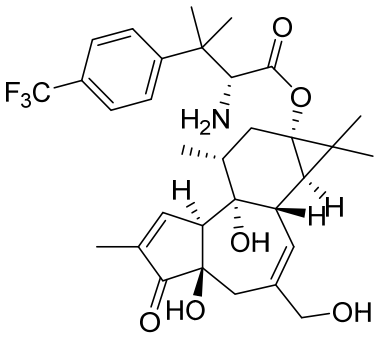
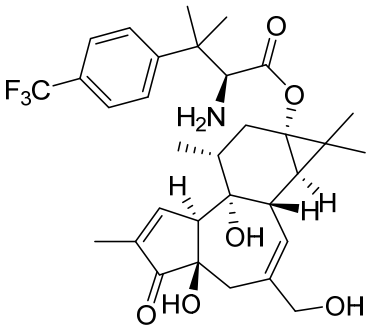
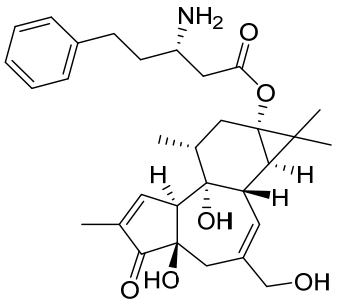


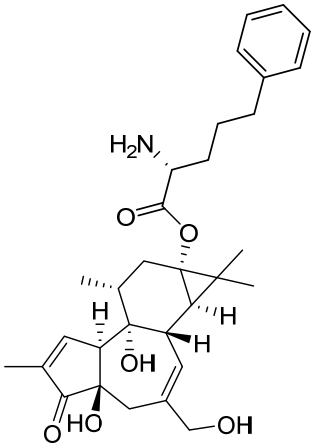
K101-C134901



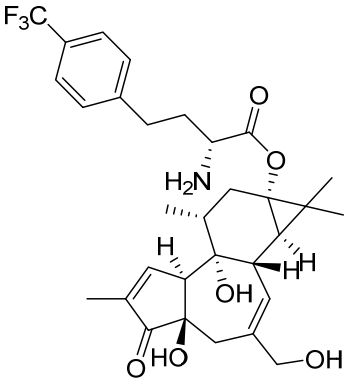
K101-C134902



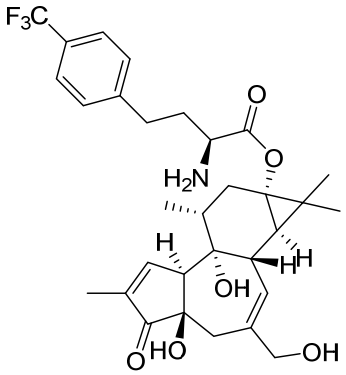
K101-C1350



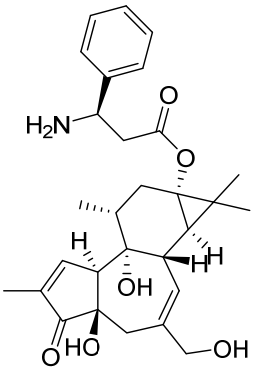
K101-C1351



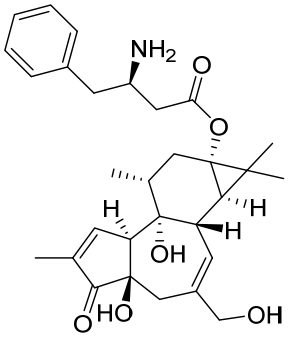
K101-C135601



K101-C135602



K101-C1357



K101-C1358

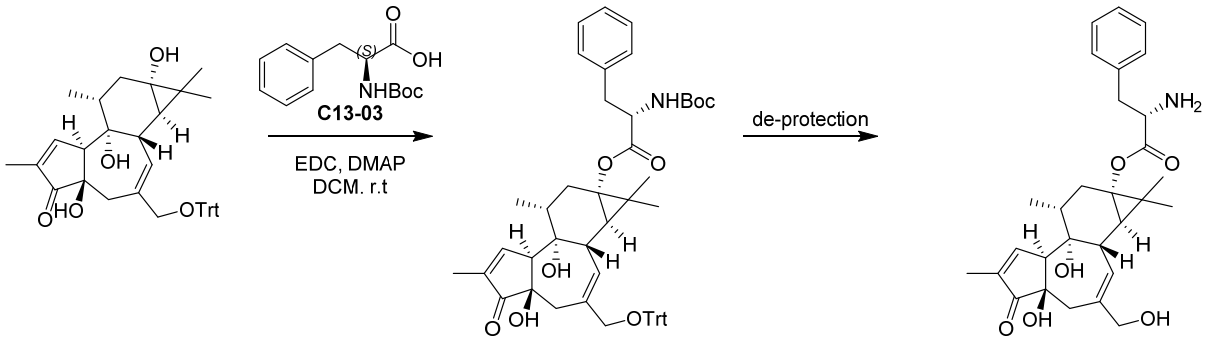
(eluting with: PE/EtOAc=2/1) to give **K101-C1302-A** (34.00 mg, 42.45 μmol, 53.72% yield, 98.736% purity) as a white solid.

[0317] 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.

[0318] LC-MS (m/z): 571.3 $[M+Na]^+$

[0319] ^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



K101-C20Tr-B **K101-C1303-A** **K101-C1303**

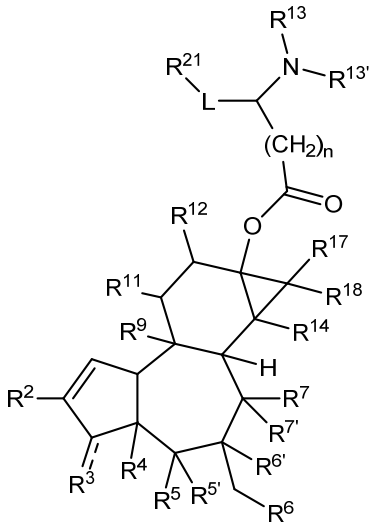
[00253] Preparation of Compound **K101-C1303-A**: To a solution of **K101-C20Tr-B** (30.00 mg, 50.78 μmol, 1.00 eq) in DCM (2.00 mL) were added (2S)-2-(tert-butoxycarbonylamino)-3-phenyl-propanoic acid (C13-03) (26.95 mg, 101.57 μmol, 2.00 eq), DMAP (24.82 mg, 203.13 μmol, 4.00 eq) and EDC (19.47 mg, 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.

[00254] ^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. A compound of formula (II):



(II)

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

wherein

R^2 is a C_1-C_4alkyl;

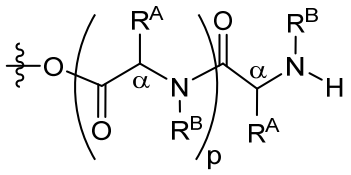
R^3 is O double bonded to the ring carbon when (- - -) is a bond, or $–OR^a$; wherein R^a is H or $–C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

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 H, 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, or $–OC(O)R^c$, wherein 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;

$R^{6'}$ and $R^{7'}$ are 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, 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^l, 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;

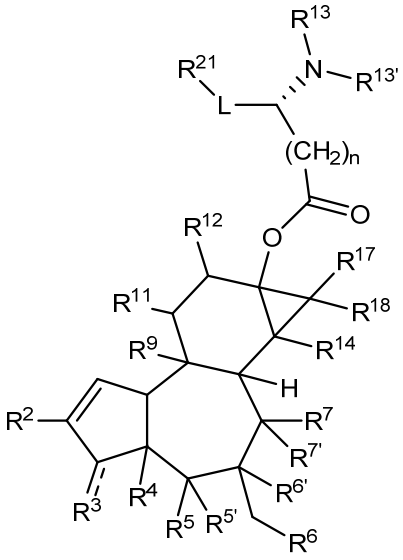
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

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.

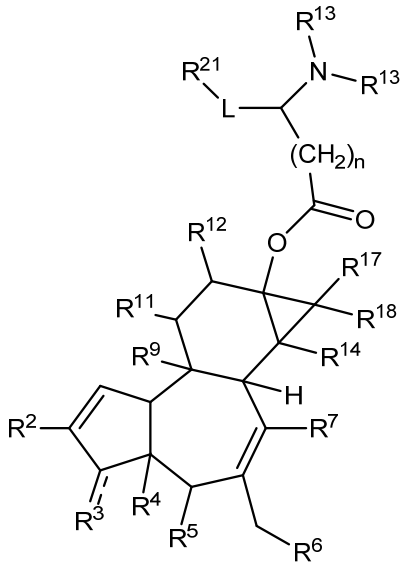
2. The compound of claim 1, having the structure of formula (II'):



(II')

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

3. The compound of claim 1, having the structure of formula (IIa):



(IIa)

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

wherein

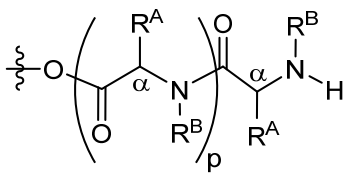
R^2 is a C_1-C_4alkyl;

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, or -$OC(O)R^c$, wherein 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, 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;

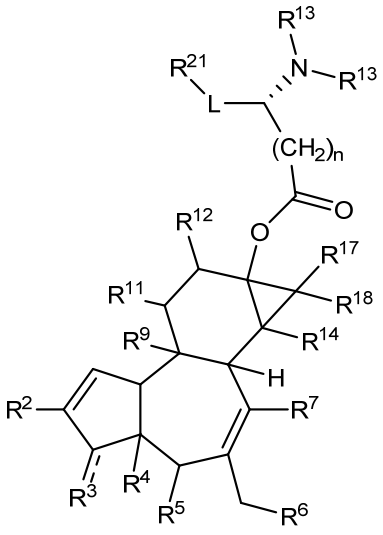
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

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.

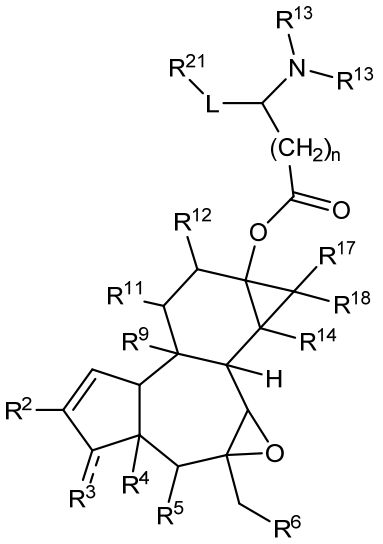
4. The compound of claim 3, having the structure of formula (IIa'):



(IIa')

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

5. The compound of claim 1, having the structure of formula (IIb):



(IIb)

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

wherein

R^2 is a C_1-C_4alkyl;

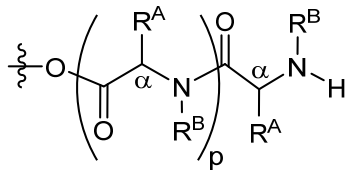
R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-

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, or -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; 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;

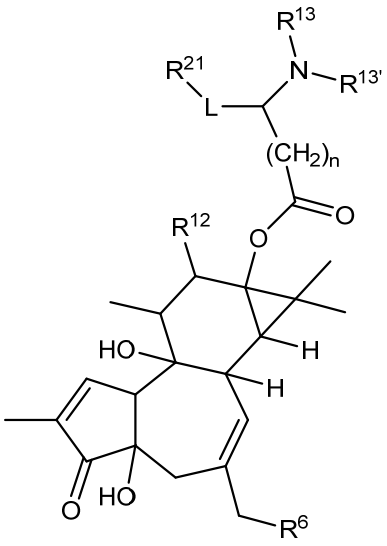
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

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.

6. The compound of claim 3, having the structure of formula (IIc):



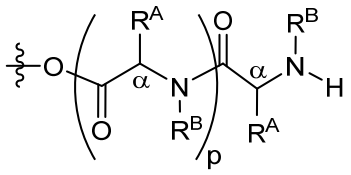
(IIc)

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

wherein

R^6 is OH, halo, or $-OC(O)R^c$, wherein 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^{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, 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;

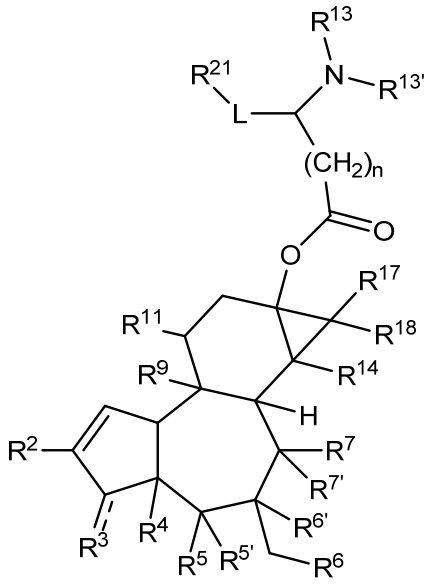
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

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.

7. The compound of claim 1 having the structure of formula (III):



(III)

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

wherein

R^2 is a C_1-C_4alkyl;

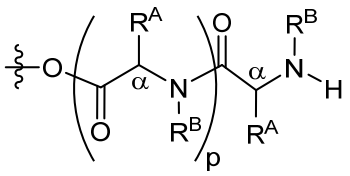
R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is H or -$C(O)R^{a1}$, wherein R^{a1} is C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl;

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 H, 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, or -$OC(O)R^c$, wherein 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;

$R^{6'}$ and $R^{7'}$ are 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;

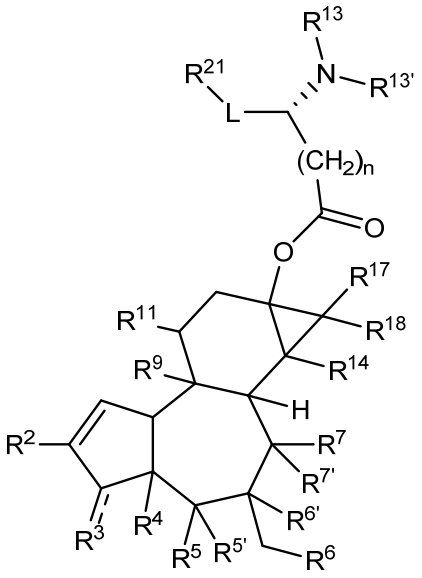
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

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.

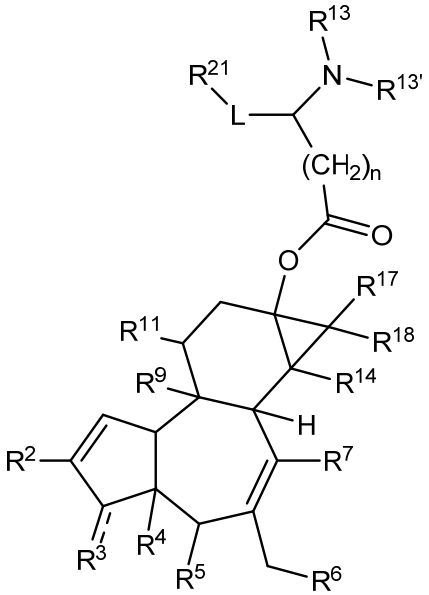
8. The compound of claim 7 having the structure of formula (III'):



(III')

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

9. The compound of claim 7 having the structure of formula (IIIa):



(IIIa)

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

wherein

R^2 is a C_1-C_4alkyl;

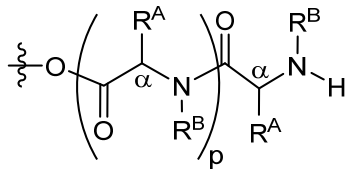
R^3 is O double bonded to the ring carbon when (- - -) is a bond, or -OR^a; wherein R^a is

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, or -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; 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;

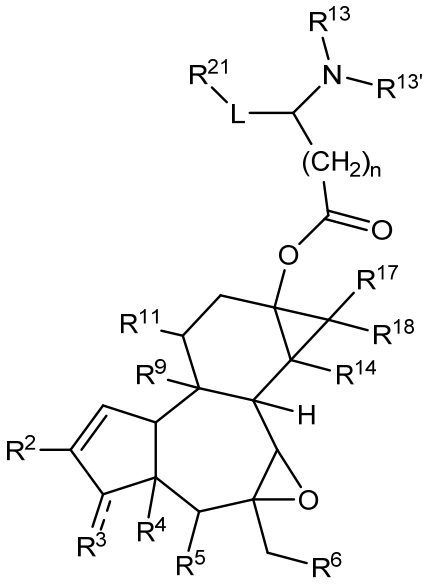
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

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.

10. The compound of claim 7 having structure of formula (IIIb):



(IIIb)

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

wherein

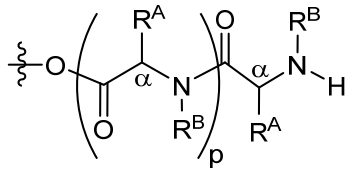
R^2 is a C_1-C_4alkyl;

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, or -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; 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-

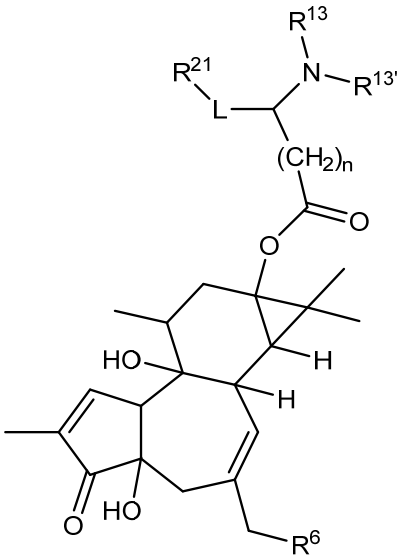
C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

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.

11. The compound of claim 7 having the structure of formula (IIIc):



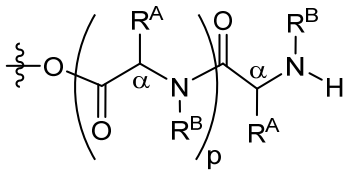
(IIIc)

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

wherein

R^6 is OH, halo, or -OC(O)R^c, wherein 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^{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;

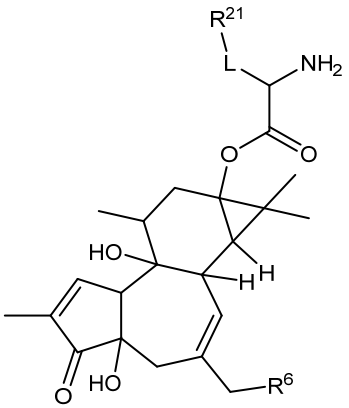
each R^j is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_7cycloalkyl, C_0-C_6alkylheterocyclyl, C_0-C_6alkylaryl, or C_0-C_6alkylheteroaryl, wherein the C_3-C_7cycloalkyl, heterocyclyl, alkylaryl, or heteroaryl is optionally substituted with 1 to 3 of J^1;

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.

12. The compound of claim 11 having the structure of formula (IIIe):



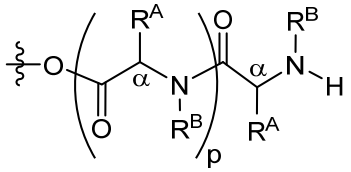
(IIIe)

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

wherein

R^6 is OH, halo, or -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; 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.

13. The compound of any one of claims 1 to 12, wherein R^{21} is C_3-C_7cycloalkyl, wherein the C_3-C_7cycloalkyl is optionally substituted with 1 to 3 of J^1.

14. The compound of claim 13, 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.

15. The compound of any one of claims 1 to 12, wherein R^{21} is heterocyclyl, wherein the heterocyclyl is optionally substituted with 1 to 3 of J^1.

16. The compound of claim 15, 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.

17. The compound of any one of claims 1 to 12, wherein

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

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

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

18. The compound of claim 17, 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.

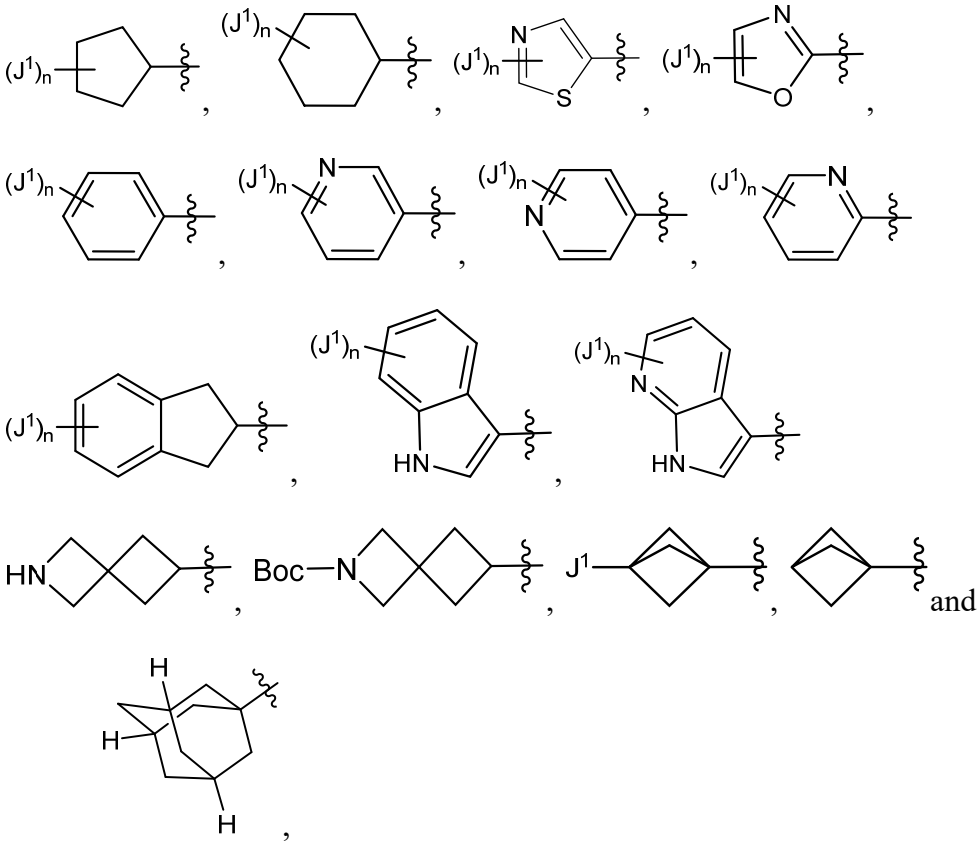
19. The compound of any one of claims 1 to 12, wherein

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

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

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.

20. The compound of any one of claims 1 to 12, wherein R^{21} is selected from:



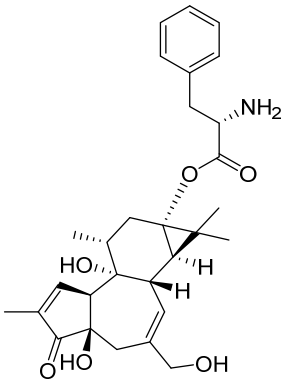
wherein J^1 is OH, CN, halo, C_1-C_4alkyl, and haloC_1-C_4alkyl, and n is 0-3.

21. The compound of any one of claims 1 to 20, wherein L is C_1-C_6alkylene, C_3-C_6alkylene or C_3-C_{12}alkylene.

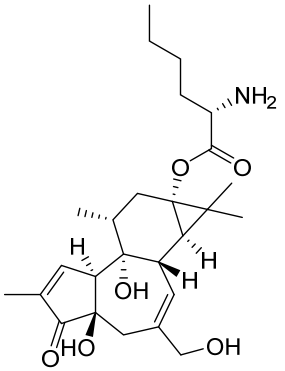
22. The compound of any one of claims 1 to 20, wherein L is C_1-C_6alkenylene, C_3-C_6alkenylene or C_3-C_{12}alkenylene.

23. The compound of any one of claims 1-22, wherein n is 0.

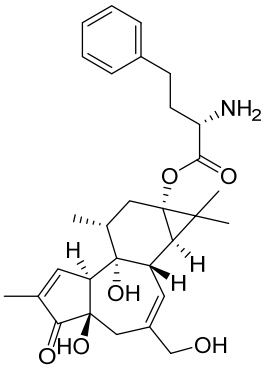
24. The compound of claim 1 selected from the group consisting of the compounds listed below:



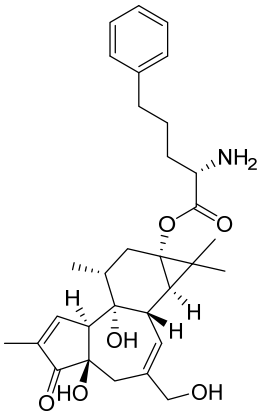
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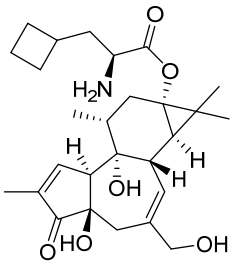
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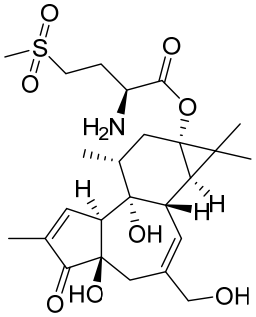
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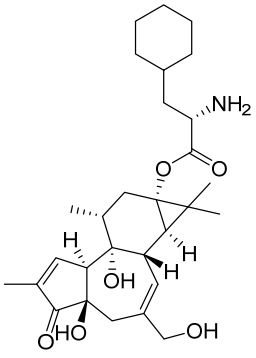
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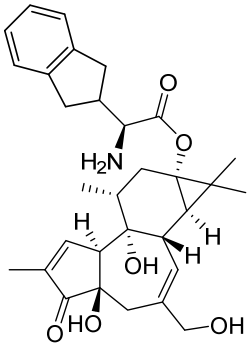
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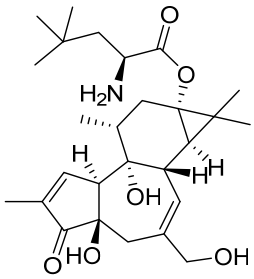


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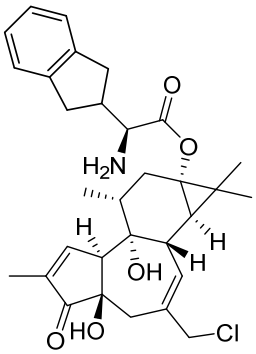
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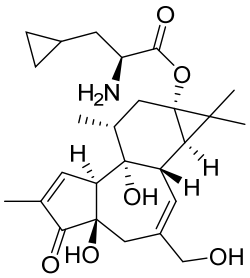


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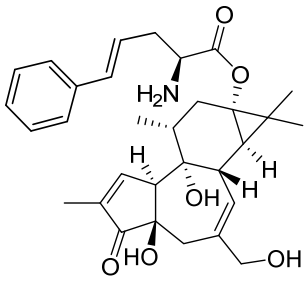
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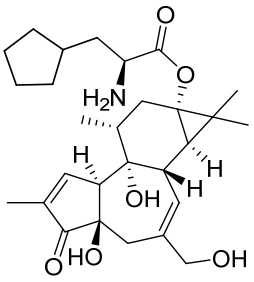
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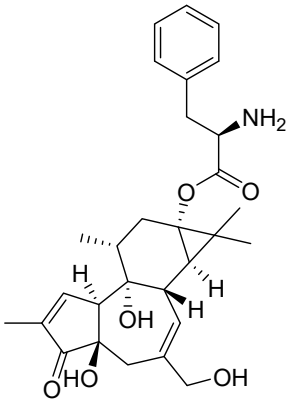
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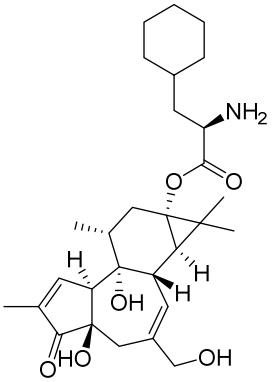
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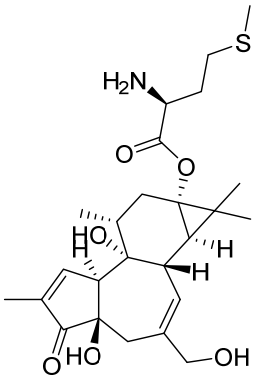
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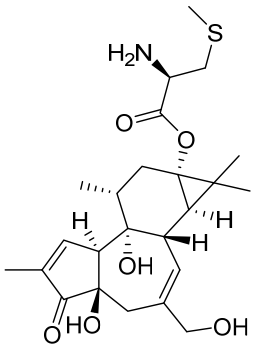
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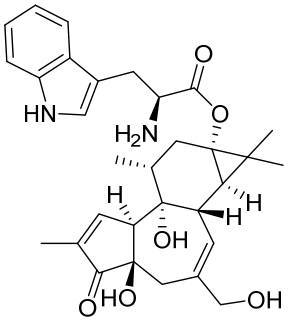
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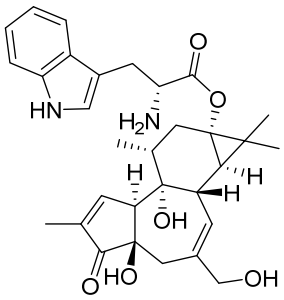
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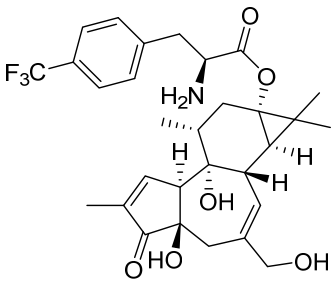
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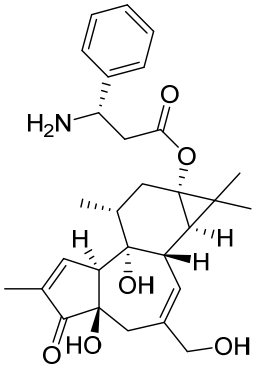
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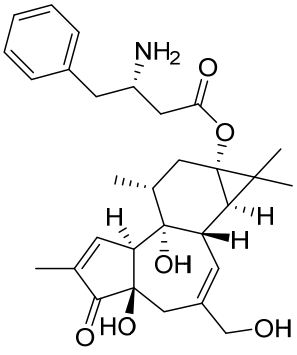
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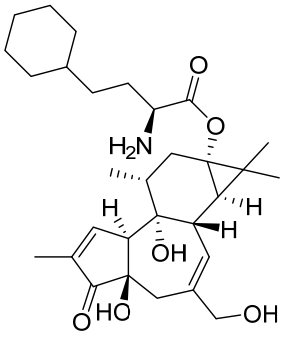
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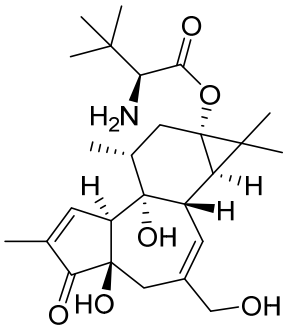
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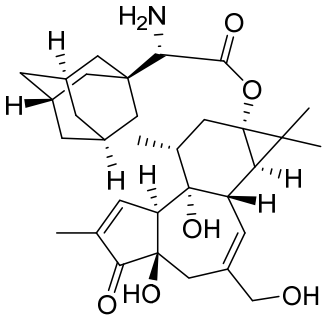
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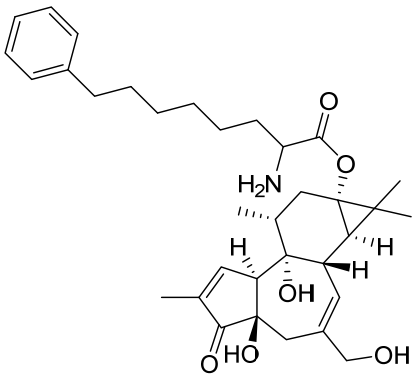
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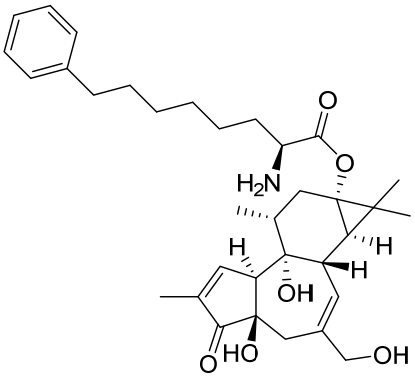
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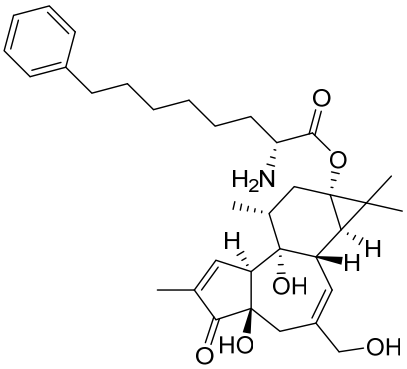
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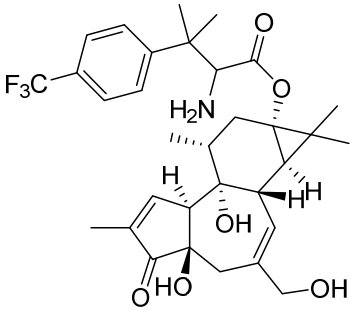
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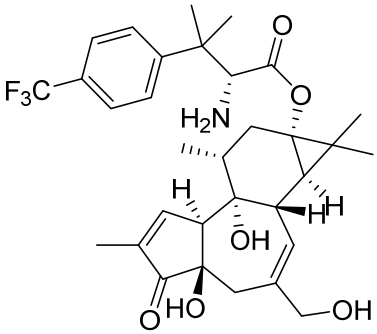
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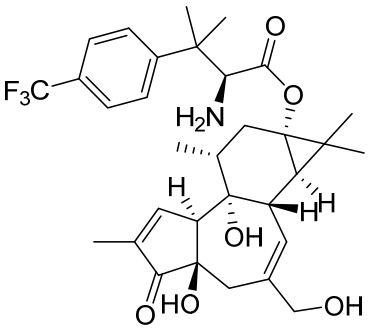
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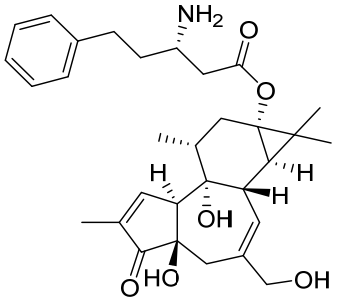
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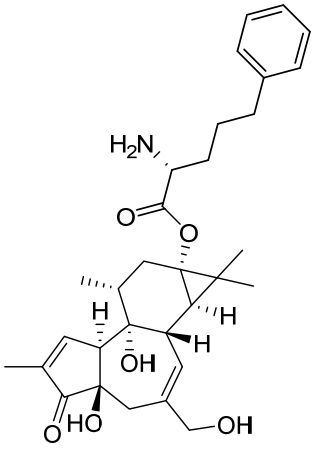
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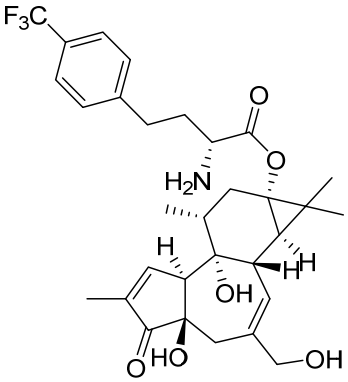
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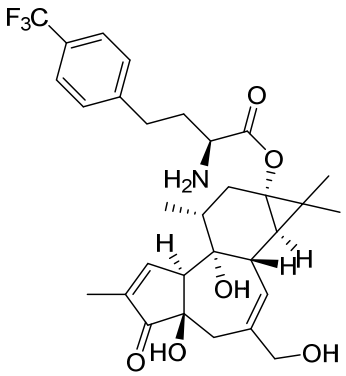
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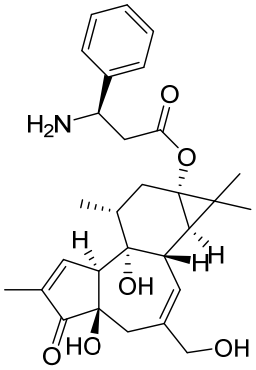
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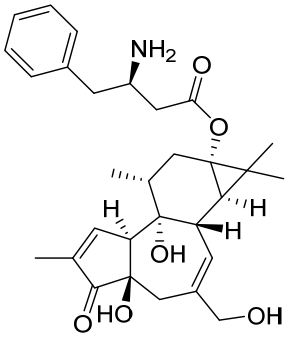
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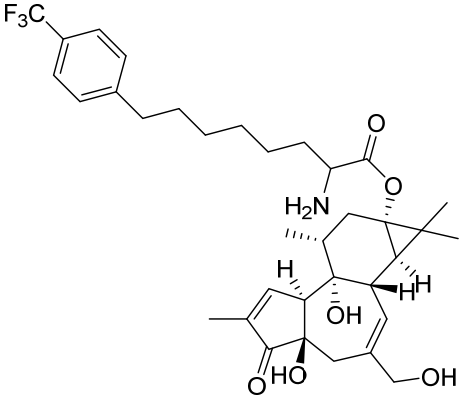
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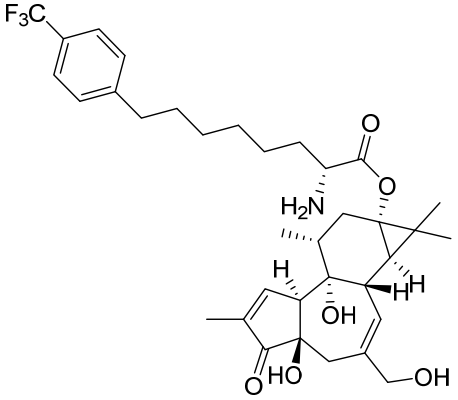
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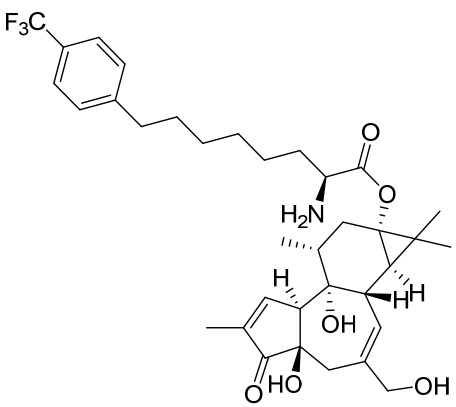
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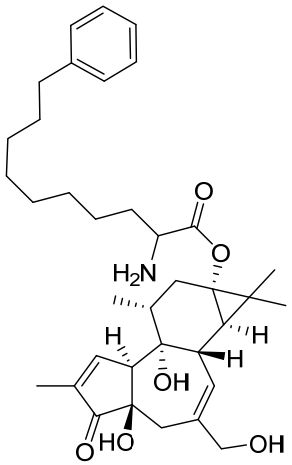
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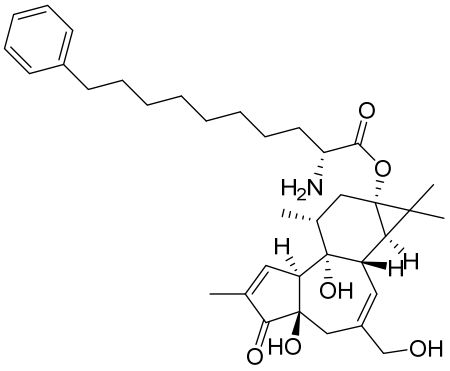
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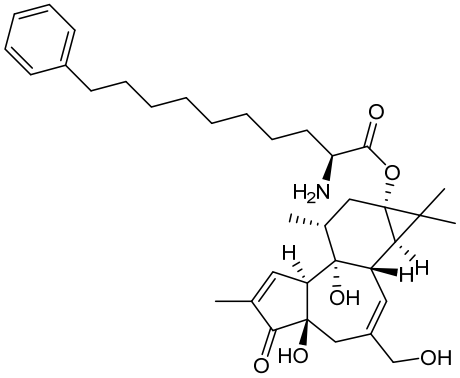
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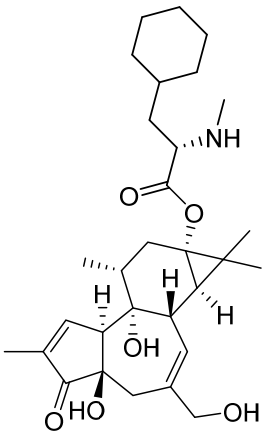
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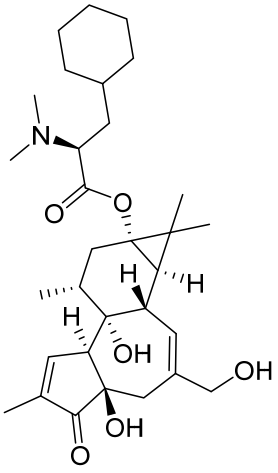
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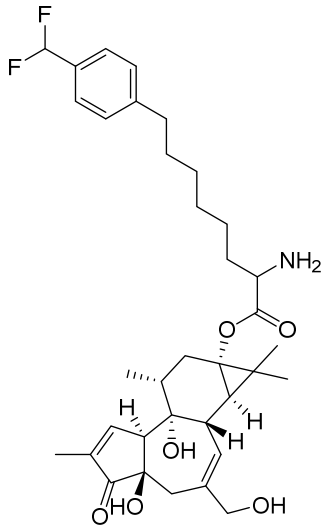
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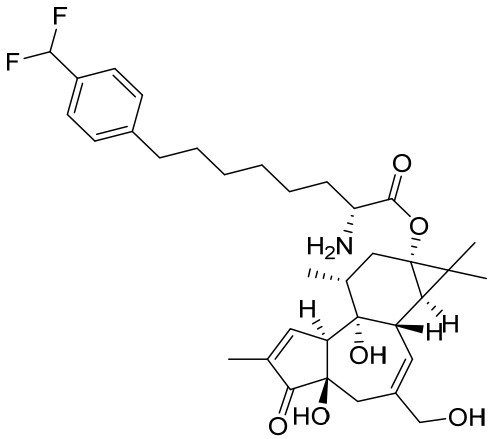
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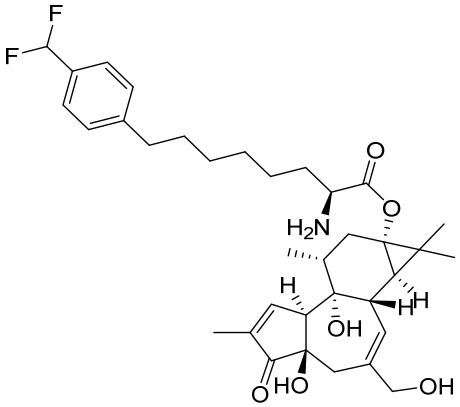
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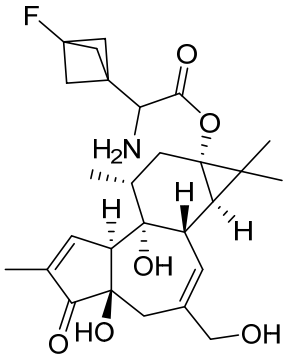
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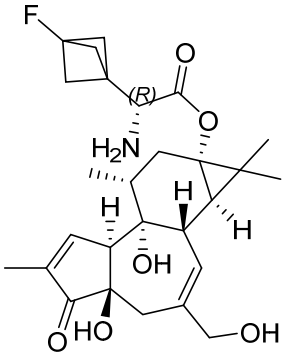
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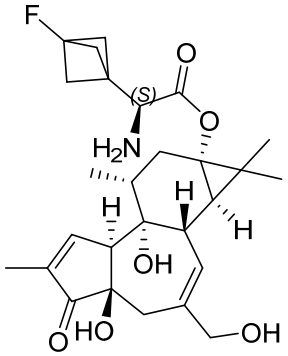
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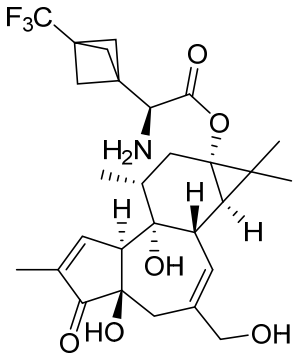
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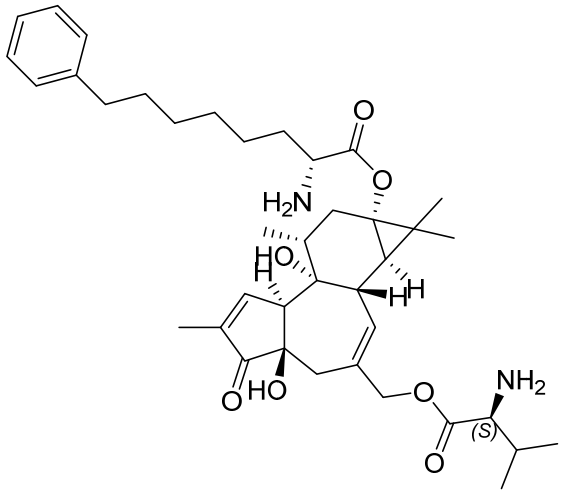
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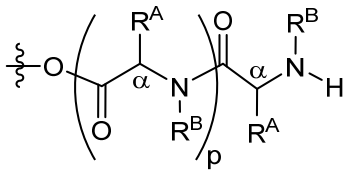


K101-C134801C2003

, or an amino acid prodrug thereof.

25. The compound of any one of claims 1 to 24, 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

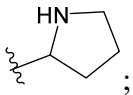
p is 0, 1, or 2.

26. The compound of claim 25, 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.

27. The compound of claim 26, 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.

28. The compound of claim 26, 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.

29. The compound of claim 26, 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).

30. The compound of any one of claims 25 to 29, wherein each of the α-carbon of the amino acid other than glycine is in the L or D configuration.

31. A pharmaceutical composition comprising a compound of any one of claims 1 to 30, and a pharmaceutically acceptable carrier.

32. A method of activating protein kinase C, comprising contacting *in vitro* a mammalian cell with an effective amount of a compound of any one of claims 1 to 30.

33. The method of claim 32, wherein the cell is a cancer cell.

34. Use of a compound of any one of claims 1 to 30 in the preparation of a medicament for treating cancer.

35. The use of claim 34, wherein the cancer is selected from the group consisting of adrenocortical cancer, anal cancer, biliary cancer, bladder cancer, bone cancer, brain cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, head and neck cancer, intestinal cancer, liver cancer, lung cancer, oral cancer, ovarian cancer, pancreatic cancer, renal cancer, prostate cancer, salivary gland cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, sarcoma, and soft tissue carcinomas.

36. The use of claim 34, wherein the cancer is a hematological cancer; or

wherein the cancer is a leukemia or lymphoma; or

wherein the cancer is selected from the group consisting of 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.