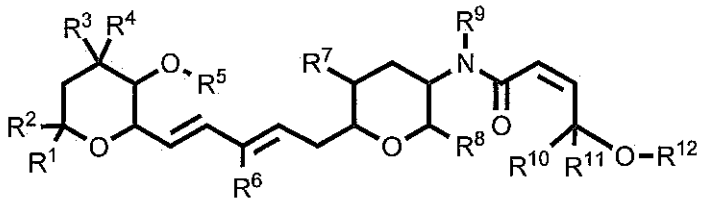
[0006] One family of protein complexes involved in transcription pathways are spliceosomes. Spliceosomes typically include over 100 proteins that work together to control the excision of exons (i.e., splicing of introns) from genomic material during the transcription. Compounds that interfere with the 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

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.

[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 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 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 (R)-isopropylidene glyceraldyhyde, 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 efficiency (> 98 % ee) and a good yield.

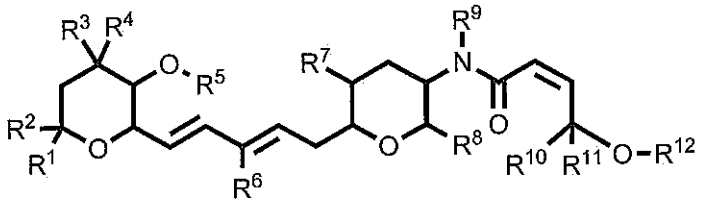
DETAILED DESCRIPTION

[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 metathesis of a cyclic epoxy alcohol to a amide, as described herein.

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

CLAIMS

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



(I)

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

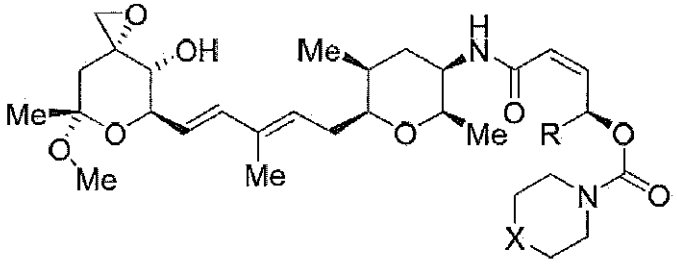
R^5 is selected from the group consisting of H, a hydroxyl protecting group, and C_{1-6}-alkyl.

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:



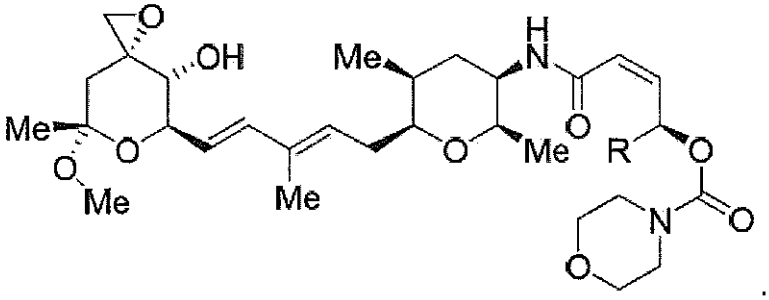
wherein

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.