

ANTI-CANCER AGENTS AND PREPARATION THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional
5 Appl. Ser. No. 61/906,133, filed November 19, 2013, which is incorporated by
reference as if fully set forth herein.

STATEMENT OF U.S. GOVERNMENT SUPPORT

[0002] This invention was made with government support under
GM053386 awarded by the National Institutes of Health. The government has
10 certain rights in the invention.

FIELD OF THE INVENTION

[0003] Embodiments of the present invention relate to compounds that
can be used to treat disease, e.g., cancer, and compositions and prodrugs
including, or resulting in, these compounds. Methods of making the compounds
15 are also disclosed.

BACKGROUND

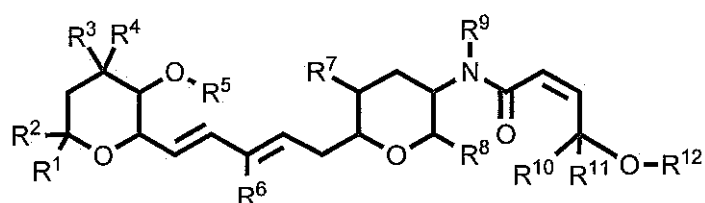
[0004] The American Cancer Society estimates that cancer costs the U.S.
economy almost \$200 billion per year due to the costs of medical treatment
(about \$80 billion per year) and lost productivity due to death and/or disability
20 (about \$120 billion per year). Of course, there is also a human toll as loved ones
are diagnosed, treated, and sometimes die from many forms of cancer. Because
of the high social and economic costs of cancer, new cancer treatments are a top
priority for institutions such as the U.S. National Institutes of Health as well as
major pharmaceutical companies.

SUMMARY

[0005] Proliferative diseases, such as cancer, cause harm to the body
with the rapid growth of cells that interfere with the health function of nearby (or
far-away) tissues. Because the cells replicate quickly, compounds that disrupt
transcription pathways are valuable in fighting the disease. That is, if it is
30 possible to disrupt the function of one or more proteins that play a role in a
transcription pathway, the proliferation (and potential metastasis) of cancerous
cells will be limited. Such a disruption would at least help a patient gain
additional months or years of life.

[0006] One family of protein complexes involved in transcription pathways are spliceosomes. Spliceosomes typically include over 100 proteins that work together to control the excision of exons (i.e., splicing of introns) from genomic material during the transcription. Compounds that interfere with the function of spliceosomes or a spliceosome-regulation protein are valuable for slowing or stopping the spread of proliferative disease.

[0006a] In one aspect of the present disclosure, there is provided a compound according to Formula I or a pharmaceutically acceptable salt thereof:



(I)

wherein

R¹ and R² are each independently OH or C₁₋₆-alkoxy

R³ and R⁴, together with the carbon atom to which they are bound, form an epoxide ring;

R⁵ is selected from the group consisting of H, a hydroxyl protecting group, C₁₋₆-alkyl,

C(O)R¹³, C(O)OR¹³, and C(O)NR¹⁴R¹⁵, wherein each R¹³ is independently H or C₁₋₆-alkyl;

R⁶ is selected from the group consisting of H and C₁₋₆-alkyl; and

R⁷ is C₁₋₆-alkyl; and

R⁸, R⁹, R¹⁰, and R¹¹ are independently selected from the group consisting of H and C₁₋₆-alkyl

R¹² is C(O)NR¹⁴R¹⁵ wherein

R¹⁴ and R¹⁵ together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclic ring.

[0006b] In another aspect of the present disclosure, there is provided an antibody conjugate, comprising at least one compound as described herein conjugated to an antibody.

[0006c] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as described herein or a pharmaceutically acceptable salt thereof and

one or more pharmaceutically acceptable carriers, diluents, excipients or combinations thereof.

[0006d] In a further aspect of the present disclosure, there is provided a compound as described herein or a pharmaceutically acceptable salt thereof for
5 treating a patient in need of relief from cancer.

[0007] Embodiments of the present disclosure include compounds that are effective at limiting the growth of proliferative cells and useful as therapeutic cancer agents. Embodiments of the present disclosure also include compositions comprising these compounds as well as pro-drugs that result in the compounds
10 when administered to a patient. The compounds are useful for the treatment of cancer, in particular solid tumor cell cancers, such as breast, lung, cervical, prostate, ovarian, pancreatic, and renal cell cancer. The compounds, compositions, and prodrugs can be administered to a patient in need of treatment for proliferative disease, e.g., cancer.

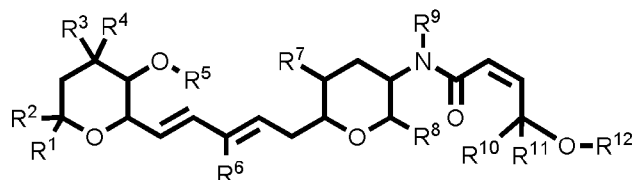
[0008] Embodiments of the present disclosure additionally include methods of making the therapeutic compounds of the various embodiments of the present disclosure. The methods include the cross metathesis of an epoxy alcohol fragment with an amide fragment in the presence of a catalyst. In an embodiment, the method includes forming the epoxy alcohol fragment from an
20 (R)-isopropylidene glyceraldehyde, forming the amide fragment using a Corey-Bakshi-Shibata (CBS) reduction, an Achmatowicz rearrangement, a stereoselective Michael addition, and coupling the first and second fragments with a cross-metathesis reaction. The method can be performed in about 20 steps under standard reaction conditions and proceeds with high enantiomeric
25 efficiency (> 98 % ee) and a good yield.

DETAILED DESCRIPTION

[0009] Embodiments of the invention include a family of novel compounds that can be used as therapeutic anti-cancer agents. The agents can be synthesized in a straightforward synthesis that includes a catalytic cross
30 metathesis of a cyclic epoxy alcohol to an amide, as described herein.

[0010] Various embodiments of the present invention are directed to compounds having Formula I and stereoisomers, pharmaceutically acceptable

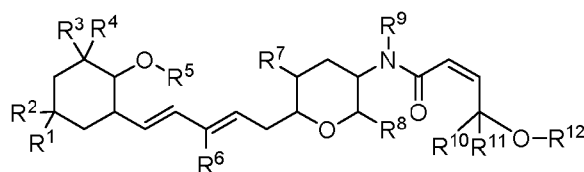
salts, prodrugs (e.g., ester) or antibody conjugates (see, e.g., U.S. Patent No. 8,663,643, which is incorporated by reference as if fully set forth herein) thereof:



I

- 5 wherein
 R^1 and R^2 are independently selected from the group consisting of H, OH, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, $-(CH_2)_nC(O)NR^{16}R^{17}$ (wherein R^{16} and R^{17} are selected independently from the group consisting of H, C₁₋₆-alkyl, and C₁₋₆-alkyl substituted with one to three groups independently selected from halo,
10 hydroxy, C₁₋₆-alkoxy, and aryl; or R^{16} and R^{17} , together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclic or heteroaromatic ring), and C₁₋₆-alkyl substituted with one to three groups independently selected from halo, hydroxy, C₁₋₆-alkoxy, and O-hydroxy protecting group;
15 R^3 and R^4 are selected independently from the group consisting of OH, C₁₋₆-alkyl (optionally substituted with Cl, F, NO₂, OH, or LG, wherein LG is a leaving group such as a -O-mesyl, -O-tosyl or -O-besyl leaving group), C(O) R^{13} , F, Cl, NO₂, wherein each R^{13} is independently H or C₁₋₆-alkyl; or R^3 and R^4 , together with the carbon atom to which they are bound, form an epoxide ring;
20 R^5 and R^{12} are independently selected from the group consisting of H, a hydroxyl protecting group, C₁₋₆-alkyl, C(O) R^{13} , C(O)OR¹³, and C(O)NR¹⁴R¹⁵, wherein each R^{13} is independently H or C₁₋₆-alkyl, and wherein R^{14} and R^{15} are selected independently from the group consisting of H and C₁₋₆-alkyl; or R^{14} and R^{15} , together with the nitrogen atom to which they are bound, form a 5- to 6-
25 membered heterocyclic or heteroaromatic ring;
 R^6 is selected from the group consisting of H and C₁₋₆-alkyl; and
 R^7 is C₁₋₆-alkyl; and
 R^8 , R^9 , R^{10} , and R^{11} are independently selected from the group consisting of H and C₁₋₆-alkyl.

[0011] Various other embodiments of the present invention are directed to compounds having Formula Ia and stereoisomers, pharmaceutically acceptable salts, prodrugs (e.g., ester) or antibody conjugates thereof:

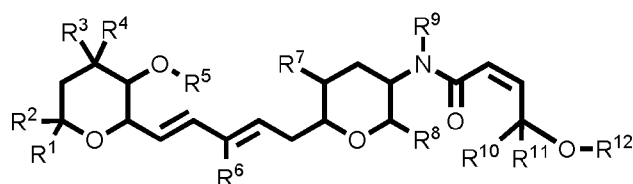


Ia

wherein

- R^1 and R^2 are independently selected from the group consisting of H, OH, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{2-6} -alkenyloxy, $-(CH_2)_nC(O)NR^{16}R^{17}$ (wherein R^{16} and R^{17} are selected independently from the group consisting of H, C_{1-6} -alkyl, and C_{1-6} -alkyl substituted with one to three groups independently selected from halo, hydroxy, C_{1-6} -alkoxy, and aryl; or R^{16} and R^{17} , together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclic or heteroaromatic ring), and C_{1-6} -alkyl substituted with one to three groups independently selected from halo, hydroxy, C_{1-6} -alkoxy, and O-hydroxy protecting group;
- R^3 and R^4 are selected independently from the group consisting of OH, C_{1-6} -alkyl (optionally substituted with Cl, F, NO_2 , OH, or LG, wherein LG is a leaving group such as a -O-mesyl, -O-tosyl or -O-besyl leaving group), $C(O)R^{13}$, F, Cl, NO_2 , wherein each R^{13} is independently H or C_{1-6} -alkyl; or R^3 and R^4 , together with the carbon atom to which they are bound, form an epoxide ring;
- R^5 and R^{12} are independently selected from the group consisting of H, a hydroxyl protecting group, C_{1-6} -alkyl, $C(O)R^{13}$, $C(O)OR^{13}$, and $C(O)NR^{14}R^{15}$, wherein each R^{13} is independently H or C_{1-6} -alkyl, and wherein R^{14} and R^{15} are selected independently from the group consisting of H and C_{1-6} -alkyl; or R^{14} and R^{15} , together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclic or heteroaromatic ring;
- R^6 is selected from the group consisting of H and C_{1-6} -alkyl; and
- R^7 is C_{1-6} -alkyl; and
- R^8 , R^9 , R^{10} , and R^{11} are independently selected from the group consisting of H and C_{1-6} -alkyl.

[0012] Still other embodiments of the present invention are directed to a process for preparing a compound having Formula I and a stereoisomer, pharmaceutically acceptable salt, prodrug (e.g., ester) or antibody conjugate thereof:

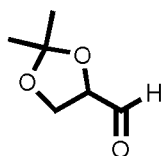


I

wherein

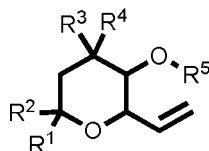
- R¹ and R² are independently selected from the group consisting of H, OH, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, -(CH₂)_nC(O)NR¹⁶R¹⁷ (wherein R¹⁶ and R¹⁷ are selected independently from the group consisting of H, C₁₋₆-alkyl, and C₁₋₆-alkyl substituted with one to three groups independently selected from halo, hydroxy, C₁₋₆-alkoxy, and aryl; or R¹⁴ and R¹⁵, together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclic or heteroaromatic ring), and C₁₋₆-alkyl substituted with one to three groups independently selected from halo, hydroxy, C₁₋₆-alkoxy, and O-hydroxy protecting group;
- R³ and R⁴ are selected independently from the group consisting of OH, C₁₋₆-alkyl (optionally substituted with Cl, F, NO₂, OH, or LG, wherein LG is a leaving group such as a -O-mesyl, -O-tosyl or -O-besyl leaving group), C(O)R¹³, F, Cl, NO₂, wherein each R¹³ is independently H or C₁₋₆-alkyl; or R³ and R⁴, together with the carbon atom to which they are bound, form an epoxide ring;
- R⁵ and R¹² are independently selected from the group consisting of H, a hydroxyl protecting group, C₁₋₆-alkyl, C(O)R¹³, C(O)OR¹³, and C(O)NR¹⁴R¹⁵, wherein each R¹³ is independently H or C₁₋₆-alkyl, and wherein R¹⁴ and R¹⁵ are selected independently from the group consisting of H and C₁₋₆-alkyl; or R¹⁴ and R¹⁵, together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclic or heteroaromatic ring;
- R⁶ is selected from the group consisting of H and C₁₋₆-alkyl; and
- R⁷ is C₁₋₆-alkyl;
- R⁸, R⁹, R¹⁰, and R¹¹ are independently selected from the group consisting of H and C₁₋₆-alkyl;

the method comprising converting a compound of the Formula II:



II

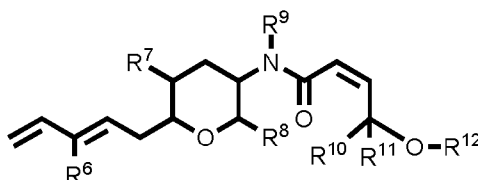
to a compound of the Formula III:



III

wherein R¹, R², R³, R⁴, and R⁵ are each defined herein; and

contacting a compound of Formula III with a compound of the Formula IV:



IV

wherein R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are defined herein;

in the presence of an olefin metathesis catalyst to form a compound of Formula I.

[0013] As used herein, the term “C₁₋₆-alkyl” refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 6 carbon atoms. This term includes, but is not limited to, linear and branched hydrocarbyl groups such as methyl (CH₃-), ethyl (CH₃CH₂-), n-propyl (CH₃CH₂CH₂-), isopropyl ((CH₃)₂CH-), n-butyl (CH₃CH₂CH₂CH₂-), isobutyl ((CH₃)₂CHCH₂-), sec-butyl ((CH₃)(CH₃CH₂)CH-), t-butyl ((CH₃)₃C-), n-pentyl (CH₃CH₂CH₂CH₂CH₂-), and neopentyl ((CH₃)₃CCH₂-). The term C₁₋₆-alkyl also includes cycloalkyl groups including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0014] As used herein, the term “C₂₋₆-alkenyl” (e.g., in C₂₋₆-alkenyloxy) refers to monovalent unsaturated hydrocarbyl groups having from 2 to 6 carbon atoms. This term includes, but is not limited to, linear and branched hydrocarbyl groups such as vinyl (CH₂=CH-), propenyl (CH₂=CHCH₂-), and

isopropenyl ((CH₃)(CH₂)C-). The term C₂₋₆-alkyl also includes cycloalkenyl groups including, but not limited to, cyclopentenyl and cyclohexenyl.

[0015] The term “heteroaryl” as used herein refers to an aromatic heterocycle ring of 5 to 14 members, such as 5 to 6 members, having at least one
5 heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom. Heteroaryls may be monocyclic, bicyclic, or tricyclic ring systems. Representative heteroaryls are triazolyl, tetrazolyl, oxadiazolyl, pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl,
10 isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, quinazolinyl, pyrimidyl, azepinyl, oxepinyl, and quinoxalinyl.

[0016] As used herein, the term “aryl” broadly refers to cyclic aromatic hydrocarbons that do not contain heteroatoms in the ring. Such aryl groups may
15 be substituted or unsubstituted. Aryl groups include, but are not limited to, phenyl, biphenyl, fluorenyl, phenanthrenyl, and naphthyl groups.

[0017] As used herein, the term “heterocycle” or “heterocycloalkyl” as used herein refers to 5- to 14-membered ring systems, such as 5- to 6-membered ring systems, which are either saturated, unsaturated, and which contain from 1
20 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized. Heterocycles may be monocyclic, bicyclic, or tricyclic ring systems. The bicyclic or tricyclic ring systems may be spiro-fused. The bicyclic and tricyclic ring systems may
25 encompass a heterocycle or heteroaryl fused to a benzene ring. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Representative examples of heterocycles include, but are not limited to, aziridinyl, oxiranyl, thuiranyl, triazolyl, tetrazolyl, azirinyl, diaziridinyl, diazirinyl, oxaziridinyl, azetidinyl, azetidinonyl, oxetanyl,
30 thietanyl, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, oxazinyl, thiazinyl, diazinyl, dioxanyl, triazinyl, tetrazinyl, imidazolyl, tetrazolyl, pyrrolidinyl, isoxazolyl, furanyl, furazanyl, pyridinyl, oxazolyl, benzoxazolyl, benzisoxazolyl, thiazolyl, benzthiazolyl, thiophenyl, pyrazolyl, triazolyl, pyrimidinyl, benzimidazolyl, isoindolyl, indazolyl, benzodiazolyl, benzotriazolyl,

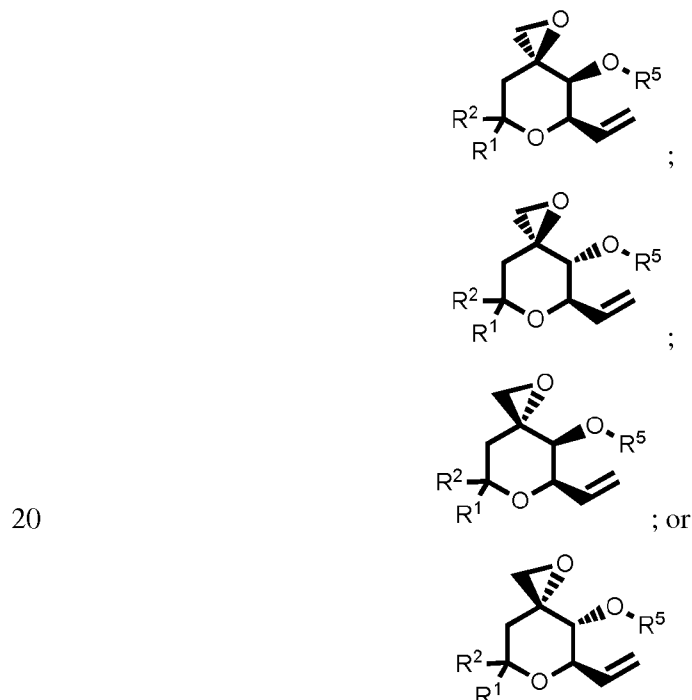
benzoxazolyl, benzisoxazolyl, purinyl, indolyl, isoquinolinyl, quinolinyl, and quinazolinyl.

[0018] The term “hydroxy” refers to the group -OH.

[0019] The term “hydroxy protecting group” refers to protecting groups
5 for an -OH group. Suitable hydroxy protecting groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous such protecting groups are described in T. W. Greene and P. G. M. Wuts, PROTECTING GROUPS IN ORGANIC
SYNTHESIS, 3rd ed., Wiley, New York. Such hydroxy protecting groups
10 include C₁₋₆ alkyl ethers, benzyl ethers, p-methoxybenzyl ethers, silyl ethers, and the like.

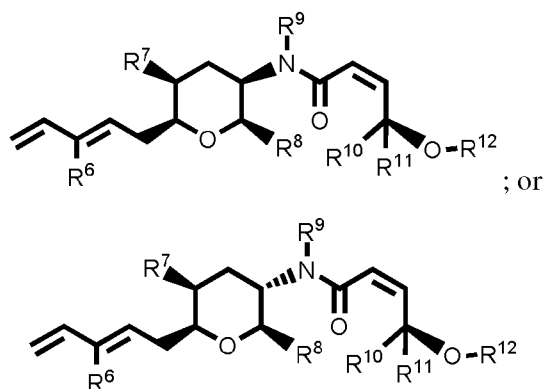
[0020] The term “C₁₋₆-alkoxy” refers to the group -O-(C₁₋₆-alkyl) wherein C₁₋₆-alkyl is defined herein. C₁₋₆-alkoxy includes, but is not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy, sec-butoxy, and n-
15 pentoxy.

[0021] In some embodiments, a compound of the Formula III is a compound of the formula:



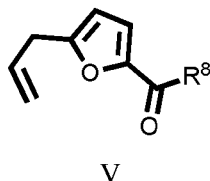
wherein R¹, R², and R⁵ are defined herein.

[0022] In some embodiments, a compound of the Formula IV is a compound of the formula:

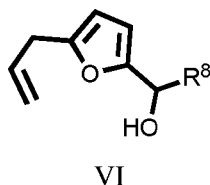


wherein R^6 - R^{12} are defined herein.

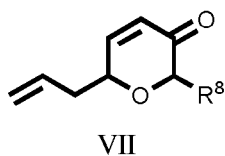
- [0023] In some embodiments, the compound of Formula IV, or a stereoisomer, pharmaceutically acceptable salt, prodrug (e.g., ester) or antibody conjugate thereof, is prepared from a compound of the Formula V:



- wherein R^8 is defined herein. The compound of the Formula IV can be prepared via process comprising:
- contacting a compound of the Formula V with a suitable reducing agent (e.g., a Corey-Bakshi-Shibata (CBS) reduction using borane and a chiral oxazaborolidine) to obtain a compound of the Formula VI:

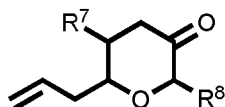


- wherein R^8 is defined herein;
- contacting the compound of the Formula VI with a suitable metal catalyst (e.g., $VO(acac)_2$ to effect an Achmatowicz rearrangement) to obtain a compound of the Formula VII:



wherein R^8 is defined herein;

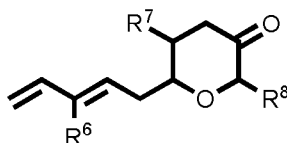
contacting the compound of the Formula VII with a compound of the R^7Li , wherein R^7 is defined herein, with a suitable metal salt (e.g., $CuBr \cdot S(CH_3)_2$) to obtain a compound of the Formula VIII:



5

VIII

contacting the compound of the Formula VIII with a suitable olefin metathesis catalyst (e.g., a suitable Grubbs' second generation olefin metathesis catalyst), wherein R^7 and R^8 are defined herein, to obtain a compound of the Formula IX:

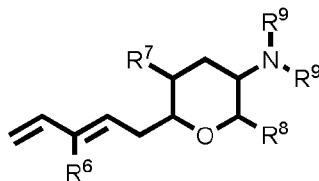


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IX

wherein R^6 , R^7 , and R^8 are defined herein;

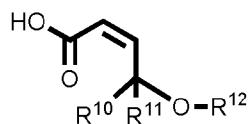
converting the compound of the Formula IX to a compound of the Formula X:



X

15 wherein R^6 , R^7 , R^8 , and R^9 are defined herein, under reductive amination conditions; and

contacting the compound of the Formula X with a compound of the Formula XI:

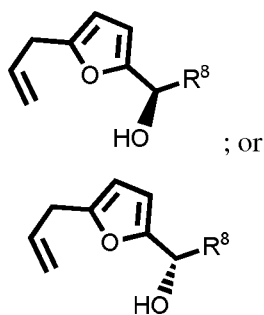


20

XI

to obtain a compound of the Formula IV.

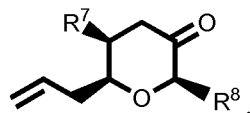
[0024] In some embodiments, the compound of the Formula VI is a compound of the formula:



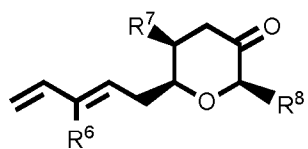
[0025] In some embodiments, the compound of the Formula VII is a compound of the formula:



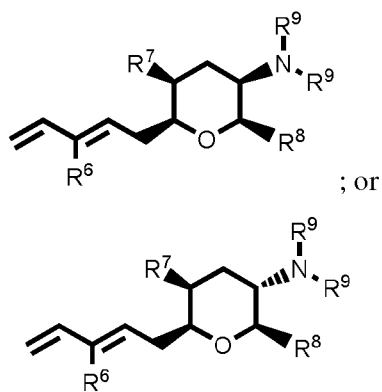
[0026] In some embodiments, the compound of the Formula VIII is a compound of the formula:



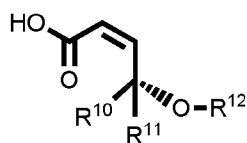
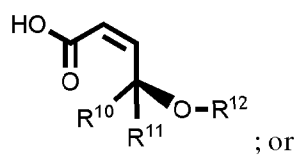
10 [0027] In some embodiments, the compound of the Formula IX is a compound of the formula:



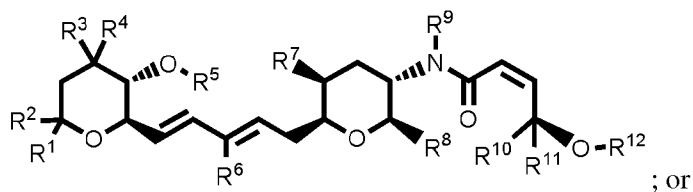
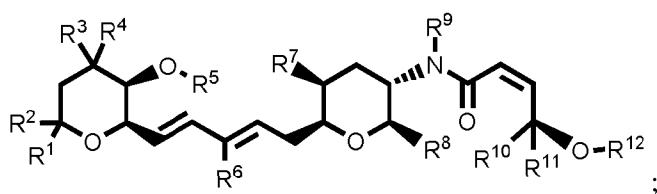
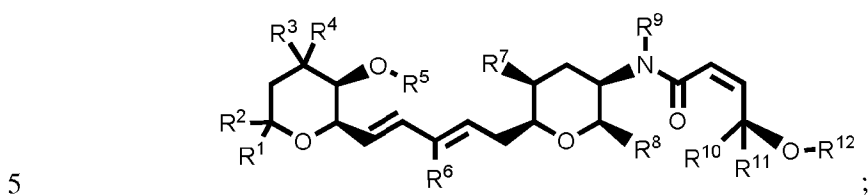
[0028] In some embodiments, the compound of the Formula X is a compound of the formula:



15 [0029] In some embodiments, the compound of the Formula XI is a compound of the formula:

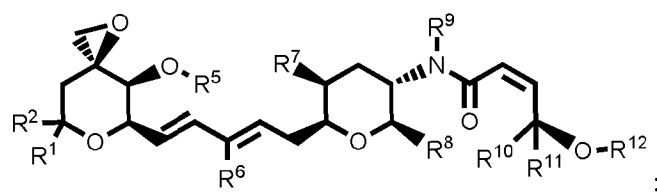
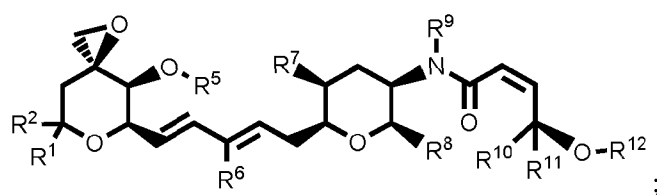


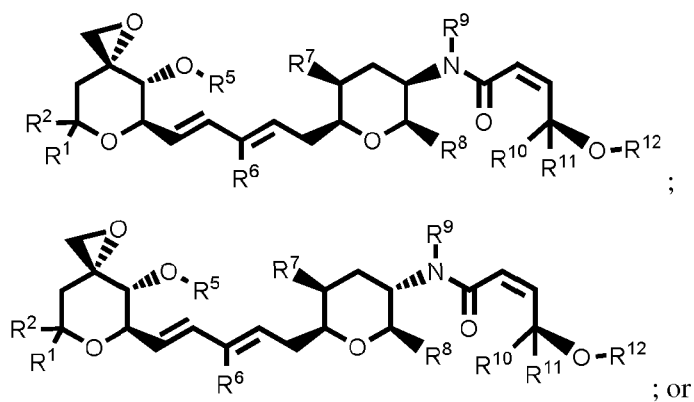
[0030] In some embodiments, the compound of the Formula I is a compound of the formula:



a pharmaceutically acceptable salt, prodrug (e.g., ester) or antibody conjugate thereof.

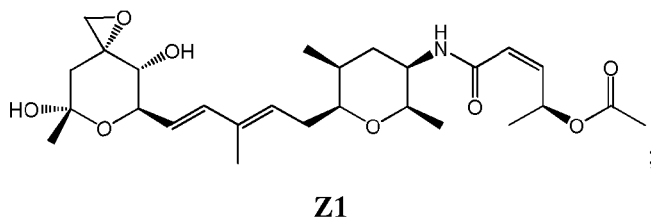
[0031] In other embodiments, the compound of the Formula I is a compound of the formula:



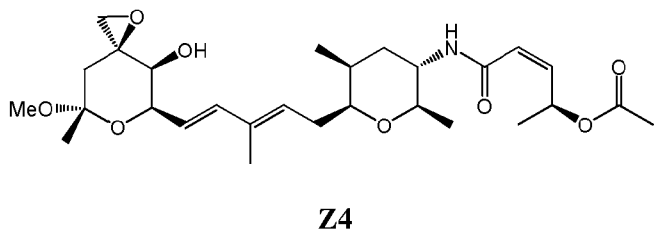
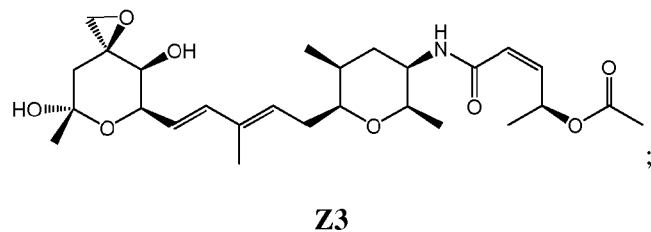
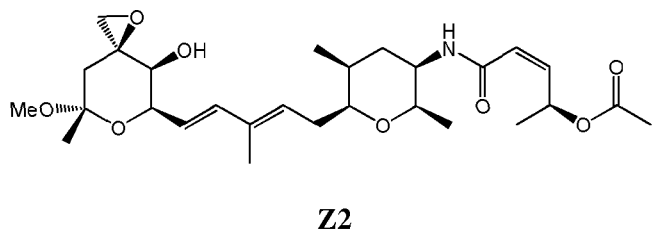


a pharmaceutically acceptable salt, prodrug (e.g., ester) or antibody conjugate thereof.

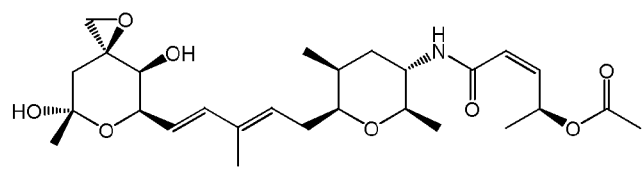
- 5 **[0032]** Embodiments of the invention include any one of compounds **Z1-Z7**, as well as combinations thereof, which are potent spliceosome inhibitors, and may be administered as anti-cancer agents and which can be synthesized by the methods described herein:



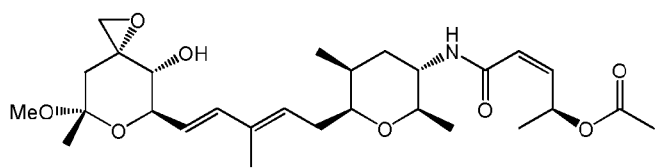
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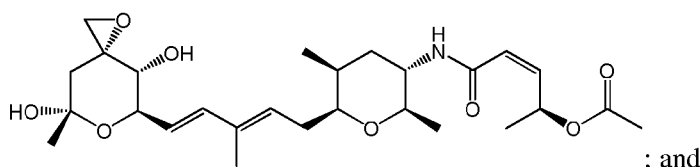
15



Z5



Z6



Z7

5

pharmaceutically acceptable salts, prodrugs (e.g., ester) or antibody conjugates thereof. The compounds may be included in a composition or delivered as a prodrug. The compounds Z1-Z7 can be prepared via the processes described herein for compounds of the Formula I.

[0033] “Pharmaceutically acceptable salt” generally refers to pharmaceutically acceptable salts of a compound, which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, and tetraalkylammonium; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, and oxalate.

[0034] As used herein, the term “prodrug” means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide an active compound, particularly a compound of the embodiments of the present invention. Examples of prodrugs include, but are not limited to, derivatives and metabolites of a compound of the invention that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues.

Specific prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by Burger's Medicinal Chemistry and Drug Discovery 6th ed. (Donald J. Abraham ed., 2001, Wiley) and Design and Application of Prodrugs (H. Bundgaard ed., 1985, Harwood Academic Publishers GmbH).

[0035] Those of ordinary skill in the art will recognize that compounds described herein (e.g., compounds Z1-Z7) contain chiral centers. All

diastereomers of the compounds described herein are contemplated herein, as well as racemates. Those of ordinary skill in the art will also recognize that compounds described herein (e.g., compounds Z1-Z7) comprise at three two double bonds each of which can have the E (engegen) or the Z (zusammen) configuration. All isomers of the compounds described herein (e.g., E,E,E; Z,Z,Z; E,Z,E; E,E,Z; Z,E,E; Z,E,Z, and Z,Z,E) are contemplated herein.

[0036] Various embodiments of the present invention also contemplate pharmaceutical compositions comprising one or more compounds of the various embodiments of the present invention (e.g. compounds Z1-Z7) and one or more pharmaceutically acceptable carriers, diluents, excipients or combinations

thereof. A "pharmaceutical composition" refers to a chemical or biological composition suitable for administration to a subject (e.g., mammal). Such compositions may be specifically formulated for administration via one or more of a number of routes, including but not limited to buccal, cutaneous, epicutaneous, epidural, infusion, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, pulmonary, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. In addition, administration can by means of capsule, drops, foams, gel, gum, injection, liquid, patch, pill, porous pouch, powder, tablet, or other suitable means of administration.

[0037] A "pharmaceutical excipient" or a "pharmaceutically acceptable excipient" comprises a carrier, sometimes a liquid, in which an active therapeutic agent is formulated. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical

and/or biological stability, and release characteristics. Examples of suitable formulations can be found, for example, in Remington, The Science And Practice of Pharmacy, 20th Edition, (Gennaro, A. R., Chief Editor), Philadelphia College of Pharmacy and Science, 2000, which is incorporated by reference in its entirety.

[0038] As used herein “pharmaceutically acceptable carrier” or “excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, sublingual, or oral administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0039] Pharmaceutical compositions may be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

[0040] In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the compounds described herein can be formulated in a time release formulation, for example in a

composition that includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers may be used, such as
5 ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[0041] Oral forms of administration are also contemplated herein. The
10 pharmaceutical compositions of the present invention may be orally administered as a capsule (hard or soft), tablet (film coated, enteric coated or uncoated), powder or granules (coated or uncoated) or liquid (solution or suspension). The formulations may be conveniently prepared by any of the methods well-known in the art. The pharmaceutical compositions of the present
15 invention may include one or more suitable production aids or excipients including fillers, binders, disintegrants, lubricants, diluents, flow agents, buffering agents, moistening agents, preservatives, colorants, sweeteners, flavors, and pharmaceutically compatible carriers.

[0042] For each of the recited embodiments, the compounds can be
20 administered by a variety of dosage forms as known in the art. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, chewable tablets, quick dissolve tablets, effervescent tablets, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions,
25 tablets, multi-layer tablets, bi-layer tablets, capsules, soft gelatin capsules, hard gelatin capsules, caplets, lozenges, chewable lozenges, beads, powders, gum, granules, particles, microparticles, dispersible granules, cachets, douches, suppositories, creams, topicals, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, ingestibles, injectables (including
30 subcutaneous, intramuscular, intravenous, and intradermal), infusions, and combinations thereof.

[0043] Other compounds which can be included by admixture are, for example, medically inert ingredients (e.g., solid and liquid diluent), such as lactose, dextrosesaccharose, cellulose, starch or calcium phosphate for tablets or

capsules, olive oil or ethyl oleate for soft capsules and water or vegetable oil for suspensions or emulsions; lubricating agents such as silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; gelling agents such as colloidal clays; thickening agents such as gum tragacanth or sodium alginate, 5 binding agents such as starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinylpyrrolidone; disintegrating agents such as starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuff; sweeteners; wetting agents such as lecithin, polysorbates or laurylsulphates; and other therapeutically acceptable accessory ingredients, such 10 as humectants, preservatives, buffers and antioxidants, which are known additives for such formulations.

[0044] Liquid dispersions for oral administration can be syrups, emulsions, solutions, or suspensions. The syrups can contain as a carrier, for example, saccharose or saccharose with glycerol and/or mannitol and/or sorbitol. 15 The suspensions and the emulsions can contain a carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

[0045] The amount of active compound in a therapeutic composition according to various embodiments of the present invention may vary according 20 to factors such as the disease state, age, gender, weight, patient history, risk factors, predisposition to disease, administration route, pre-existing treatment regime (e.g., possible interactions with other medications), and weight of the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several 25 divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by the exigencies of therapeutic situation.

[0046] "Dosage unit form," as used herein, refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to 30 produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the

treatment of sensitivity in individuals. In therapeutic use for treatment of conditions in mammals (e.g., humans) for which the compounds of the present invention or an appropriate pharmaceutical composition thereof are effective, the compounds of the present invention may be administered in an effective amount.

- 5 The dosages as suitable for this invention may be a composition, a pharmaceutical composition or any other compositions described herein.

[0047] For each of the recited embodiments, the dosage is typically administered once, twice, or thrice a day, although more frequent dosing intervals are possible. The dosage may be administered every day, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, and/or every 7 days (once a week). In one embodiment, the dosage may be administered daily for up to and including 30 days, preferably between 7-10 days. In another embodiment, the dosage may be administered twice a day for 10 days. If the patient requires treatment for a chronic disease or condition, the dosage may be administered for as long as signs and/or symptoms persist. The patient may require “maintenance treatment” where the patient is receiving dosages every day for months, years, or the remainder of their lives. In addition, the composition of this invention may be to effect prophylaxis of recurring symptoms. For example, the dosage may be administered once or twice a day to prevent the onset of symptoms in patients at risk, especially for asymptomatic patients.

[0048] The compositions described herein may be administered in any of the following routes: buccal, epicutaneous, epidural, infusion, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, pulmonary, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. The preferred routes of administration are buccal and oral. The administration can be local, where the composition is administered directly, close to, in the locality, near, at, about, or in the vicinity of, the site(s) of disease or systemic, wherein the composition is given to the patient and passes through the body widely, thereby reaching the site(s) of disease. Local administration can be administration to the cell, tissue, organ, and/or organ system, which encompasses and/or is affected by the disease, and/or where the disease signs and/or symptoms are active or are likely to occur. Administration can be topical with a local effect, composition is

applied directly where its action is desired. Administration can be enteral wherein the desired effect is systemic (non-local), composition is given via the digestive tract. Administration can be parenteral, where the desired effect is systemic, composition is given by other routes than the digestive tract.

5 [0049] In some embodiments, the various embodiments of the present invention contemplate compositions comprising a therapeutically effective amount of one or more compounds of the various embodiments of the present invention (e.g. at least one compound Z1-Z7). In some embodiments, the compositions are useful in a method for treating cancer, the method comprising
10 administering a therapeutically effective amount of one or more compounds of the various embodiments of the present invention to a patient in need thereof. In some aspects, the various embodiments of the present invention contemplate a compound of the various embodiments of the present invention for use as a medicament for treating a patient in need of relief from cancer. In some
15 embodiments, the cancer includes, but is not limited to, solid tumor cell cancers including, but not limited to, pancreatic cancer; bladder cancer; colorectal cancer; breast cancer, including metastatic breast cancer; prostate cancer, including androgen-dependent and androgen-independent prostate cancer; renal cancer, including, e.g., metastatic renal cell carcinoma; hepatocellular cancer;
20 lung cancer, including, e.g., non-small cell lung cancer (NSCLC), bronchioloalveolar carcinoma (BAC), and adenocarcinoma of the lung; ovarian cancer, including, e.g., progressive epithelial or primary peritoneal cancer; cervical cancer; gastric cancer; esophageal cancer; head and neck cancer, including, e.g., squamous cell carcinoma of the head and neck; melanoma;
25 neuroendocrine cancer, including metastatic neuroendocrine tumors; brain tumors, including, e.g., glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma; bone cancer; and soft tissue sarcoma. Examples of hematologic malignancy include acute myeloid leukemia (AML); chronic myelogenous leukemia (CML), including accelerated
30 CML and CML blast phase (CML-BP); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkins disease (HD); non-Hodgkin's lymphoma (NHL), including follicular lymphoma and mantle cell lymphoma; B-cell lymphoma; T-cell lymphoma; multiple myeloma (MM); Waldenstrom's macroglobulinemia; myelodysplastic syndromes (MDS), including refractory

anemia (RA), refractory anemia with ringed siderblasts (RARS), (refractory anemia with excess blasts (RAEB), and RAEB in transformation (RAEB-T); and myeloproliferative syndromes., such as breast, lung, cervical, prostate, ovarian, pancreatic, and renal cell cancer.

5 **[0050]** The term “therapeutically effective amount” as used herein, refers to that amount of one or more compounds of the various embodiments of the present invention (e.g. at least one compound Z1-Z7) that elicits a biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes
10 alleviation of the symptoms of the disease or disorder being treated. In some embodiments, the therapeutically effective amount is that which may treat or alleviate the disease or symptoms of the disease at a reasonable benefit/risk ratio applicable to any medical treatment. However, it is to be understood that the total daily usage of the compounds and compositions described herein may be
15 decided by the attending physician within the scope of sound medical judgment. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors, including the condition being treated and the severity of the condition; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender and
20 diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidentally with the specific compound employed; and like factors well known to the researcher, veterinarian, medical doctor or other clinician. It is also appreciated that the therapeutically effective
25 amount can be selected with reference to any toxicity, or other undesirable side effect, that might occur during administration of one or more of the compounds described herein.

30 **[0051]** In some embodiments, a therapeutically effective amounts of the compounds of the various embodiments of the present invention can range from approximately 0.05 to 50 mg per kilogram body weight of the recipient per day; such as about 0.1-25 mg/kg/day, or from about 0.5 to 10 mg/kg/day. Thus, for administration to a 70 kg person, for instance, the dosage range can be about 35-70 mg per day.

[0052] In some embodiments, one or more of the compounds of the various embodiments of the present invention can be administered in combination with at least one other anticancer agent including, but not limited to docetaxel, paclitaxel, bevacizumab (Avastin™).

5 Incorporation by Reference

[0053] References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, have been made throughout this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes. Such

10 documents include, but are not limited to:

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And

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5 A.; Wender, P. A. Nature Chem. 2012, 4, 705–710. All of which are incorporated by reference in their entireties.

Equivalents

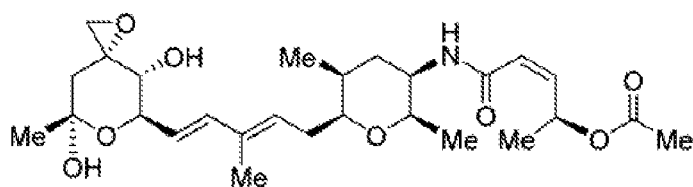
[0054] Various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will
10 become apparent to those skilled in the art from the full contents of this document, including references to the scientific and patent literature cited herein. The subject matter herein contains important information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

15 [0055] The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it
20 should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those of ordinary skill in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended
25 claims.

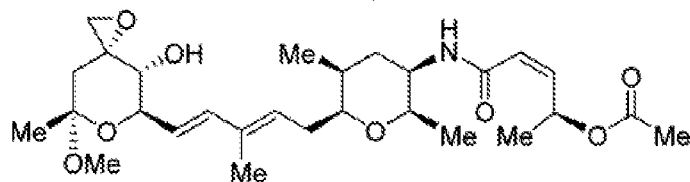
Examples

[0056] The present invention can be better understood by reference to the following example which is offered by way of illustration. The present invention is not limited to the example(s) given herein.

30 [0057] A synthetic scheme for compounds **Z1-Z7** is shown below with respect to FR901464 (**1**) and Spliceostatin A (**2**), shown below, which are not compounds of the invention.



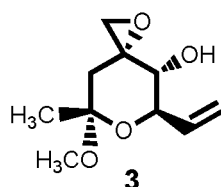
FR901464, 1



Spliceostatin A, 2

Nonetheless, it should be understood that the synthetic scheme is generally
 5 unique, and greatly simplifies the synthetic steps as compared to, e.g., the total
 synthesis of **1** described by Thompson, C.F., *et al.*, *J. Am. Chem. Soc.* 122
 10482–10483 (2000); and Thompson, C.F., *et al.*, *J. Am. Chem. Soc.* 123: 9974–
 9983 (2001), both of which are incorporated by reference as if fully set forth
 herein. Compounds **Z1-Z7** can be synthesized by making suitable substitutions
 10 in the synthesis of the cyclic epoxy alcohol (compound **3** in Scheme 1) as shown
 in Scheme 1 herein.

Example 1: Synthesis of epoxy alcohol segment **3**

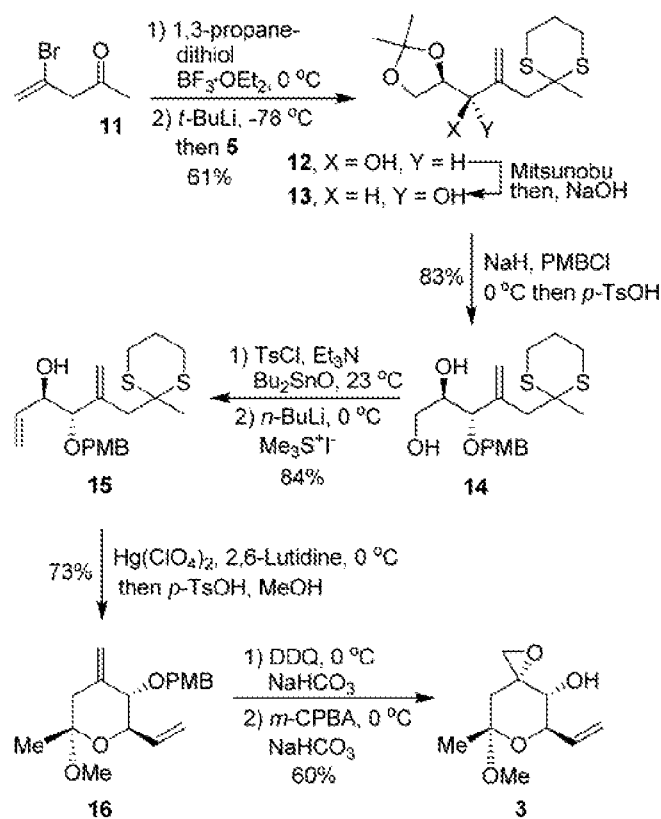


[0058] The synthesis of epoxy alcohol segment **3** is shown in Scheme 1.
 15 Commercially available bromo ketone **11** was protected as its dithiane
 derivative. Lithiation of the resulting dithiane with *t*-BuLi at 78 °C for 1 hours
 followed by reaction with (R)-isopropylidene glyceraldehyde provided a mixture
 (1:1) of diastereomers **12** and **13** in 61% yield in two steps. This lack of
 stereoselectivity was somewhat unexpected, especially given the presence of
 20 chelating atoms at both R and β positions of (R)-isopropylidene glyceraldehyde.
 In an attempt to improve antidiastereoselectivity, we investigated this addition
 reaction in the presence of a number of Lewis acids such as CeCl₃, ZnCl₂, and

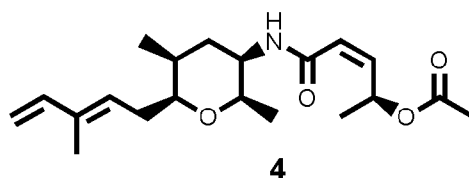
MgBr₂, in THF and ether. However, there was no further improvement in the diastereomeric ratio.

[0059] The isomers were separated by silica gel chromatography. The *syn*-isomer **12** was converted to desired anti-isomer **13** by a Mitsunobu reaction in the presence of p-nitrobenzoic acid followed by NaOH-mediated hydrolysis of the benzoate ester. The hydroxyl group of **13** was protected as a para-methoxy benzyl (PMB) ether, and subsequent removal of the isopropylidene group was carried out by the addition of p-TsOH in a one pot operation to provide diol **14**. The primary alcohol was selectively mono-tosylated using tosyl chloride (TsCl) and Et₃N in the presence of dibutyltin oxide. Reaction of the resulting mono-tosylate with an excess of Corey-Chaykovsky dimethylsulfonium, methylide prepared by treatment of trimethylsulfonium iodide with n-BuLi, furnished allylic alcohol **15** in 84% yield. A similar functional group transformation was previously reported by Carreira and co-workers. See Bode, J.W. and Carreira E.M., *J. Org. Chem.* 66: 6410–6424 (2001), which is incorporated by reference as if fully set forth herein. The dithiane group of **15** was then removed by using an excess of Hg(ClO₄)₂ in methanol in the presence of dry 2,6-lutidine. This condition resulted in the formation of the corresponding methyl ketal as a mixture of anomers, which upon treatment with a catalytic amount of p-TsOH in methanol at 0 °C provided a single diastereomer **16**. Removal of the PMB group in **16** with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) followed by alcohol directed epoxidation with m-chloroperbenzoic acid (m-CPBA) afforded the desired epoxy alcohol segment **3** stereoselectively as a white solid in 19% overall yield from **11** (8 steps). The methyl ketal **3** is quite stable and easy to handle for subsequent reactions.

SCHEME 1



Example 2: Synthesis of amide 4



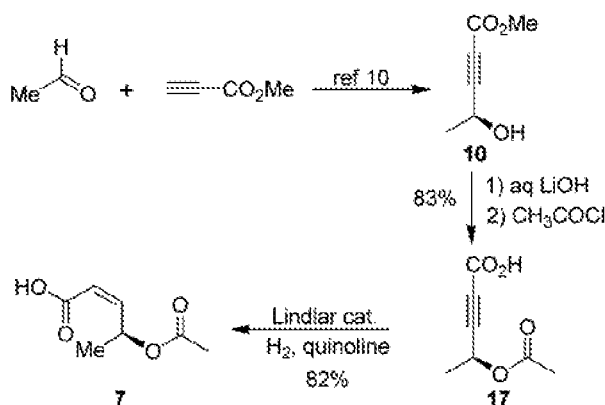
5

[0060] Amide **4** can be synthesized in a two-step process, shown below as Scheme 2A and Scheme 2B. The preparation of the *Z*-allylic acetate side chain **7** is shown in Scheme 2A. Optically active alcohol **10** was efficiently prepared by utilizing a catalytic asymmetric addition protocol reported by Trost and co-workers to provide **10** > 98% enantiomeric efficiency (ee).

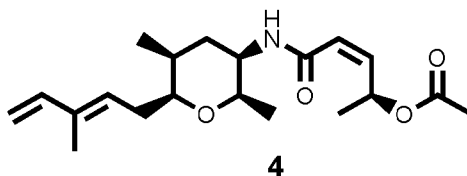
10

Saponification of methyl ester **10** with aqueous LiOH followed by acetylation with acetyl chloride provided acetate **17** in excellent yield. Hydrogenation over Lindlar's catalyst afforded the desired *cis*-alkene **7**.

SCHEME 2A



[0061] The synthesis of amide segment **4** is shown in Scheme 2B, where the amide segment **4** has the structure:



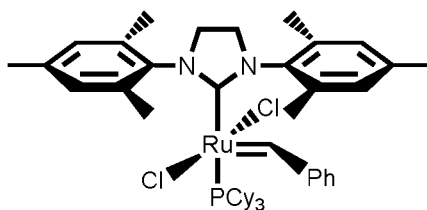
5

Enantioselective reduction of commercially available acetyl furan **18** with (S)-2-Me-CBS catalyst (also known as (S)-5,5-Diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine) and BH₃·Me₂S afforded chiral alcohol **9** in 94% yield (93% ee). An Achmatowicz rearrangement was then carried out by treatment of alcohol **9** with t-BuO₂H in the presence of a catalytic amount of VO(acac)₂ to furnish a hemiketal, which was directly reduced to enone **19** as a single diastereomer by employing the protocol described by Kishi and co-workers. Our subsequent synthetic plan required installation of the C20 (S)-methyl-bearing stereocenter. We elected to carry out a 1,4-addition to enone **19**. Accordingly, treatment of **19** with MeLi/CuBr₃·Me₂S at -78 °C for 2 hours provided the desired pyranone **8** in excellent yield (92%) and diastereoselectivity (25:1 dr, by ¹H and ¹³C NMR analysis). The observed diastereoselectivity can be explained based upon the conformational analysis of enone **19**. The stereochemical outcome of Michael addition can be rationalized by assuming stereoelectronically favorable axial attack of the cuprate as shown in the transition-state model **20**.

20

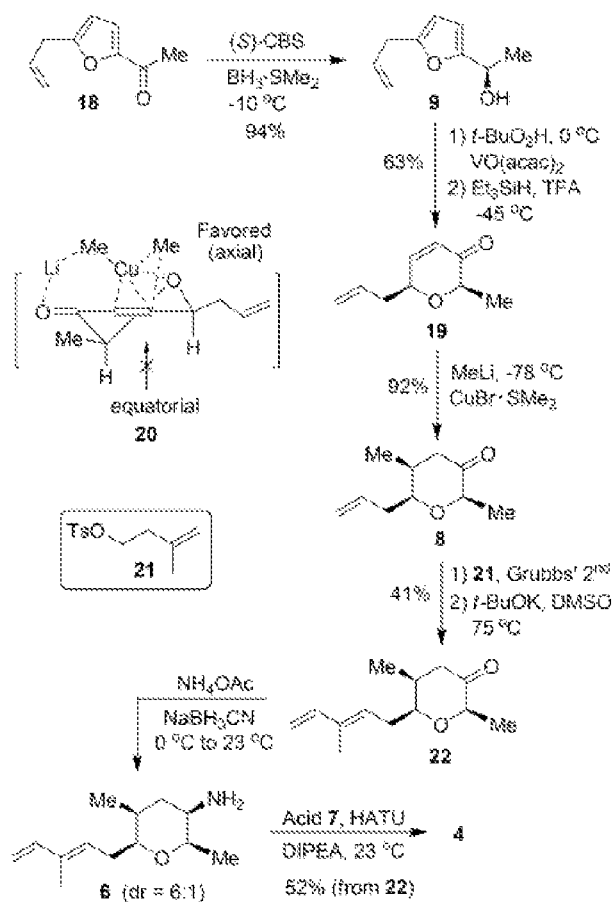
[0062] Pyranone **8** and known alkene **21** were then subjected to cross-metathesis conditions using a Grubbs'-type second generation catalyst (Scholl,

M., *et al.*, *Org. Lett.* 1: 953-956 (1999), incorporated by reference as if fully set forth herein):



to provide the corresponding terminal tosylate. Treatment of the resulting
5 tosylate with *t*-BuOK in DMSO at 75 °C for 12 hours resulted in diene **22** via
base promoted elimination in 41% yield over two steps. Reductive amination of
22 with ammonium acetate and NaBH₃ CN afforded the corresponding primary
amine **6** as a major product (6:1 dr, by ¹H- and ¹³C NMR analysis). The crude
amine **6** and its epimer were directly treated with acid **7** using standard
10 amidation conditions to give the amide **4** along with minor C-14 epimer, which
were separated by column chromatography.

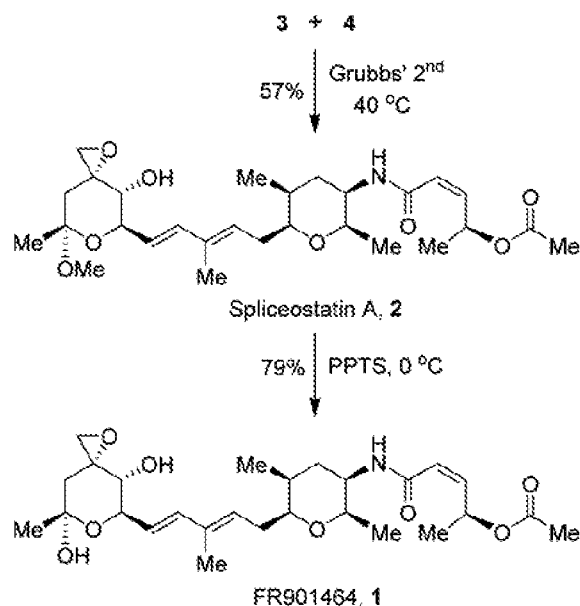
SCHEME 2B



[0063] In the final step, FR901464 (**1**), Spliceostatin A (**2**), a compound of the invention, i.e., compounds **Z1-Z7**, or similar compounds can be created with the cross-metathesis of the epoxy alcohol segment **3** and the amide segment **4**, as shown in Scheme 3. With the stereoselective syntheses of segments epoxy alcohol **3** (Scheme 1) and amide **4** (Scheme 2A/B), we then turned our attention to construct the C6-C7 double bond of the target molecules. As shown in Scheme 3, cross-metathesis of the two fragments proceeded smoothly in the presence of Grubbs' second-generation catalyst to afford spliceostatin A (**2**) as a white solid in 57% isolated yield based upon one recycle of unreacted **3** and **4** under the same conditions. Compounds **Z1-Z7** can be formed with similar yields and enantiomeric efficiency. The removal of the methylketal in **2** was achieved by exposure of **2** to pyridinium p-toluene sulfonate (PPTS) in wet THF at 0 °C, which provided FR901464 (**1**) as a white powder in good yield. The ¹H and ¹³C NMR of our synthetic FR901464[[α]_D-13.0 (c 0.45, CH₂Cl₂)] is identical

to the reported spectra of natural $[[\alpha]_D-12.0$ (c 0.5, CH_2Cl_2)] and synthetic FR901464.

SCHEME 3

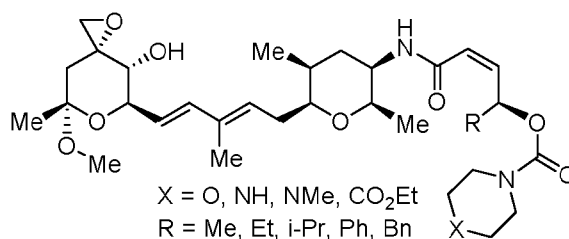


5

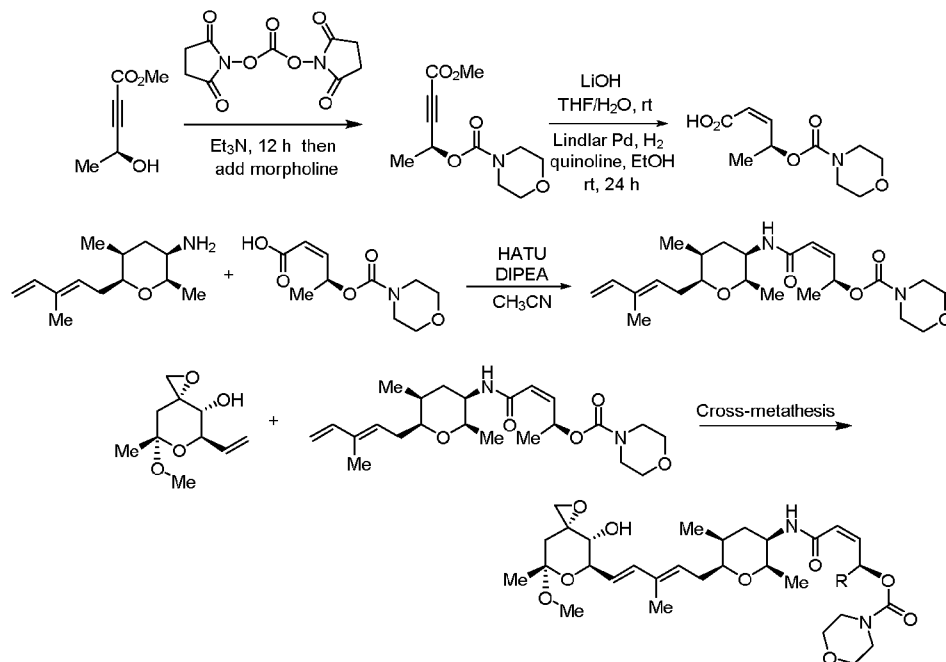
[0064] Thus, embodiments of the present invention provide a concise and enantioselective strategy for the syntheses of FR901464, Spliceostatin A, or compounds **Z1-Z7** in about 20 total steps with the longest linear sequence of about 10 steps. The syntheses includes the use of readily available chiral pool
10 (R)-isopropylidene glyceraldehyde **5** to form an A-ring fragment, a CBS reduction, an Achmatowicz rearrangement, and a stereoselective Michael addition for the construction of a B-ring fragment, and a cross-metathesis reaction for coupling the two fragments. The synthesis is short, convergent and amenable to the synthesis of structural variants not disclosed, which are intended
15 to be encompassed in the synthetic methods.

Example 3

[0065] The compound of the formula:



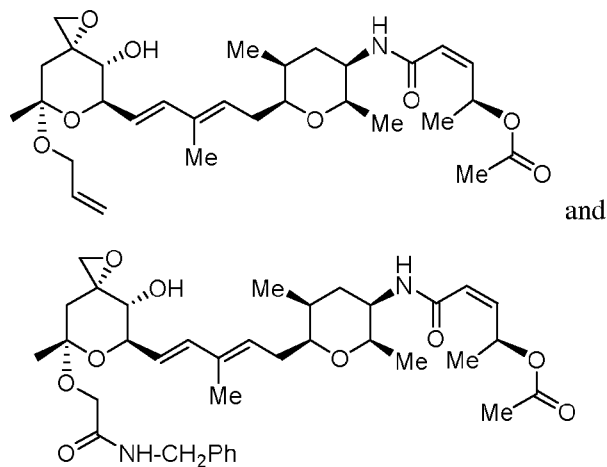
was synthesized according to the synthetic scheme shown below in Scheme 4:



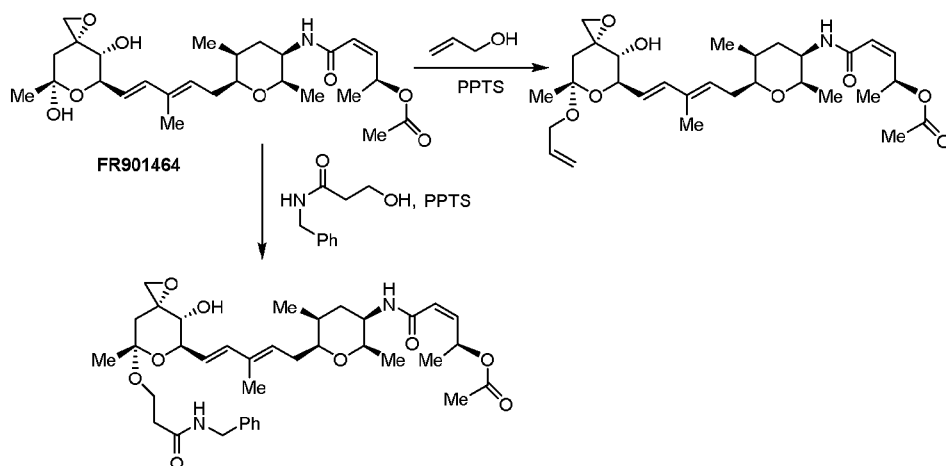
Scheme 4

Example 4

- 5 [0066] The compound of the formulae:



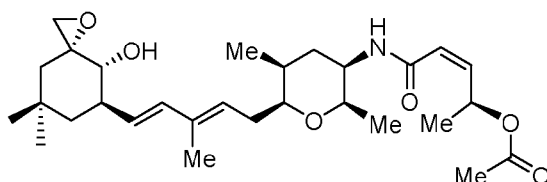
were synthesized according to the synthetic scheme shown below in Scheme 5:



Scheme 5

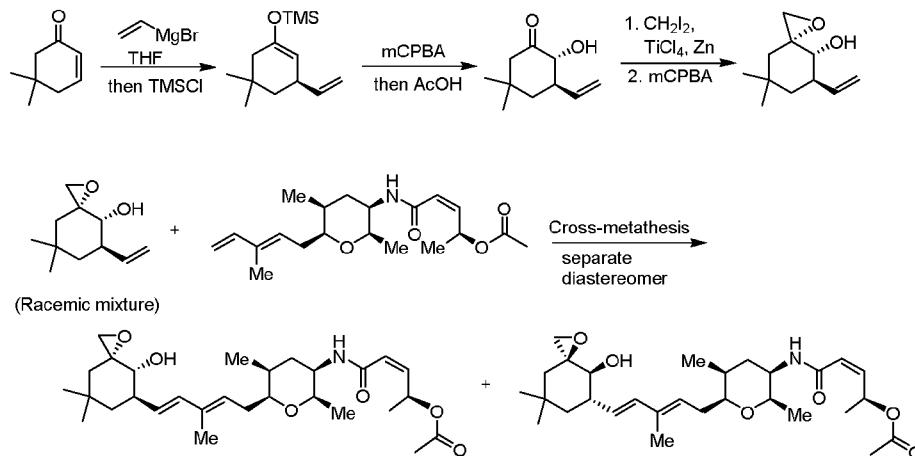
Example 4

[0067] The compound of the formula:



5

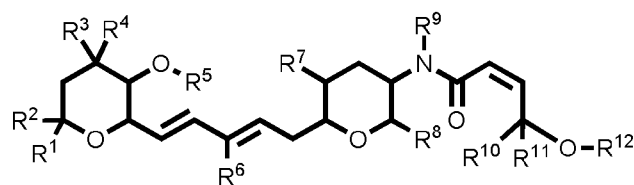
was synthesized according to the synthetic scheme shown below in Scheme 6:



Scheme 6

[0068] The following embodiments are provided, the numbering of which is not to be construed as designating levels of importance:

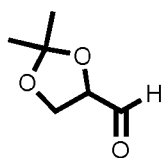
[0069] Embodiment 1 relates to a process for preparing a compound having Formula I, or a stereoisomer, pharmaceutically acceptable salt, prodrug (e.g., ester) or antibody conjugate thereof:



I

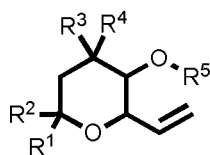
wherein

- R^1 and R^2 are independently selected from the group consisting of H, OH, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{2-6} -alkenyloxy, $-(CH_2)_nC(O)NR^{16}R^{17}$ (wherein R^{16} and R^{17} are selected independently from the group consisting of H, C_{1-6} -alkyl, and C_{1-6} -alkyl substituted with one to three groups independently selected from halo, hydroxy, C_{1-6} -alkoxy, and aryl; or R^{16} and R^{17} , together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclic or heteroaromatic ring), and C_{1-6} -alkyl substituted with one to three groups independently selected from halo, hydroxy, C_{1-6} -alkoxy, and O-hydroxy protecting group;
- R^3 and R^4 are selected independently from the group consisting of OH, C_{1-6} -alkyl (optionally substituted with Cl, F, NO_2 , OH, or LG, wherein LG is a leaving group), $C(O)R^{13}$, F, Cl, NO_2 , wherein each R^{13} is independently H or C_{1-6} -alkyl; or R^3 and R^4 , together with the carbon atom to which they are bound, form an epoxide ring;
- R^5 and R^{12} are independently selected from the group consisting of H, a hydroxyl protecting group, C_{1-6} -alkyl, $C(O)R^{13}$, $C(O)OR^{13}$, and $C(O)NR^{14}R^{15}$, wherein each R^{13} is independently H or C_{1-6} -alkyl, and wherein R^{14} and R^{15} are selected independently from the group consisting of H and C_{1-6} -alkyl; or R^{14} and R^{15} , together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclic or heteroaromatic ring;
- R^6 is selected from the group consisting of H and C_{1-6} -alkyl; and
- R^7 is C_{1-6} -alkyl;
- R^8 , R^9 , R^{10} , and R^{11} are independently selected from the group consisting of H and C_{1-6} -alkyl;
- the method comprising converting a compound of the Formula II:



II

to a compound of the Formula III:

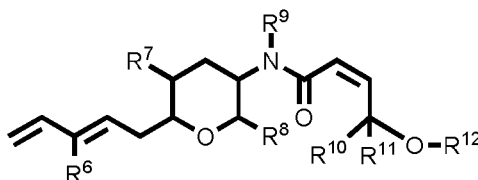


III

5

wherein R^1 , R^2 , R^3 , R^4 , and R^5 are defined herein; and

contacting a compound of Formula III with a compound of the Formula IV:

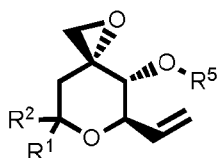


IV

10 wherein R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , and R^{12} are defined herein;

in the presence of an olefin metathesis catalyst to form a compound of Formula I.

[0070] Embodiment 2 relates to the process of Embodiment 1, wherein the compound of the Formula III is a compound of the formula:



15

III

R^1 and R^2 are independently selected from the group consisting of H, OH, C_{1-6} -alkyl, and C_{1-6} -alkyl substituted with one to three groups independently selected from halo, hydroxy, C_{1-6} -alkoxy, and O-hydroxy protecting group;

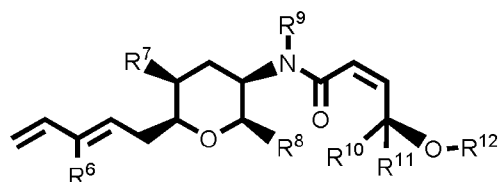
20 R^5 is selected from the group consisting of H, a hydroxyl protecting group, C_{1-6} -alkyl, $C(O)R^{13}$, $C(O)OR^{13}$, and $C(O)NR^{14}R^{15}$, wherein each R^{13} is independently H or C_{1-6} -alkyl, and wherein R^{14} and R^{15} are selected independently from the group consisting of H and C_{1-6} -alkyl; or R^{14} and R^{15} , together with the nitrogen

atom to which they are bound, form a 5- to 6-membered heterocyclic or heteroaromatic ring.

[0071] Embodiment 3 relates to the process of Embodiments 1-2, wherein R^1 is H; R^2 is C_{1-6} -alkyl and R^5 is H.

5 **[0072]** Embodiment 4 relates to the process of Embodiments 1-3, wherein R^2 is $-CH_3$.

[0073] Embodiment 5 relates to the process of Embodiments 1-4, wherein the compound of the Formula IV is a compound of the formula:



IV

R^6 is selected from the group consisting of H and C_{1-6} -alkyl; and

R^7 is C_{1-6} -alkyl;

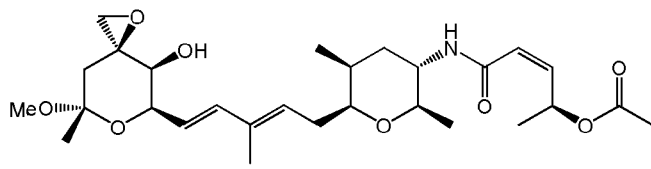
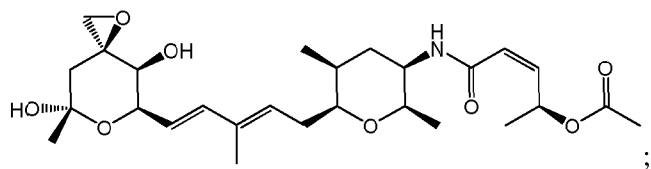
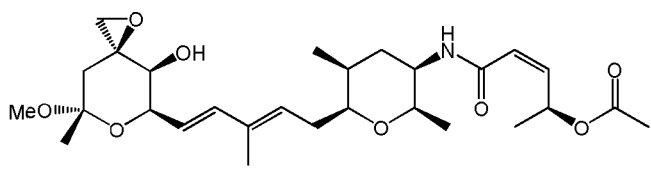
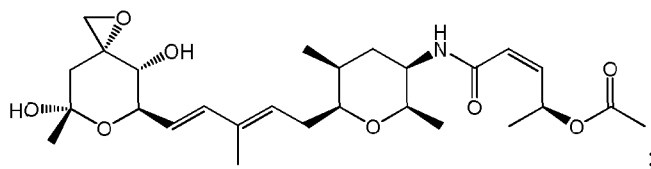
R^8 , R^9 , R^{10} , and R^{11} are independently selected from the group consisting of H and C_{1-6} -alkyl; and

15 R^{12} is selected from the group consisting of H, a hydroxyl protecting group, C_{1-6} -alkyl, $C(O)R^{13}$, $C(O)OR^{13}$, and $C(O)NR^{14}R^{15}$, wherein each R^{13} is independently H or C_{1-6} -alkyl, and wherein R^{14} and R^{15} are selected independently from the group consisting of H and C_{1-6} -alkyl; or R^{14} and R^{15} , together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclic or
20 heteroaromatic ring.

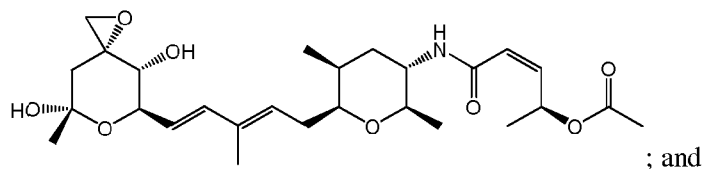
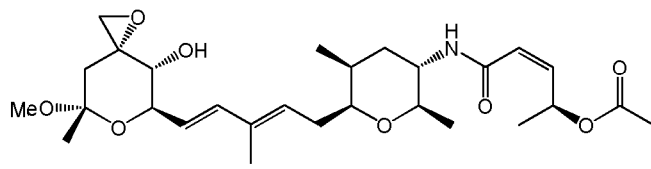
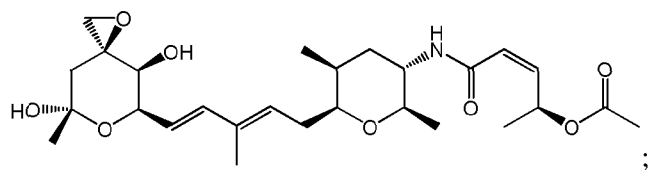
[0074] Embodiment 6 relates to the process of Embodiments 1-5, wherein R^6 , R^7 , R^8 , and R^{11} are independently C_{1-6} -alkyl; R^9 and R^{10} are H; and R^{12} is $C(O)R^{13}$, wherein R^{13} is C_{1-6} -alkyl.

[0075] Embodiment 7 relates to the process of Embodiments 1-6,
25 wherein R^6 , R^7 , R^8 , and R^{11} are $-CH_3$; R^9 and R^{10} are H; and R^{12} is $C(O)R^{13}$, wherein R^{13} is $-CH_3$.

[0076] Embodiment 8 relates to the process of Embodiments 1-7, wherein the compound of the Formula I is a compound selected from the group consisting of:

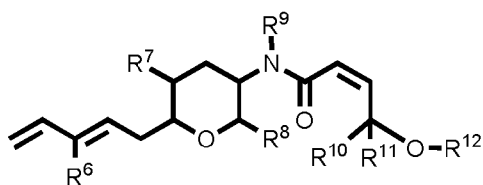


5



pharmaceutically acceptable salts, prodrugs or antibody conjugate thereof.

[0077] Embodiment 9 relates to a process for preparing a compound
 10 having Formula IV, or a stereoisomer, pharmaceutically acceptable salt, prodrug
 or antibody conjugate thereof:



IV

wherein R^6 is selected from the group consisting of H and C_{1-6} -alkyl;

R^7 is C_{1-6} -alkyl;

R^8 , R^9 , R^{10} , and R^{11} are independently selected from the group consisting of H

5 and C_{1-6} -alkyl; and

R^{12} is selected from the group consisting of H, a hydroxyl protecting group, C_{1-6} -alkyl, $C(O)R^{13}$, $C(O)OR^{13}$, and $C(O)NR^{14}R^{15}$, wherein each R^{13} is independently

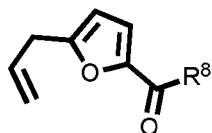
H or C_{1-6} -alkyl, and wherein R^{14} and R^{15} are selected independently from the group consisting of H and C_{1-6} -alkyl; or R^{14} and R^{15} , together with the nitrogen

10 atom to which they are bound, form a 5- to 6-membered heterocyclic or

heteroaromatic ring;

the process comprising:

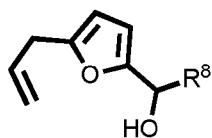
contacting a compound of the Formula V:



15

V

wherein R^8 is defined herein, with a reducing agent to obtain a compound of the Formula VI:

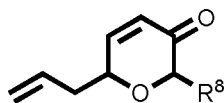


20

VI

wherein R^8 is defined herein;

contacting the compound of the Formula VI with a metal catalyst to obtain a compound of the Formula VII:

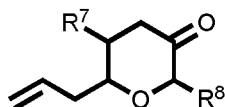


25

VII

wherein R^8 is defined herein;

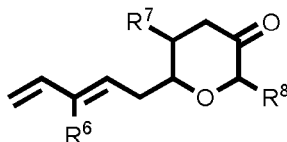
contacting the compound of the Formula VII with a compound of the R^7Li , wherein R^7 is defined herein, with a metal salt to obtain a compound of the Formula VIII:



5

VIII

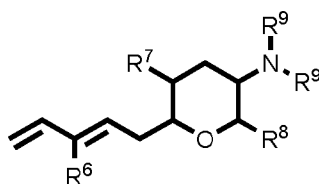
contacting the compound of the Formula VIII with an olefin metathesis catalyst, wherein R^7 and R^8 are defined herein, to obtain a compound of the Formula IX:



IX

10 wherein R^7 , R^8 , R^9 , R^{10} , and R^{11} are defined herein;

converting the compound of the Formula IX to a compound of the Formula X:

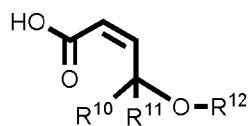


X

wherein R^6 , R^7 , R^8 , and R^9 are defined herein, under reductive amination

15 conditions; and

contacting the compound of the Formula X with a compound of the Formula XI:



XI

wherein R^{10} , R^{11} , and R^{12} are defined herein;;

20 to obtain a compound of the Formula IV.

[0078] Embodiment 10 relates to the process of Embodiment 9, wherein the reducing agent is a chiral reducing agent.

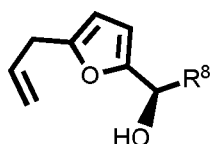
[0079] Embodiment 11 relates to the process of Embodiment 10, wherein the chiral reducing agent comprises a chiral oxazaborolidine.

[0080] Embodiment 12 relates to the process of Embodiment 9, wherein the metal catalyst effects an Achmatowicz rearrangement.

[0081] Embodiment 13 relates to the process of Embodiment 9, wherein the metal catalyst is VO(acac)₂.

5 [0082] Embodiment 14 relates to the process of Embodiment 9, wherein the metal salt comprises CuBr.

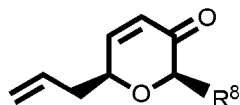
[0083] Embodiment 15 relates to the process of Embodiments 9-14, wherein the compound of the Formula VI is a compound of the formula:



10 wherein R⁸ is selected from the group consisting of H and C₁₋₆-alkyl.

[0084] Embodiment 16 relates to the process of Embodiments 9-15, wherein R⁸ is -CH₃.

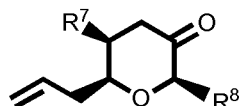
[0085] Embodiment 17 relates to the process of Embodiments 9-16, wherein the compound of the Formula VII is a compound of the formula:



15 wherein R⁸ is selected from the group consisting of H and C₁₋₆-alkyl.

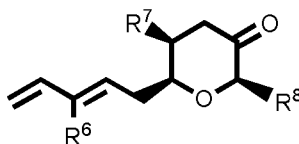
[0086] Embodiment 18 relates to the process of Embodiments 9-17, wherein R⁸ is -CH₃.

[0087] Embodiment 19 relates to the process of Embodiments 9-18, wherein, the compound of the Formula VIII is a compound of the formula:



wherein R⁷ and R⁸ are independently C₁₋₆-alkyl.

[0088] Embodiment 20 relates to the process of Embodiments 9-19, wherein the compound of the Formula IX is a compound of the formula:

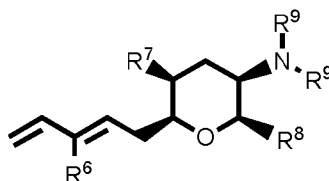


wherein R⁶ is selected from the group consisting of H and C₁₋₆-alkyl;

R^7 is C_{1-6} -alkyl; and

R^8 is selected from the group consisting of H and C_{1-6} -alkyl.

[0089] Embodiment 21 relates to the process of Embodiments 9-20, wherein the compound of the Formula X is a compound of the formula:

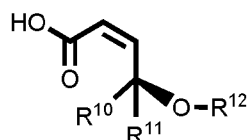


wherein R^6 is selected from the group consisting of H and C_{1-6} -alkyl;

R^7 is C_{1-6} -alkyl; and

R^8 and R^9 are independently selected from the group consisting of H and C_{1-6} -alkyl.

[0090] Embodiment 22 relates to the process of Embodiments 9-21, wherein the compound of the Formula XI is a compound of the formula:



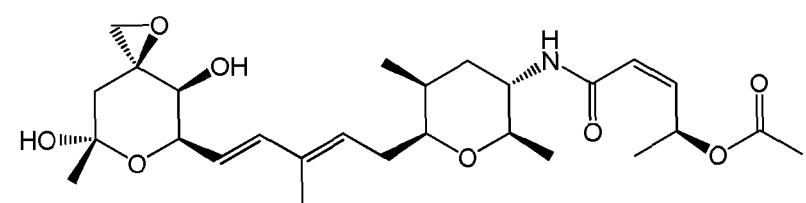
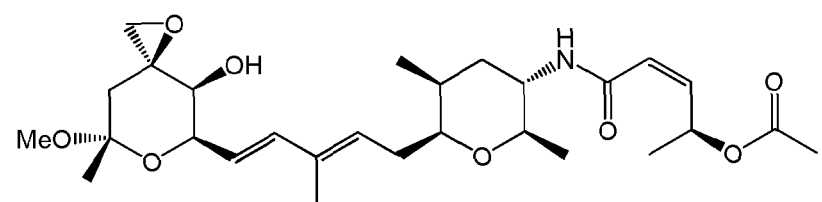
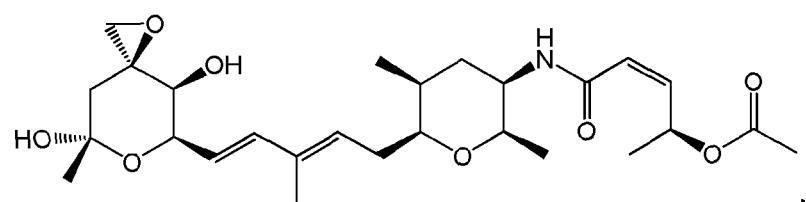
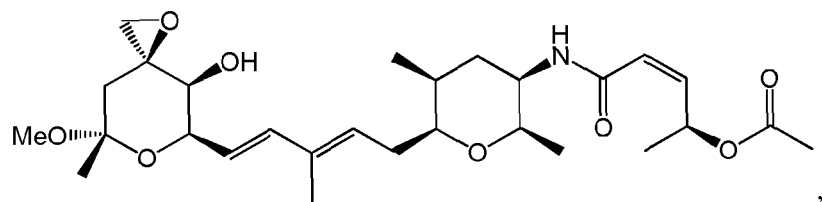
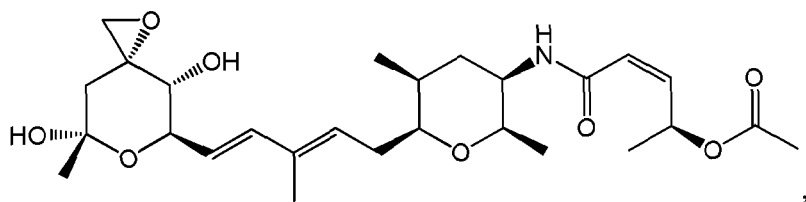
R^{10} and R^{11} are independently selected from the group consisting of H and C_{1-6} -alkyl; and

R^{12} is selected from the group consisting of H, a hydroxyl protecting group, C_{1-6} -alkyl, $C(O)R^{13}$, $C(O)OR^{13}$, and $C(O)NR^{14}R^{15}$, wherein each R^{13} is independently H or C_{1-6} -alkyl, and wherein R^{14} and R^{15} are selected independently from the group consisting of H and C_{1-6} -alkyl; or R^{14} and R^{15} , together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclic or heteroaromatic ring.

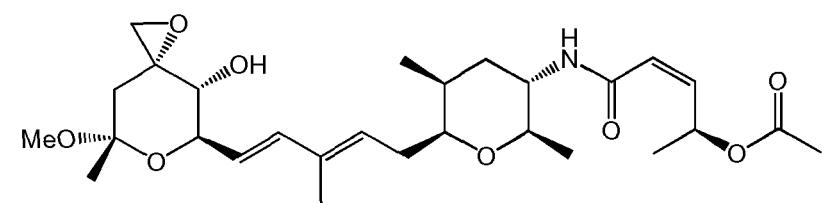
[0091] Embodiment 23 relates to the process of Embodiments 9-22, wherein R^{11} is C_{1-6} -alkyl; R^{10} is H; and R^{12} is $C(O)R^{13}$, wherein R^{13} is C_{1-6} -alkyl.

[0092] Embodiment 24 relates to the process of Embodiments 9-23, wherein R^{11} is $-CH_3$.

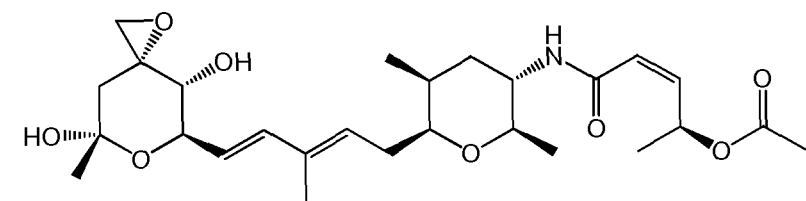
[0093] Embodiment 25 relates to a compound selected from the group consisting of:



5



, and

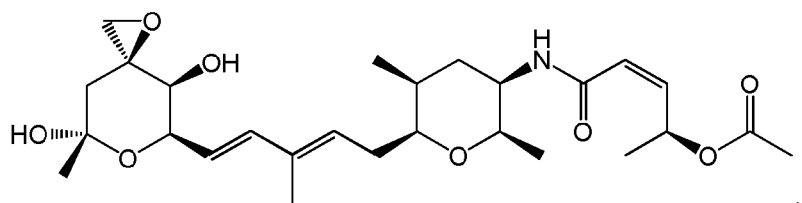
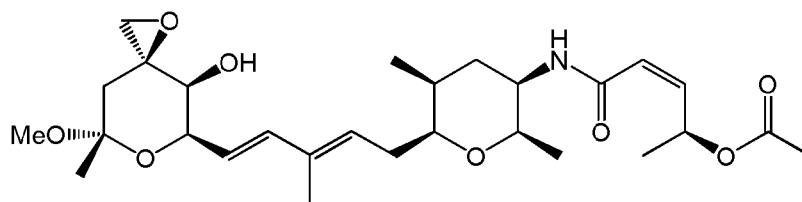
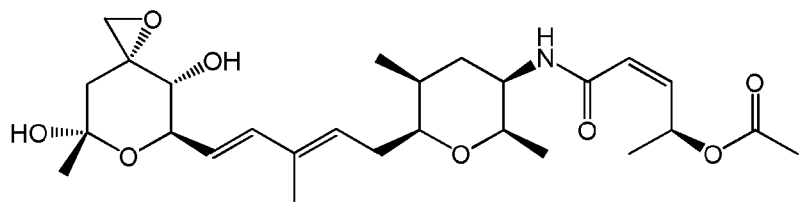


or a salt,

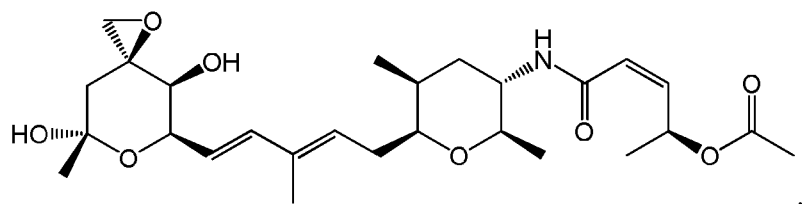
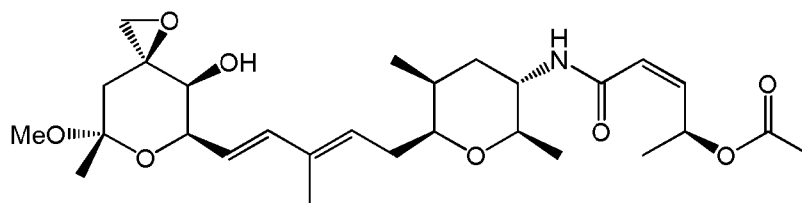
prodrug or antibody conjugate thereof.

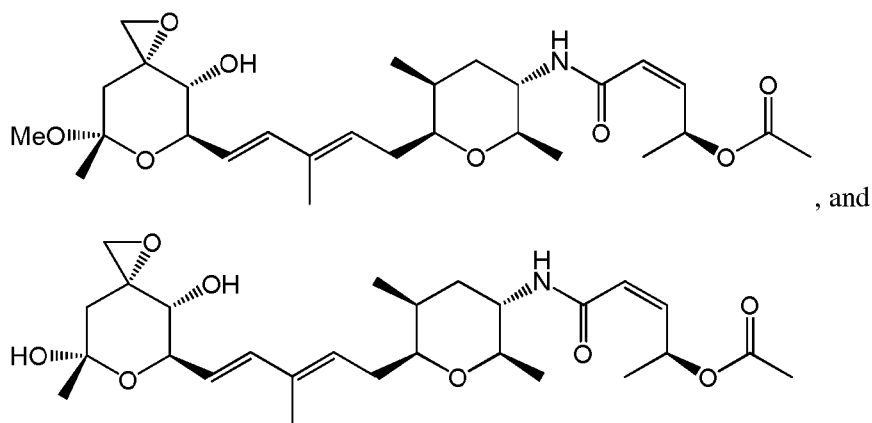
[0094] Embodiment 26 relates to a pharmaceutical composition comprising one or more of the compounds of Embodiment 25, or salts, prodrugs or antibody conjugates thereof, and a pharmaceutically acceptable carrier or excipient.

- 5 **[0095]** Embodiment 27 relates to a prodrug that is converted in vivo into a compound selected from the group consisting of:



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[0096] Embodiment 28 relates to a method of treating cancer in a subject in need of such treatment, comprising administering a therapeutically-effective amount of one or more compounds of Embodiment 25 or a salt, prodrug or antibody conjugate thereof.

[0097] Embodiment 29 relates to the method of Embodiment 28, wherein the cancer is a solid-tumor cancer.

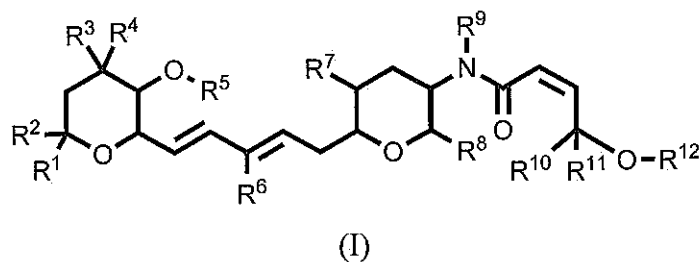
[0098] Embodiment 30 relates to the method of Embodiment 28, wherein the cancer is selected from cervical, prostate, lung, ovarian, breast, renal cell, and pancreatic cancers.

[0099] Embodiment 31 relates to the method of Embodiments 28-30, wherein a therapeutically-effective amount of the one or more compounds is administered at least twice within a 60 day period.

[00100] Embodiment 32 relates to the method of Embodiments 28-31, further comprising administering one or more of the compounds of Embodiment 25 in combination with at least one other anticancer agent.

CLAIMS

1. A compound according to Formula I or a pharmaceutically acceptable salt thereof:



wherein

R^1 and R^2 are each independently OH or C_{1-6} -alkoxy

R^3 and R^4 , together with the carbon atom to which they are bound, form an epoxide ring;

R^5 is selected from the group consisting of H, a hydroxyl protecting group, C_{1-6} -alkyl, $C(O)R^{13}$, $C(O)OR^{13}$, and $C(O)NR^{14}R^{15}$, wherein each R^{13} is independently H or C_{1-6} -alkyl;

R^6 is selected from the group consisting of H and C_{1-6} -alkyl; and

R^7 is C_{1-6} -alkyl; and

R^8 , R^9 , R^{10} , and R^{11} are independently selected from the group consisting of H and C_{1-6} -alkyl

R^{12} is $C(O)NR^{14}R^{15}$ wherein

R^{14} and R^{15} together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclic ring.

2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein

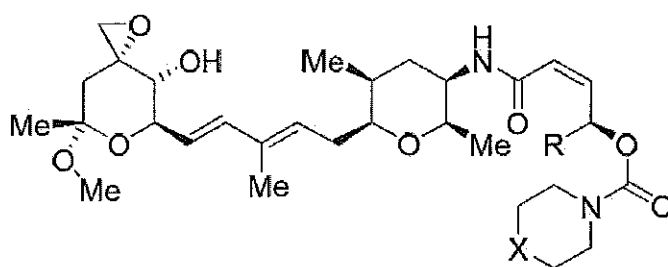
R^5 is selected from the group consisting of H, a hydroxyl protecting group, and C_{1-6} -alkyl.

3. The compound according to claim 2 or a pharmaceutically acceptable salt thereof, wherein

R^5 is H; and

R^8 is C_{1-6} -alkyl.

4. The compound according to claim 3 or a pharmaceutically acceptable salt thereof, wherein the compound conforms to the formula:



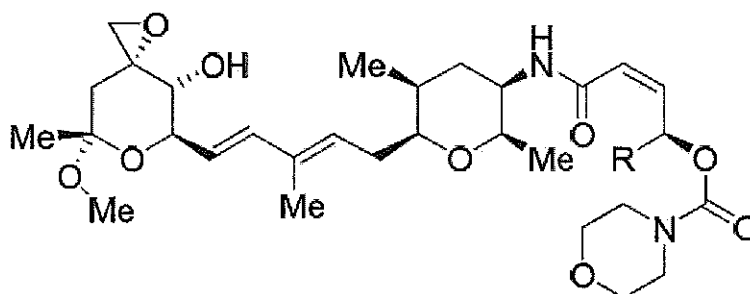
wherein

X is selected from the group consisting of O, NH, and NMe; and

R is selected from the group consisting of Me, Et, i-Pr, phenyl, and benzyl.

5. The compound according to claim 4 or a pharmaceutically acceptable salt thereof, wherein X is NH.

6. The compound according to claim 3 or a pharmaceutically acceptable salt thereof, wherein the compound is:



7. An antibody conjugate, comprising at least one compound according to claim 1 conjugated to an antibody.

8. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, diluents, excipients or combinations thereof.

9. A compound according to claim 1 or a pharmaceutically acceptable salt thereof for treating a patient in need of relief from cancer.