine), 2-methylthioethyl (methionine), carbamoylmethyl (asparagine), 2-carbamoylethyl (glutamine), carboxymethyl (aspartic acid), 2-carboxyethyl (glutamic acid), 4-aminobutan-1-yl (lysine), 4-amino-3-hydroxybutan-1-yl (hydroxylysine), 3-aminopropan-1-yl (ornithine), 3-guanidinopropan-1-yl (arginine), or 3-ureido-propan-1-yl (citrulline);

each R^B is H, or R^B together with the adjacent R_A and the N atom form a prolyl side chain:



; and

p is 0, 1 or 2; or

wherein each R^A is independently methyl (alanine), propan-2-yl (valine), 2-methylpropan-1-yl (leucine), imidazol-4-ylmethyl (histidine), hydroxymethyl (serine), 1-hydroxyethyl (threonine), carbamoylmethyl (asparagine), 2-carbamoylethyl (glutamine), 4-aminobutan-1-yl (lysine), carboxymethyl (aspartic acid), 3-guanidinopropan-1-yl (arginine), benzyl (phenylalanine), or 4-aminobutan-1-yl (lysine);

R^B is H; and

p 0, 1, or 2; or

wherein each R^A is independently propan-2-yl (valine), 2-methylpropan-1-yl (leucine), carboxymethyl (aspartic acid), benzyl (phenylalanine), or 4-aminobutan-1-yl (lysine);

each R^B is H; and

p is 0, 1, or 2.

45. The use of claim 44,

wherein p is 0; or

wherein p is 1; or

wherein p is 1;

first of R^A is propan-2-yl (valine) and second of R^A is propan-2-yl (valine); and each of R^B is H (dipeptide Val-Val); or

first of R^A is 2-methylpropan-1-yl (leucine), and second of R^A is 2-methylpropan-1-yl (leucine); and each of R^B is H (dipeptide Leu-Leu); or

first of R^A is methyl (alanine) and second of R^A is methyl (alanine); and each of R^B is H (dipeptide Ala-Ala); or

first of R^A is 4-aminobutan-1-yl (lysine); second of R^A is 4-aminobutan-1-yl (lysine); and each of R^B is H (dipeptide Lys-Lys); or

first of R^A is hydrogen; second of R^A is 4-aminobutan-1-yl, and each of R^B is H (dipeptide Gly-Lys).

46. The use of any one of claims 43-45, wherein each of the α-carbon of the amino acid other than glycine is in the L or D configuration.