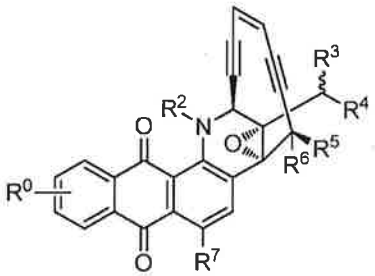
CLAIMS

What is claimed is:

1. A compound having a structure represented by formula (I)



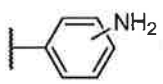
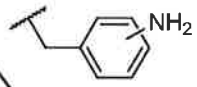
(I)

wherein

R^0 is NHR^{1a}, $NHC(=O)OR^{1b}$, $NHC(=O)NHR^{1b}$, $OC(=O)NHR^{1b}$, $(CH_2)_{1-4}NHR^{1a}$, F, Cl, Br, OR^{1b}, or SR^{1b};

R^{1a} is H, C_1-C_6 alkyl, $(CH_2)_nNH_2$, $C(=O)(CH_2)_nNH_2$, $C(=O)CHR^8NH_2$, or $C(=O)R^9NH_2$;

R^{1b} is H, C_1-C_6 alkyl, $(CH_2)_nNH_2$,

 or  ;

R^2 is H, R^{10}, $C(=O)R^{10}$, or $C(=O)OR^{10}$;

R^3 is H or unsubstituted or substituted C_1-C_6 alkyl;

R^4 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^5 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^6 is H or unsubstituted or substituted C_1-C_6 alkyl; or R^5 and R^6 combine to form =O;

R^7 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^8 is the side chain residue of an α-amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, γ-carboxyglutamic acid, citrulline, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, serine, threonine, tryptophan, tyrosine, and valine;

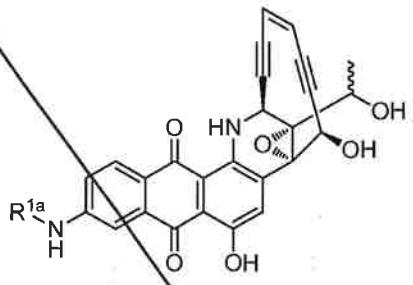
R^9 is unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, unsubstituted or substituted alkylarylene, unsubstituted or substituted cycloalkylene or unsubstituted or substituted heterocycloalkylene;

each R^{10} is independently unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted arylalkyl, unsubstituted or substituted aryl; or unsubstituted or substituted heteroaryl; and

n is 2, 3, 4, 5, or 6;

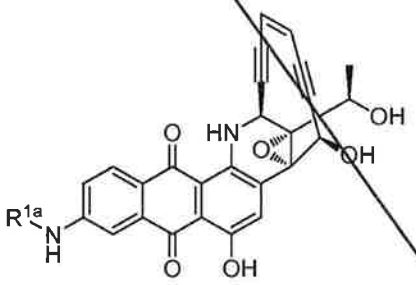
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, having a structure represented by formula (Ia):



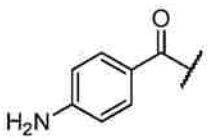
(Ia)

3. A compound according to claim 1, having a structure represented by formula (Ib):



(Ib)

4. A compound according to claim 3, wherein R^{1a} is selected from the group consisting of H, Me,



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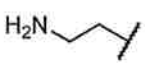

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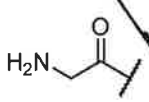

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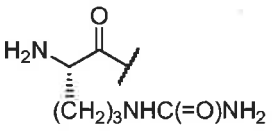

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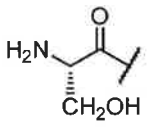

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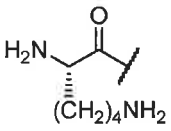

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5. A conjugate comprising a compound according to claim 1 covalently linked to a targeting moiety that specifically or preferentially binds to a chemical entity on a target cell,.

6. A conjugate according to claim 5, wherein the targeting moiety is an antibody or an antigen binding portion thereof, the target cell is a tumor cell, and the chemical entity is a tumor associated antigen .

7. A conjugate according to claim 5, having a structure represented by formula (III)

$$[D(X^D)_aC(X^Z)_b]_mZ \qquad \text{(III)}$$

wherein

Z is a targeting moiety;

X^D is a first spacer moiety;

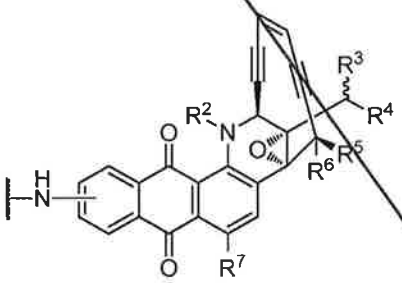
X^Z is a second spacer moiety;

C is a cleavable group;

subscripts a and b are independently 0 or 1;

subscript m is1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

D is selected from the group consisting of



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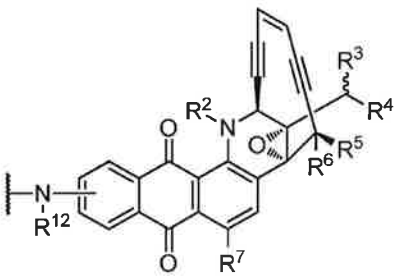

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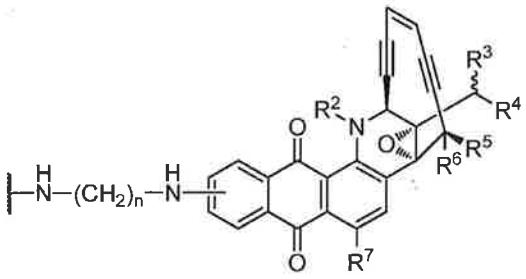

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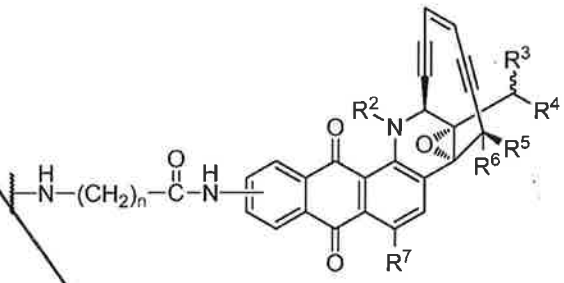

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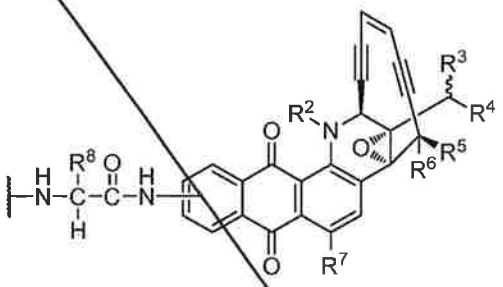

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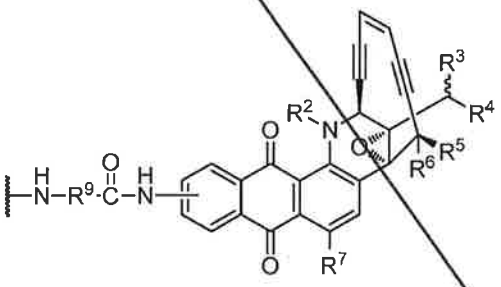


;

wherein

R^2 is H, R^{10}, $C(=O)R^{10}$, or $C(=O)OR^{10}$;

R^3 is H or unsubstituted or substituted C_1-C_6 alkyl;

R^4 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^5 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^6 is H or unsubstituted or substituted C_1-C_6 alkyl; or R^5 and R^6 combine to form =O;

R^7 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^8 is the side chain residue of an α-amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, γ-carboxyglutamic acid, citrulline, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, serine, threonine, tryptophan, tyrosine, and valine;

R^9 is unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, unsubstituted or substituted alkylarylene, unsubstituted or substituted cycloalkylene or unsubstituted or substituted heterocycloalkylene;

each R^{10} is independently unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted arylalkyl, unsubstituted or substituted aryl; or unsubstituted or substituted heteroaryl;

R^{12} is C_1-C_6 alkyl; and

n is 2, 3, 4, 5, or 6.

8. A composition having a structure according to formula (IV)

$$D\text{-}(X^D)_a C(X^Z)_b\text{-}R^{31} \qquad \text{(IV)}$$

wherein

R^{31} is a reactive functional group;

X^D is a first spacer moiety;

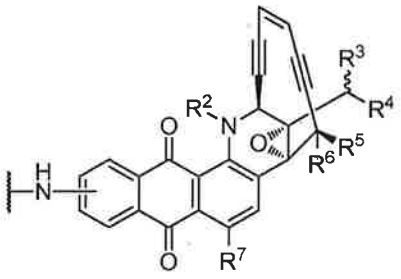
X^Z is a second spacer moiety;

C is a cleavable group;

subscripts a and b are independently 0 or 1;

subscript m is1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

D is selected from the group consisting of



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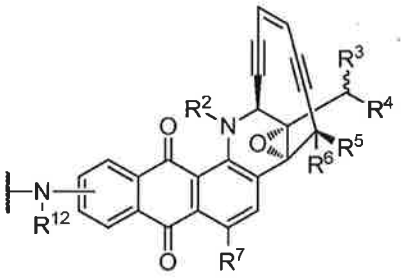

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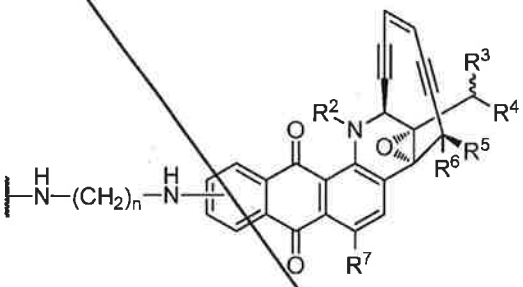

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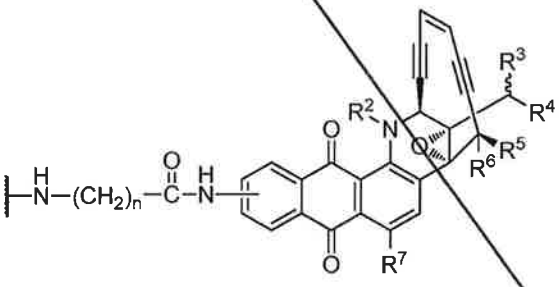

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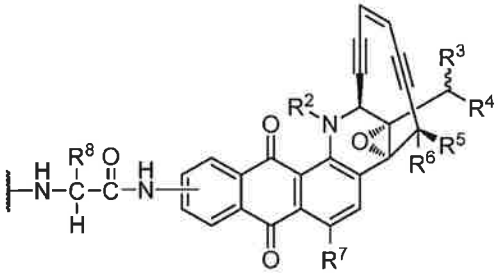

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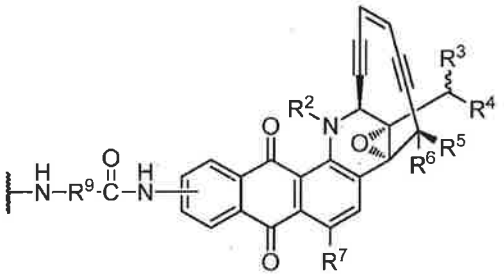

;

wherein

R^2 is H, R^{10}, $C(=O)R^{10}$, or $C(=O)OR^{10}$;

R^3 is H or unsubstituted or substituted C_1-C_6 alkyl;

R^4 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^5 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^6 is H or unsubstituted or substituted C_1-C_6 alkyl; or R^5 and R^6 combine to form =O;

R^7 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^8 is the side chain residue of an α-amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, γ-carboxyglutamic acid, citrulline, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, serine, threonine, tryptophan, tyrosine, and valine;

R^9 is unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, unsubstituted or substituted alkylarylene, unsubstituted or substituted cycloalkylene or unsubstituted or substituted heterocycloalkylene;

each R^{10} is independently unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted arylalkyl, unsubstituted or substituted aryl; or unsubstituted or substituted heteroaryl;

R^{12} is C_1-C_6 alkyl; and

n is 2, 3, 4, 5, or 6.

9. A composition according to claim 8, wherein R^{31} is is $-NH_2$, -OH, $-CO_2H$, -SH, maleimido, cyclooctyne, azido, hydroxylamino, or N-hydroxysuccinimido.

10. A method of treating a cancer in a subject suffering from such cancer, comprising administering to the subject a therapeutically effective amount of a compound according to claim 1, or a conjugate thereof with a targeting moiety.

11. A method according to claim 10, wherein the compound is conjugated to a targeting moiety that is an antibody.

12. A method according to claim 11, wherein the antibody binds to an antigen that is overexpressed or uniquely expressed by the cancer.

13. A method according to claim 10, wherein the cancer is selected from the group consisting of leukemia, renal cancer, ovarian cancer, lung cancer, colon cancer, breast cancer, and prostate cancer.

14. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

15. A pharmaceutical composition according to claim 14, wherein the compound is conjugated to a targeting moiety.

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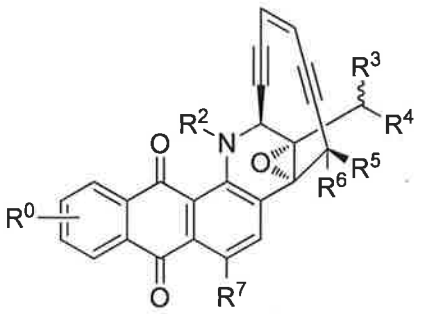
CLAIMS

1. A compound having a structure represented by formula (I)



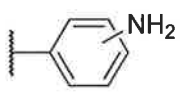
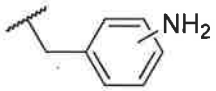
(I)

wherein

R^0 is NHR^{1a}, $NHC(=O)OR^{1b}$, $NHC(=O)NHR^{1b}$, $OC(=O)NHR^{1b}$, $(CH_2)_{1\text{-}4}NHR^{1a}$, F, Cl, Br, OR^{1a}, or SR^{1b};

R^{1a} is H, C_1-C_6 alkyl, $(CH_2)_nNH_2$, $C(=O)(CH_2)_nNH_2$, $C(=O)CHR^8NH_2$, or $C(=O)R^9NH_2$;

R^{1b} is H, C_1-C_6 alkyl, $(CH_2)_nNH_2$,

 or  ;

R^2 is H, R^{10}, $C(=O)R^{10}$, or $C(=O)OR^{10}$;

R^3 is H or unsubstituted or substituted C_1-C_6 alkyl;

R^4 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^5 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^6 is H or unsubstituted or substituted C_1-C_6 alkyl; or R^5 and R^6 combine to form =O;

R^7 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^8 is the side chain residue of an α-amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, γ-carboxyglutamic acid, citrulline, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, serine, threonine, tryptophan, tyrosine, and valine;

R^9 is unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, unsubstituted or substituted alkylarylene, unsubstituted or substituted cycloalkylene or unsubstituted or substituted heterocycloalkylene;

each R^{10} is independently unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted arylalkyl, unsubstituted or substituted aryl; or unsubstituted or substituted heteroaryl;

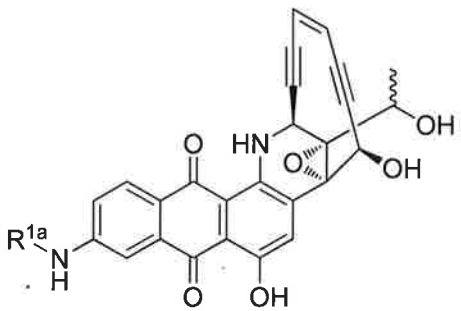
wherein the substituents of the substituted moieties are independently of each other chosen from alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, halo, haloalkyl, hydroxyl, hydroxyalkyl, cyano, nitro, alkoxy, -O(hydroxyalkyl), -O(haloalkyl), -O(cycloalkyl), -O(heterocycloalkyl), -O(aryl), alkylthio, arylthio, =O, =NH, =N(alkyl), =NOH, =NO(alkyl), -C(=O)(alkyl), -C(=O)H, $-CO_2H$, -C(=O)NHOH, -C(=O)O(alkyl), -C(=O)O(hydroxyalkyl), $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, -OC(=O)(alkyl), -OC(=O)(hydroxyalkyl), -OC(=O)O(alkyl), -OC(=O)O(hydroxyalkyl), $-OC(=O)NH_2$, -OC(=O)NH(alkyl), $-OC(=O)N(alkyl)_2$, azido, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(aryl), -NH(hydroxyalkyl), -NHC(=O)(alkyl), -NHC(=O)H, $-NHC(=O)NH_2$, -NHC(=O)NH(alkyl), $-NHC(=O)N(alkyl)_2$, $-NHC(=NH)NH_2$, $-OSO_2(alkyl)$, -SH, -S(alkyl), -S(aryl), -S(cycloalkyl), -S(=O)alkyl, $-SO_2(alkyl)$, $-SO_2NH_2$, $-SO_2NH(alkyl)$, and $-SO_2N(alkyl)_2$;

and

n is 2, 3, 4, 5, or 6;

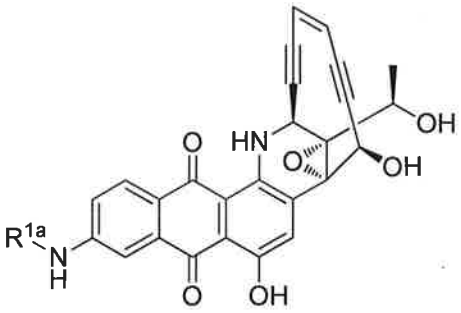
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, having a structure represented by formula (Ia):



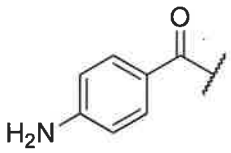
(Ia)

3. A compound according to claim 1, having a structure represented by formula (Ib):



(Ib)

4. A compound according to claim 3, wherein R^{1a} is selected from the group consisting of H, Me,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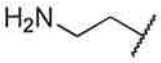
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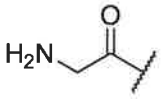
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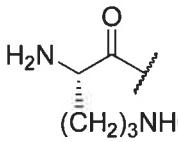
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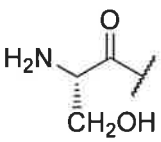
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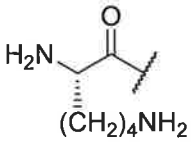

.

5. A conjugate, having a structure represented by formula (III)

$$[D(X^D)_aC(X^Z)_b]_mZ \qquad \text{(III)}$$

wherein

Z is a targeting moiety;

X^D is a first spacer moiety;

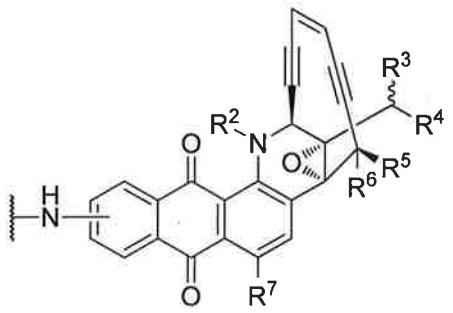
X^Z is a second spacer moiety;

C is a cleavable group;

subscripts a and b are independently 0 or 1;

subscript m is1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

D is selected from the group consisting of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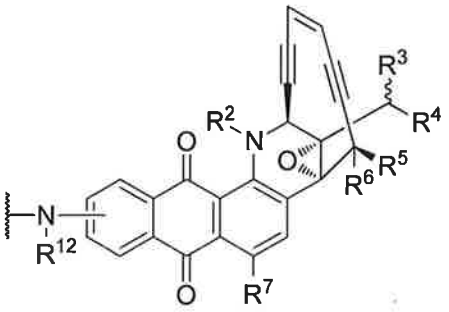

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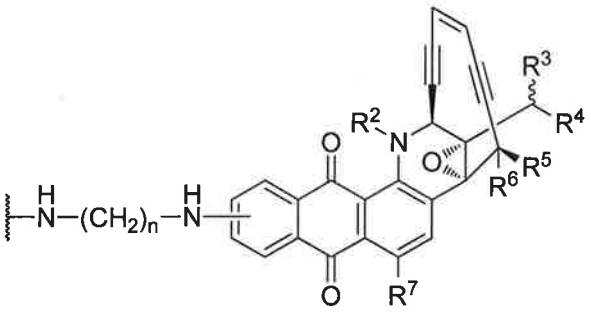

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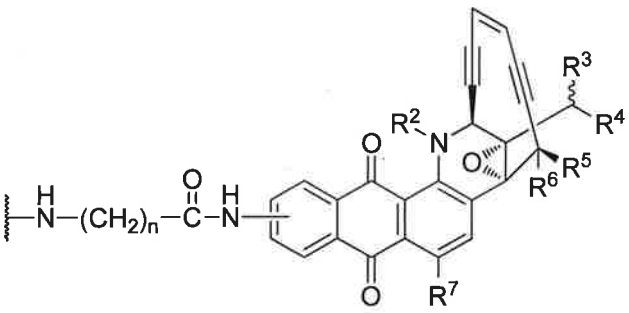

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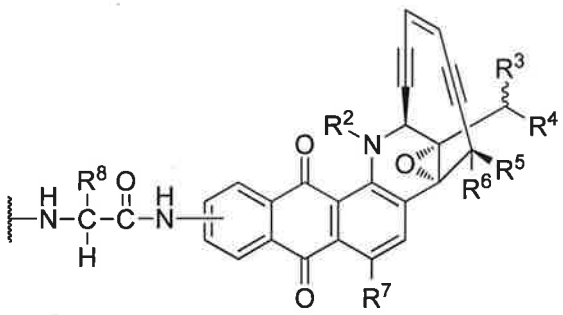

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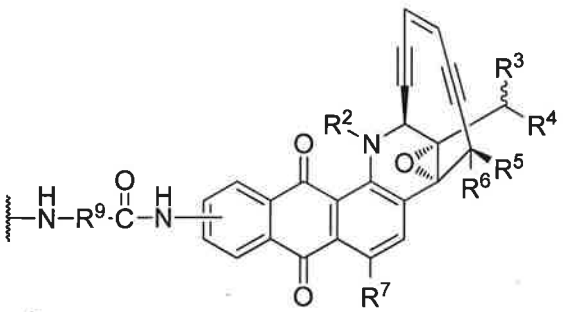


;

wherein

R^2 is H, R^{10}, $C(=O)R^{10}$, or $C(=O)OR^{10}$;

R^3 is H or unsubstituted or substituted C_1-C_6 alkyl;

R^4 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^5 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^6 is H or unsubstituted or substituted C_1-C_6 alkyl; or R^5 and R^6 combine to form =O;

R^7 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^8 is the side chain residue of an α-amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, γ-carboxyglutamic acid, citrulline, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, serine, threonine, tryptophan, tyrosine, and valine;

R^9 is unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, unsubstituted or substituted alkylarylene, unsubstituted or substituted cycloalkylene or unsubstituted or substituted heterocycloalkylene;

each R^{10} is independently unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted arylalkyl, unsubstituted or substituted aryl; or unsubstituted or substituted heteroaryl;

R^{12} is C_1-C_6 alkyl;

wherein the substituents of the substituted moieties are independently of each other chosen from alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, halo, haloalkyl, hydroxyl, hydroxyalkyl, cyano, nitro, alkoxy, -O(hydroxyalkyl), -O(haloalkyl), -O(cycloalkyl), -O(heterocycloalkyl), -O(aryl), alkylthio, arylthio, =O, =NH, =N(alkyl), =NOH, =NO(alkyl), -C(=O)(alkyl), -C(=O)H, $-CO_2H$, -C(=O)NHOH, -C(=O)O(alkyl), -C(=O)O(hydroxyalkyl), $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, -OC(=O)(alkyl), -OC(=O)(hydroxyalkyl), -OC(=O)O(alkyl), -OC(=O)O(hydroxyalkyl), $-OC(=O)NH_2$,

-OC(=O)NH(alkyl), -OC(=O)N(alkyl)$_2$, azido, -NH$_2$, -NH(alkyl), -N(alkyl)$_2$, -NH(aryl), -NH(hydroxyalkyl), -NHC(=O)(alkyl), -NHC(=O)H, -NHC(=O)NH$_2$, -NHC(=O)NH(alkyl), -NHC(=O)N(alkyl)$_2$, -NHC(=NH)NH$_2$, -OSO$_2$(alkyl), -SH, -S(alkyl), -S(aryl), -S(cycloalkyl), -S(=O)alkyl, -SO$_2$(alkyl), -SO$_2$NH$_2$, -SO$_2$NH(alkyl), and -SO$_2$N(alkyl)$_2$; and

n is 2, 3, 4, 5, or 6.

6. A composition having a structure according to formula (IV)

$$D\text{-}(X^D)_aC(X^Z)_b\text{-}R^{31} \qquad \text{(IV)}$$

wherein

R^{31} is a reactive functional group;

X^D is a first spacer moiety;

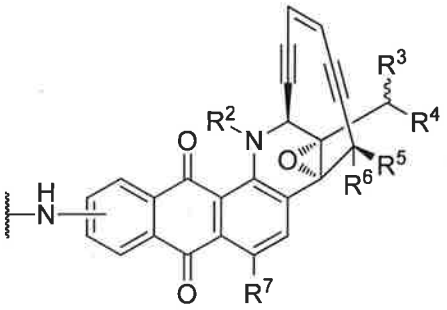
X^Z is a second spacer moiety;

C is a cleavable group;

subscripts a and b are independently 0 or 1;

subscript m is1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

D is selected from the group consisting of



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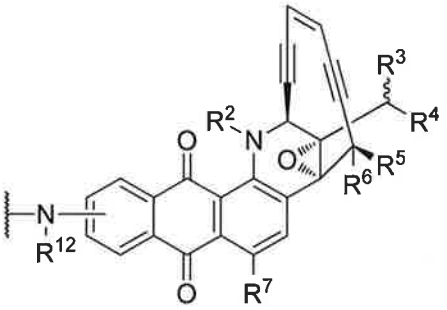

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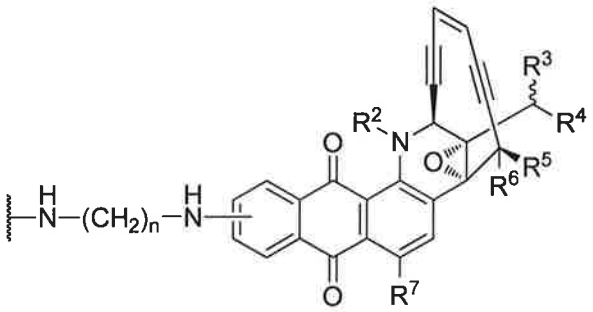

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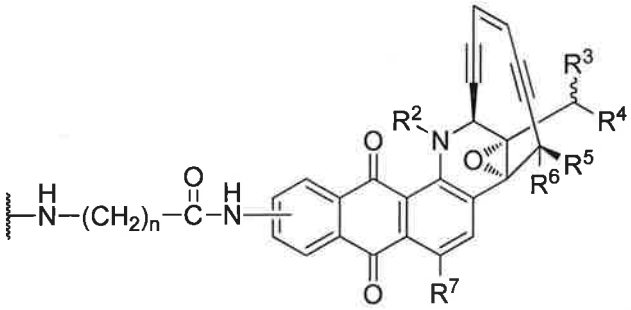

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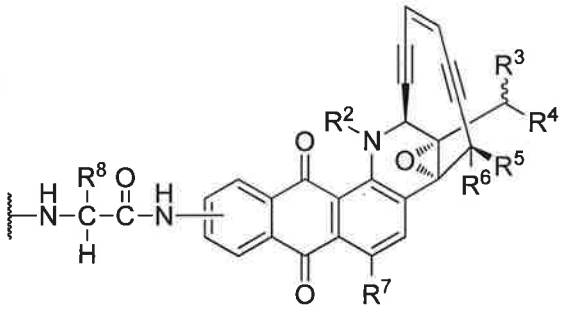

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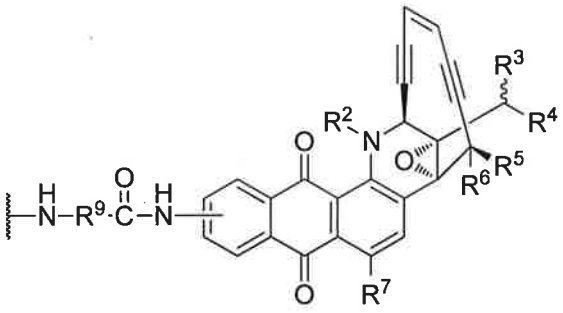

;

wherein

R^2 is H, R^{10}, $C(=O)R^{10}$, or $C(=O)OR^{10}$;

R^3 is H or unsubstituted or substituted C_1-C_6 alkyl;

R^4 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^5 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^6 is H or unsubstituted or substituted C_1-C_6 alkyl; or R^5 and R^6 combine to form =O;

R^7 is OH, SH, NH_2, OR^{10}, SR^{10}, NHR^{10}, $N(R^{10})_2$, $NHC(=O)OR^{10}$, $OC(=O)NHR^{1b}$, $OC(=O)R^{10}$, $SC(=O)R^{10}$, or $NHC(=O)R^{10}$;

R^8 is the side chain residue of an α-amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, γ-carboxyglutamic acid, citrulline, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, serine, threonine, tryptophan, tyrosine, and valine;

R^9 is unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, unsubstituted or substituted alkylarylene, unsubstituted or substituted cycloalkylene or unsubstituted or substituted heterocycloalkylene;

each R^{10} is independently unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted arylalkyl, unsubstituted or substituted aryl; or unsubstituted or substituted heteroaryl;

R^{12} is C_1-C_6 alkyl;

wherein the substituents of the substituted moieties are independently of each other chosen from alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, halo, haloalkyl, hydroxyl, hydroxyalkyl, cyano, nitro, alkoxy, -O(hydroxyalkyl), -O(haloalkyl), -O(cycloalkyl), -O(heterocycloalkyl), -O(aryl), alkylthio, arylthio, =O, =NH, =N(alkyl), =NOH, =NO(alkyl), -C(=O)(alkyl), -C(=O)H, $-CO_2H$, -C(=O)NHOH, -C(=O)O(alkyl), -C(=O)O(hydroxyalkyl), $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, -OC(=O)(alkyl), -OC(=O)(hydroxyalkyl), -OC(=O)O(alkyl), -OC(=O)O(hydroxyalkyl), $-OC(=O)NH_2$, -OC(=O)NH(alkyl), $-OC(=O)N(alkyl)_2$, azido, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(aryl), -NH(hydroxyalkyl), -NHC(=O)(alkyl), -NHC(=O)H, $-NHC(=O)NH_2$, -NHC(=O)NH(alkyl), $-NHC(=O)N(alkyl)_2$, $-NHC(=NH)NH_2$, $-OSO_2(alkyl)$, -SH, -S(alkyl), -S(aryl), -S(cycloalkyl), -S(=O)alkyl, $-SO_2(alkyl)$, $-SO_2NH_2$, $-SO_2NH(alkyl)$, and $-SO_2N(alkyl)_2$; and

n is 2, 3, 4, 5, or 6.

7. A composition according to claim 6, wherein R^{31} is is $-NH_2$, -OH, $-CO_2H$, -SH, maleimido, cyclooctyne, azido, hydroxylamino, or N-hydroxysuccinimido.

8. A compound according to any of claims 1 to 4 or a conjugate according to claim 5 for use in a method of treating a cancer in a subject suffering from such cancer.

9. A compound according to any of claims 1 to 4 for use in a method of treating a cancer according to claim 8, wherein the compound is conjugated to a targeting moiety that is an antibody.

10. A compound according to any of claims 1 to 4 for use in a method of treating a cancer according to claim 9, wherein the antibody binds to an antigen that is overexpressed or uniquely expressed by the cancer.

11. A compound according to any of claims 1 to 4 or a conjugate according to claim 5 for use in a method of treating a cancer according to claim 8, wherein the cancer is selected from the group consisting of leukemia, renal cancer, ovarian cancer, lung cancer, colon cancer, breast cancer, and prostate cancer.

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier.

13. A pharmaceutical composition comprising a conjugate according to claim 5 and a pharmaceutically acceptable carrier.