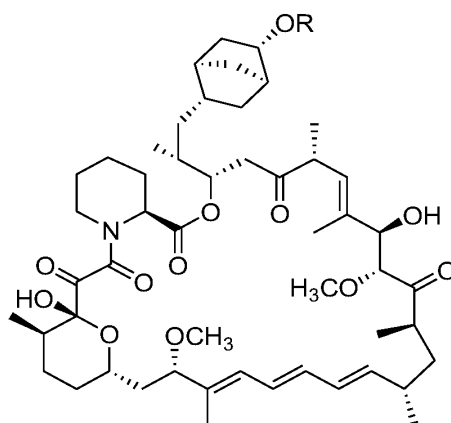


CLAIMS

What is claimed is:

1. A compound of Formula I:



Formula I

wherein:

R is selected from H or $-C(O)(CR^3R^4)_b(CR^5R^6)_d(CR^7R^8R^9)$;

R^3 and R^4 are each, independently, hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, trihalomethyl, or -F;

R^5 and R^6 are each, independently, hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, $-(CR^3R^4)_fOR^{10}$, $-CF_3$, -F, or CO_2R^{11} ;

R^7 is hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, $-(CR^3R^4)_fOR^{10}$, $-CF_3$, -F, or CO_2R^{11} ;

R^8 and R^9 are each, independently, hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, $-(CR^3R^4)_fOR^{10}$, $-CF_3$, -F, or CO_2R^{11} , or R^8 and R^9 can be taken together to form X or a cycloalkyl ring of 3-8 carbon atoms that is optionally mono-, di-, or tri-substituted with $-(CR^3R^4)_fOR^{10}$;

R^{10} is hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, tri- $(C_1$ to C_6 alkyl)silyl, tri- $(C_1$ to C_6 alkyl)silylethyl, triphenylmethyl, benzyl, C_2 to C_8 alkoxymethyl, tri- $(C_1$ to C_6 alkyl)silylethoxymethyl, chloroethyl, or tetrahydropyranyl;

R^{11} is hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, or a C_7 to C_{10} phenylakyl;

X is 5-(2,2-di- $(C_1$ to C_6 alkyl)[1,3]dioxanyl, 5-(2,2-di- $(C_3$ to C_8 cycloalkyl)[1,3]dioxanyl, 4-(2,2-di- $(C_1$ to C_6 alkyl)[1,3]dioxanyl, 4-(2,2-di- $(C_3$ to C_8 cycloalkyl)[1,3]dioxanyl, 4-(2,2-di- $(C_1$ to C_6 alkyl)[1,3]dioxalanyl, or 4-(2,2-di- $(C_3$ to C_8 cycloalkyl)[1,3]dioxalanyl;

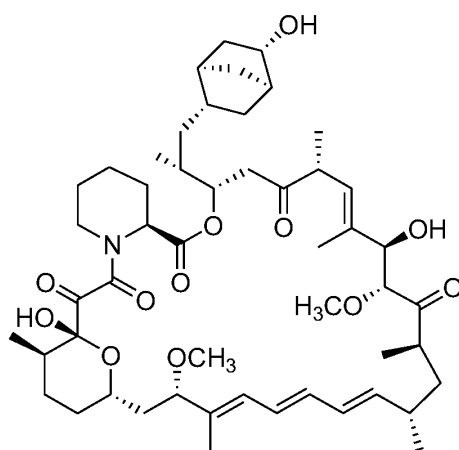
b is a whole number from 0 to 6;

d is a whole number from 0 to 6; and,

f is a whole number from 0 to 6; and/or,

a pharmaceutically acceptable salt, solvate, ester, or mixture thereof.

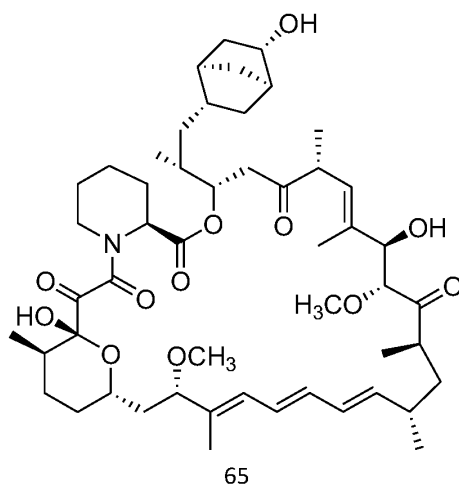
2. The compound and/or pharmaceutically acceptable salt, solvate, ester or mixture of claim 1 wherein R contains at least one moiety selected from H, $-(CR^3R^4)_fOR^{10}$, X or $-(CR^3R^4)_fOR^{10}$ substituted C₃ to C₈ cycloalkyl.
3. A composition comprising the compound, pharmaceutically acceptable salt, solvate, ester or mixture of claim 1 or 2.
4. The composition of claim 3 further comprising a pharmaceutically acceptable carrier.
5. A compound of Formula II:



(Formula II)

and/or a pharmaceutically acceptable salt, solvate, ester, or mixture thereof.

6. A composition comprising the compound, pharmaceutically acceptable salt, solvate, ester or mixture of claim 5.
7. The composition of claim 6 further comprising a pharmaceutically acceptable carrier.
8. A composition comprising about 70% or more of a compound selected from the group consisting of the compound of Formula (II),



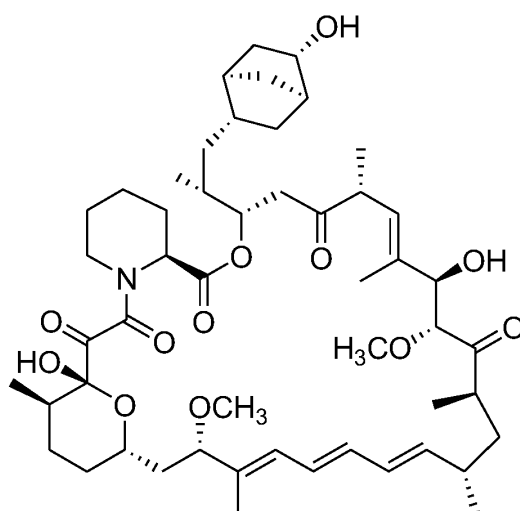
(Formula II)

a pharmaceutically acceptable salt thereof, a solvate thereof, an ester thereof of the compound of formula (I), and mixtures of the foregoing.

9. The composition of claim 8, wherein the composition comprises about 90% or more of a compound selected from the group consisting of the compound of Formula (I), pharmaceutically acceptable salts and solvates of the compound of Formula (II), and mixtures of the foregoing.

10. The composition of claim 8, wherein the composition contains an essentially pure mixture of a compound selected from the group consisting of the compound of Formula (II), pharmaceutically acceptable salts, solvates, and esters of the compound of formula (I), and mixtures of the foregoing.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, diluent or excipient and one or more polyketides, wherein if there is one polyketide it is the polyketide of Formula (II), and wherein if there is more than one polyketide in the composition then the polyketide of Formula II comprises at least about 70% of the polyketide component of the pharmaceutical composition:



Formula II

wherein a pharmaceutically acceptable salt, solvate, and/or hydrate of the compound of Formula II comprises at least 70% of the polyketide component of the pharmaceutical composition.

12. The pharmaceutical composition of claim 11, wherein the compound of Formula II is present in an amount of at least 80% of the polyketide component of the pharmaceutical composition.

13. The pharmaceutical composition of claim 11, wherein the compound of Formula II is present in an amount of at least 90% of the polyketide component of the pharmaceutical composition.

14. The pharmaceutical composition of claim 11, wherein the compound of Formula II is present in an amount of at least 95% of the polyketide component of the pharmaceutical composition.

15. The pharmaceutical composition of claim 11, wherein the compound of Formula II is present in an amount of at least 98% of the polyketide component of the pharmaceutical composition.
16. The pharmaceutical composition of claim 11, wherein the compound of Formula II is essentially the only polyketide in the pharmaceutical composition.
17. The composition of any preceding claim, wherein the solvate, if present, is a hydrate.
18. A composition of any preceding claim wherein the composition is or comprises a bead, tablet, capsule, solution, or suspension.
19. A method of inhibiting the proliferation of a cell, the method comprising contacting said cell with an antiproliferative amount of a compound, pharmaceutically acceptable salt thereof, solvate thereof, ester thereof, or mixture thereof of any preceding claim; and/or the composition of any preceding claim.
20. The method of claim 19, wherein the cell is a human cell.
21. The method of claim 19 or 20, wherein the cell is a human cancer cell.
22. The method of claim 21, wherein the human cancer cell is selected from the group consisting of a blood cancer, bone cancer, solid tumor, adenocarcinoma, brain cancer, glioblastoma, breast adenocarcinoma, bone marrow cancer, erythroleukemia, osteosarcoma, colorectal carcinoma, epidermoid carcinoma, epithelial carcinoma, uterine carcinoma, fibrosarcoma, gastric adenocarcinoma, kidney cancer, leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, leiomyoblastoma, lung carcinoma, small cell lung carcinoma, lymphoma, B cell lymphoma, Burkitt's lymphoma, T cell lymphoma, melanoma, malignant melanoma, neuroblastoma, leukemia ovarian cancer, ovary adenocarcinoma, pancreatic cancer, prostate adenocarcinoma, rhabdomyosarcoma, renal cell carcinoma, sarcoma, uterine sarcoma, squamous cell carcinoma, bladder squamous cell carcinoma, head and neck cancer, and transitional cell carcinoma.
23. The method of any one of claims 19-22 wherein the method is an *in vitro* method.
24. The method of any one of claims 19-22 wherein the method is an *in vivo* method.
25. A method of treating a mammal having a disease, the method comprising administering to said mammal an effective amount of a compound of Formula II, pharmaceutically acceptable salt thereof, solvate thereof, ester thereof, or mixture thereof and/or comprising the compound of Formula II; and/or a composition comprising Formula II.
26. The method of claim 25, wherein the mammal is human.
27. The method of claim 25 or 26, wherein the disease is cancer and the cancer is selected from the group consisting of a blood cancer, bone cancer, solid tumor, adenocarcinoma, brain cancer, glioblastoma, breast adenocarcinoma, bone marrow cancer, erythroleukemia, osteosarcoma, colorectal carcinoma, epidermoid carcinoma, epithelial carcinoma, uterine carcinoma, fibrosarcoma, gastric adenocarcinoma, kidney cancer, leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, leiomyoblastoma, lung carcinoma,

small cell lung carcinoma, lymphoma, B cell lymphoma, Burkitt's lymphoma, T cell lymphoma, melanoma, malignant melanoma, neuroblastoma, leukemia ovarian cancer, ovary adenocarcinoma, pancreatic cancer, prostate adenocarcinoma, rhabdomyosarcoma, renal cell carcinoma, sarcoma, uterine sarcoma, squamous cell carcinoma, bladder squamous cell carcinoma, head and neck cancer, and transitional cell carcinoma.

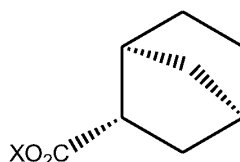
28. The method of any one of claims 25-27, wherein the compound of Formula I and/or Formula II administered as the sole active pharmaceutical agent(s); or the compound(s) of Formula I and/or Formula II is administered in combination with one or more of a chemotherapeutic agent, anti-cancer agent, or immune modulator; and/or radiation therapy and/or surgery.

29. The method of claim 25, wherein the mammal is in need of prevention of organ transplant rejection or host-versus-graft disease.

30. The method of any one of claims 25-29 wherein the administration is via a route selected from the group consisting of parenteral, oral, topical, buccal, sublingual, transdermal, a medical device, a stent, inhalation, injection, subcutaneous, intramuscular, or intravenous; wherein the administration comprises a single dose or multiple doses at the same or different dosages; and/or the members of a combination are administered physically and/or temporally simultaneously or separately.

31. The method of any one of claims 25-30 wherein the compound of Formula I and/or Formula II is provided as a bead, tablet, capsule, solution, or suspension.

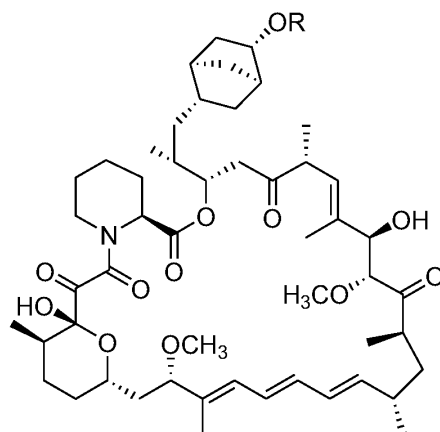
32. A process for preparing a compound of Formula (I) according to claim 1, 2, 5, or 55 or a pharmaceutically acceptable salt thereof, the process comprising a feeding starter *exo*-(1*R*,2*S*,4*R*,5*S*)-5-hydroxybicyclo[2.2.1]heptane-2-carboxylate of formula (III):



(Formula III)

where X = H, alkyl, sodium or potassium, to a rapamycin-producing strain that has been genetically altered to remove or inactivate the rapK gene or a homologue thereof.

33. A prodrug of Formula II, wherein the prodrug is a polyketide of Formula I,



(Formula I)

R is selected from H or $-C(O)(CR^3R^4)_b(CR^5R^6)_d(CR^7R^8R^9)$;

R^3 and R^4 are each, independently, hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, trihalomethyl, or -F;

R^5 and R^6 are each, independently, hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, $-(CR^3R^4)_fOR^{10}$, $-CF_3$, -F, or CO_2R^{11} ;

R^7 is hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, $-(CR^3R^4)_fOR^{10}$, $-CF_3$, -F, or CO_2R^{11} ;

R^8 and R^9 are each, independently, hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, $-(CR^3R^4)_fOR^{10}$, $-CF_3$, -F, or CO_2R^{11} , or R^8 and R^9 can be taken together to form X or a cycloalkyl ring of 3-8 carbon atoms that is optionally mono-, di-, or tri-substituted with $-(CR^3R^4)_fOR^{10}$;

R^{10} is hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, tri- $(C_1$ to C_6 alkyl)silyl, tri- $(C_1$ to C_6 alkyl)silylethyl, triphenylmethyl, benzyl, C_2 to C_8 alkoxymethyl, tri- $(C_1$ to C_6 alkyl)silylethoxymethyl, chloroethyl, or tetrahydropyranyl;

R^{11} is hydrogen, C_1 to C_6 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl, or a C_7 to C_{10} phenylakyl;

X is 5-(2,2-di- $(C_1$ to C_6 alkyl)[1,3]dioxanyl, 5-(2,2-di- $(C_3$ to C_8 cycloalkyl)[1,3]dioxanyl, 4-(2,2-di- $(C_1$ to C_6 alkyl)[1,3]dioxanyl, 4-(2,2-di- $(C_3$ to C_8 cycloalkyl)[1,3]dioxanyl, 4-(2,2-di- $(C_1$ to C_6 alkyl)[1,3]dioxalanyl, or 4-(2,2-di- $(C_3$ to C_8 cycloalkyl)[1,3]dioxalanyl;

b is a whole number from 0 to 6;

d is a whole number from 0 to 6; and,

f is a whole number from 0 to 6; and/or,

a pharmaceutically acceptable salt, solvate, ester, hydrate, or mixture thereof.

34. A composition or method of any preceding claim, wherein the prodrug of Formula I is substituted for the polyketide of Formula II.