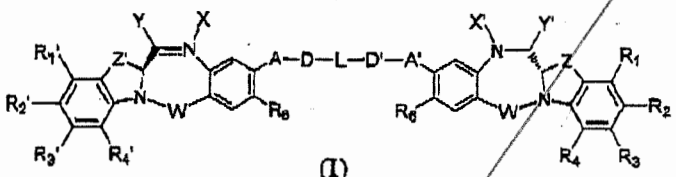
Replacement Sheet

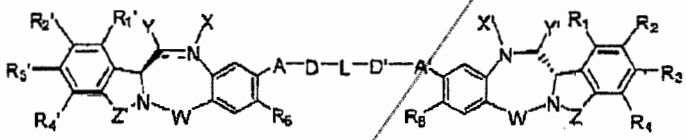
CLAIMS

We claim:

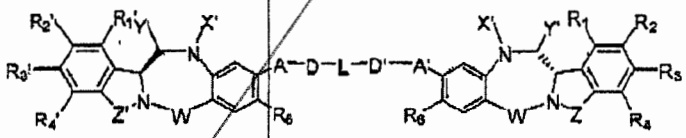
1. A cytotoxic compound comprising a linking group with a reactive group bonded thereto capable of covalently linking the cytotoxic compound to a cell binding agent (CBA), wherein said cytotoxic compound is represented by any one of the following formulas:



(I)



(III)



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond X is absent and Y is -H, or a linear or branched alkyl having 1 to 4 carbon atoms, and when it is a single bond, X is -H, the linking group with the reactive group bonded thereto, or an amine protecting moiety;

Y is -H or a leaving group selected from -OR, -OCOR', -OCOOR', -OCONR'R'', -NR'R'', -NR'COR'', -NR'NR'R'', an optionally substituted 5- or 6-membered nitrogen-containing heterocycle (*e.g.*, piperidine, tetrahydropyrrole, pyrazole, morpholine, *etc.*), a guanidinum represented by -NR'(C=NH)NR'R'', an amino acid, or a peptide represented by -NRCOP', wherein P' is an amino acid or a polypeptide containing between 2 to 20 amino acid units, -SR, -SOR', -SO_2M, -

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SO_3M, $-OSO_3M$, halogen, cyano and an azido; or,

Y is a sulfite (HSO_3^-, HSO_2^- or a salt of HSO_3^-, SO_3^{2-} or HSO_2^- formed with a cation), metabisulfite ($H_2S_2O_5$ or a salt of $S_2O_5^{2-}$ formed with a cation), mono-, di-, tri-, and tetra- thiophosphate (PO_3SH_3, $PO_2S_2H_2$, POS_3H_2, PS_4H_2 or a salt of PO_3S^{3-}, $PO_2S_2^{3-}$, POS_3^{3-} or PS_4^{3-} formed with a cation), thio phosphate ester $(R^iO)_2PS(OR^i)$, R^iS^-, R^iSO, R^iSO_2, R^iSO_3, thiosulfate (HS_2O_3 or a salt of $S_2O_3^{2-}$ formed with a cation), dithionite (HS_2O_4 or a salt of $S_2O_4^{2-}$ formed with a cation), phosphorodithioate ($P(=S)(OR^{k'})(S)(OH)$ or a salt thereof formed with a cation), hydroxamic acid ($R^{k'}C(=O)NOH$ or a salt formed with a cation), formaldehyde sulfoxylate ($HOCH_2SO_2^-$ or a salt of $HOCH_2SO_2^-$ formed with a cation, such as $HOCH_2SO_2^-Na^+$) or a mixture thereof, wherein R^i is a linear or branched alkyl having 1 to 10 carbon atoms and is substituted with at least one substituent selected from $-N(R^j)_2$, $-CO_2H$, $-SO_3H$, and $-PO_3H$; R^i can be further optionally substituted with a substituent for an alkyl described herein; R^j is a linear or branched alkyl having 1 to 6 carbon atoms; $R^{k'}$ is a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, aryl, heterocyclyl or heteroaryl;

M is -H or a cation;

R, for each occurrence, is independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R^c$, an optionally substituted aryl having 6 to 18 carbon atoms, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an optionally substituted 3- to 18-membered heterocyclic ring containing 1 to 6 heteroatoms independently selected from O, S, N and P;

R' and R'' are each independently selected from -H, -OH, -OR, -NHR, $-NR_2$, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R^c$, and an optionally substituted 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms independently selected from O, S, N and P;

R^c is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms, or the linking group with the reactive group bonded thereto;

n is an integer from 1 to 24;

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W is selected from C=O, C=S, CH_2, BH, SO and SO_2;

X' is selected from -H, an amine-protecting group, the linking group with the reactive group bonded thereto, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R^6$, an optionally substituted aryl having 6 to 18 carbon atoms, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, and an optionally substituted 3- to 18-membered heterocyclic ring containing 1 to 6 heteroatoms independently selected from O, S, N and P;

Y' is selected from -H, an oxo group, the linking group with the reactive group bonded thereto, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, an optionally substituted 6- to 18-membered aryl, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms;

R_1, R_2, R_3, R_4, R_1', R_2', R_3' and R_4' are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-R^6$, halogen, guanidinium [$-NH(C=NH)NH_2$], -OR, -NR'R'', $-NO_2$, -NCO, -NR'COR'', -SR, a sulfoxide represented by -SOR', a sulfone represented by $-SO_2R'$, a sulfonate $-SO_3^-M^+$, a sulfate $-OSO_3^-M^+$, a sulfonamide represented by $-SO_2NR'R''$, cyano, an azido, -COR', -OCOR', -OCONR'R'', and the linking group with the reactive group bonded thereto;

R_6 is -H, -R, -OR, -SR, -NR'R'', $-NO_2$, halogen or the linking group with the reactive group bonded thereto;

Z and Z' are independently selected from $-(CH_2)_{n'}-$, $-(CH_2)_{n'}-CR_7R_8-(CH_2)_{na'}-$, $-(CH_2)_{n'}-NR_9-(CH_2)_{na'}-$, $-(CH_2)_{n'}-O-(CH_2)_{na'}-$ and $-(CH_2)_{n'}-S-(CH_2)_{na'}-$;

n' and na' are the same or different, and are selected from 0, 1, 2 and 3;

R_7 and R_8 are the same or different, and are each independently selected from -H, -OH, -SH, -COOH, -NHR', a polyethylene glycol unit $-(OCH_2CH_2)_n-$, an amino acid, a peptide unit bearing 2 to 6 amino acids, an optionally substituted linear, branched or cyclic alkyl having from 1 to 10 carbon atoms;

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R_9 is independently selected from -H, an optionally substituted linear, branched or cyclic alkyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-$;

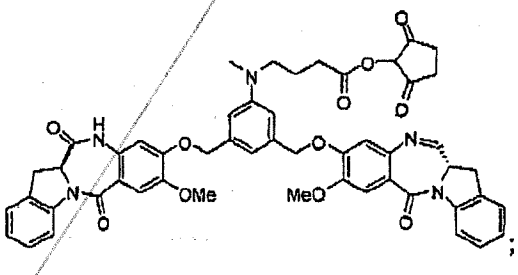
A and A' are the same or different, and are independently selected from -O-, oxo (-C(=O)-), -CRR'O-, -CRR'-, -S-, -CRR'S-, $-NR_5$ and $-CRR'N(R_5)-$,

R_5 for each occurrence is independently -H or an optionally substituted linear or branched alkyl having 1 to 10 carbon atoms;

D and D' are the same or different, and are independently absent or selected from the group consisting of an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, an amino acid, a peptide bearing 2 to 6 amino acids, and a polyethylene glycol unit $(-OCH_2CH_2)_n-$;

L is absent, the linking group with the reactive group bonded thereto, a polyethylene glycol unit $(-OCH_2CH_2)_n-$, a linear, branched or cyclic alkyl or alkenyl having 1 to 10 carbon atoms, a phenyl group, a 3 to 18-membered heterocyclic ring or a 5- to 18-membered heteroaryl ring having 1 to 6 heteroatoms independently selected from O, S, N and P, wherein the alkyl or alkenyl is optionally substituted with the linking group with the reactive group bonded thereto; phenyl or heterocyclic or heteroaryl ring can be optionally substituted, wherein the substituent can be the linking group with the reactive group bonded thereto;

provided that the compound is not any one of the following compounds:



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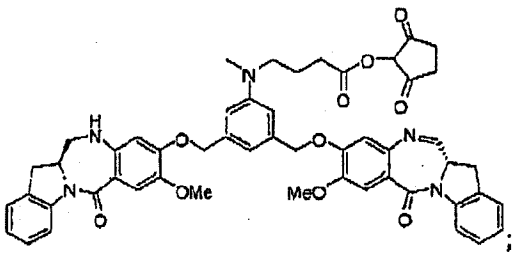

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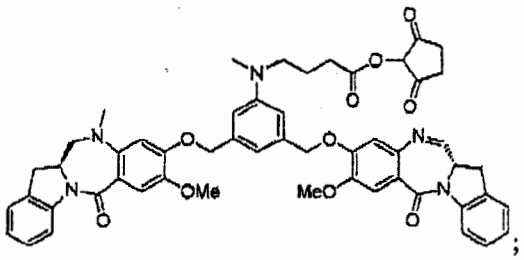
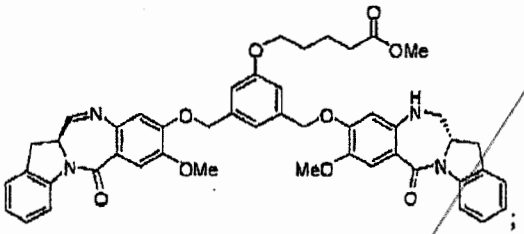
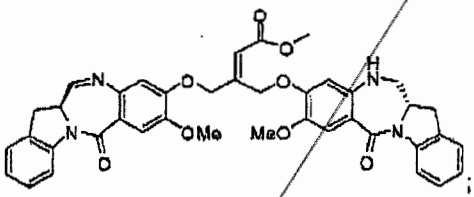

OMe
MeO

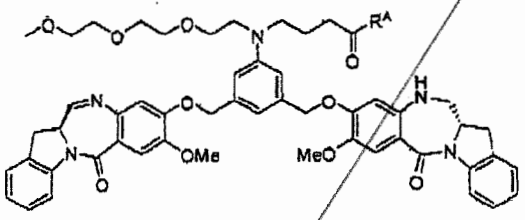
;

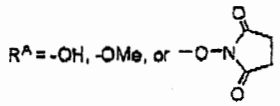

OMe
OMe
MeO

;

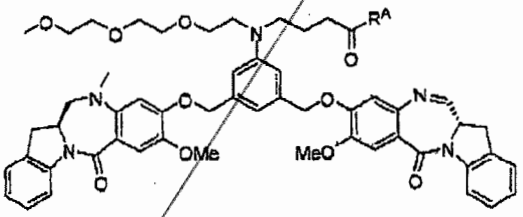

OMe
MeO

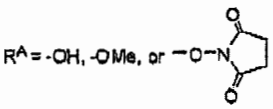
;


R^A
OMe
MeO

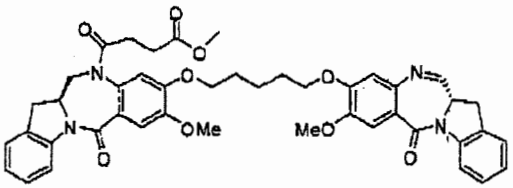

R^A = -OH, -OMe, or

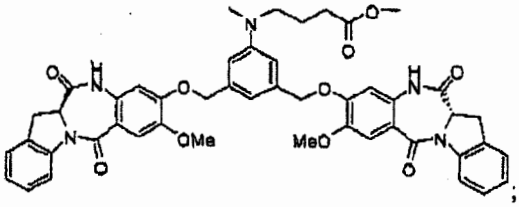
;


R^A
OMe
MeO


R^A = -OH, -OMe, or

;


OMe
MeO



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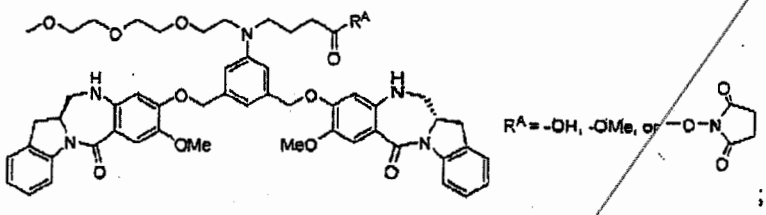

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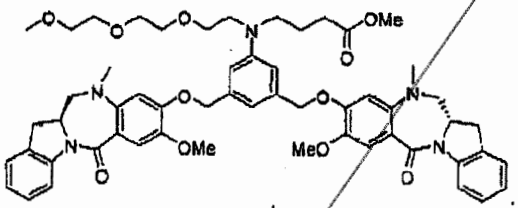

2. The compound of claim 1, wherein Y is a leaving group selected from -OR, -OCOR', -OCOOR', -OCONR'R'', -NR'R'', -NR'COR'', -NR'NR'R'', an optionally substituted 5- or 6-membered nitrogen-containing heterocycle (*e.g.*, piperidine, tetrahydropyrrole, pyrazole, morpholine, *etc.*), a guanidinum represented by -NR'(C=NH)NR'R'', an amino acid, or a peptide represented by -NRCOP', wherein P' is an amino acid or a polypeptide containing between 2 to 20 amino acid units, -SR, -SOR', $-SO_2M$, $-SO_3M$, $-OSO_3M$, halogen, cyano and an azido.

3. The compound of claim 1 or 2, wherein L is absent, or is selected from an optionally substituted phenyl group and an optionally substituted pyridyl group, wherein the phenyl and the pyridyl group bears the linking group with the reactive group bonded thereto, or L is an amine group bearing the linking group with the reactive group bonded thereto (*i.e.*, -N(linking group)-), or L is a linear, branched or cyclic alkyl or alkenyl having from 1 to 6 carbon atoms and bearing the linking group with the reactive group bonded thereto.

4. The compound of claim 1 or 2, wherein the compound is represented by any one of the following formulas:

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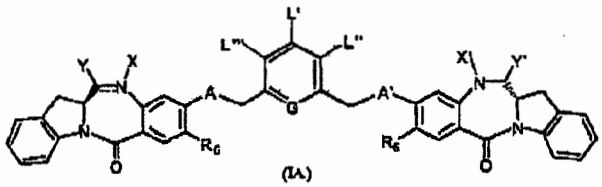

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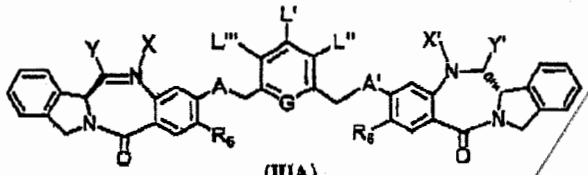
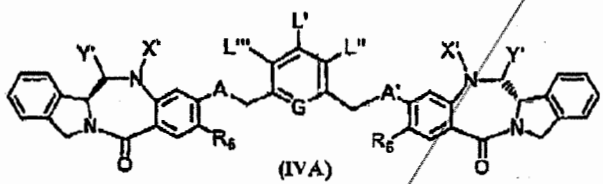


(IIIA)



(IVA)

wherein:

L', L'', and L''' are the same or different, and are independently selected from -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl of alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-R^c$, halogen, guanidinium [$-NH(C=NH)NH_2$], -OR, -NR'R'', $-NO_2$, -NR'COR'', -SR, a sulfoxide represented by -SOR', a sulfone represented by $-SO_2R'$, a sulfonate $-SO_3M$, a sulfate $-OSO_3M$, a sulfonamide represented by $-SO_2NR'R''$, cyano, an azido, -COR', -OCOR', -OCONR'R'' and the linking group with the reactive group bonded thereto, provided only one of L', L'', and L''' is the linking group with the reactive group bonded thereto; and

G is selected from -CH- or -N-.

5. The compound of claim 4, wherein one of L', L'', or L''' is the linking group with the reactive group bonded thereto, while the others are -H.

6. The compound of claim 5, wherein L' is the linking group with the reactive group bonded thereto, and L'' and L''' are -H.

7. The compound of claim 5 or 6, wherein A and A' are both -O-, R_6 is -OMe, and G is -CH-.

8. The compound of claim 5, 6, or 7, wherein L' is represented by the following formula:

$-W'-R^x-V-R^y-J,$

wherein:

W' and V are the same or different, and are each independently absent, or selected from $-CR^cR^{c'}-$, -O-, -O-C(=O)-, -C(=O)-O-, -S-, -SO-, $-SO_2-$, $-CH_2-S-$, $-CH_2O-$, $-CH_2NR^e-$, -O-(C=O)O-, -O-(C=O)N(R^e)-, -N(R^e)-, -N(R^e)-C(=O)-, -C(=O)-N(R^e)-, -N(R^e)-C(=O)O-, -N(C(=O)R^e)C(=O)-, -N(C(=O)R^e)-, $-(O-CH_2-CH_2)_n-$, -SS-, or -C(=O)-, or an amino acid, or a peptide having 2 to 8 amino acids;

R^x and R^y are the same or different, and are each independently absent or an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, an aryl bearing 6 to 10 carbon atoms or a 3- to 8-membered heterocyclic ring bearing 1 to 3 heteroatoms selected from O, N or S;

R^a and $R^{c'}$ are the same or different, and are selected from -H, a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms or $-(CH_2-CH_2-O)_n-R^k$, wherein R^k is a -H, a linear, branched cyclic alkyl having 1 to 6 carbon atoms, optionally bearing a secondary amino (*e.g.*, $-NHR^{101}$) or tertiary amino ($-NR^{101}R^{102}$) group or a 5- or 6-membered nitrogen containing heterocycle, such as piperidine or morpholine, wherein R^{101} and R^{102} are each independently a linear, branched, or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms; preferably, R^{101} and R^{102} are each independently a linear or branched alkyl having 1 to 6 carbon atoms;

n is an integer from 1 to 24;

J comprises the reactive group bonded thereto, and is selected from a maleimide, a haloacetamido, -SH, $-SSR^d$, $-CH_2SH$, -CH(Me)SH, $-C(Me)_2SH$, $-NHR^{c1}$, $-CH_2NHR^{c1}$, $-NR^{c1}NH_2$, -COOH, and -COE, wherein -COE represents a reactive ester selected from, but not limited to, N-hydroxysuccinimde ester, N-hydroxy sulfosuccinimide ester, nitrophenyl (*e.g.*, 2 or 4-nitrophenyl) ester, dinitrophenyl (*e.g.*, 2,4-dinitrophenyl) ester, sulfo-tetraflurophenyl (*e.g.*, 4-sulfo-2,3,5,6-tetrafluorophenyl) ester, and pentafluorophenyl ester, and wherein R^{c1} is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms, and,

R^d is selected from phenyl, nitrophenyl (*e.g.*, 2 or 4-nitrophenyl), dinitrophenyl (*e.g.*, 2 or 4-nitrophenyl), carboxynitrophenyl (*e.g.*, 3-carboxy-4-nitrophenyl), pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

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9. The compound of claim 8, wherein J is -SH, -SSR^d, a maleimide, or a N-hydroxysuccinimide ester.

10. The compound of claim 8 or 9, wherein:

R^c is -H or -Me;

R^e is a linear or branched alkyl having 1 to 6 carbon atoms or -$(CH_2$-CH_2-$O)_n$-R^k;

n is an integer from 2 to 8; and

R^k is -H, -Me or -CH_2CH_2-NMe_2.

11. The compound of any one of claims 8-10, wherein V is an amino acid or a peptide having 2 to 8 amino acids.

12. The compound of claim 11, wherein V is valine-citrulline, gly-gly-gly, or ala-leu-ala-leu.

13. The compound of claim 8, wherein:

W' is -O-, -N(R^e)- or -N(R^e)-C(=O)-;

R^e is -H, a linear or branched alkyl having 1 to 4 carbon atoms, or -$(CH_2$-CH_2-$O)_n$-R^k;

R^x is a linear or branched alkyl having 1 to 6 carbon atoms;

V is absent, -$(O$-CH_2-$CH_2)_n$-, -C(=O)-NH-, -S-, -NH-C(=O)-;

R^y is absent or a linear or branched alkyl having 1 to 4 carbon atoms; and

J is -SH, -SSR^d or -COE.

14. The compound of claim 8, wherein:

W' is -O-, -N(R^e)- or -N(R^e)-C(=O)-;

R^e is -H, -Me, or -$(CH_2$-CH_2-$O)_n$-Me;

n is an integer from 2 to 6;

R^x is linear or branched alkyl bearing 1 to 6 carbon atoms;

V and R^y are absent; and

J is -COE.

15. The compound of claim 13 or 14, wherein -COE is N-hydroxysuccinimide ester.

16. The compound of claim 8, wherein L' is represented by the following formula:

-W'-$[CR_{1''}R_{2''}]_n$-V-$[Cy]_{0-1}$-$[CR_{3''}R_{4''}]_b$-COE,

wherein:

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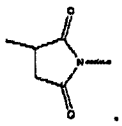
$R_{1''}$, $R_{2''}$, and $R_{3''}$ are each independently -H or -Me;

$R_{4''}$ is -H, -Me, $-SO_3H$, or $-SO_3^-M^+$, wherein M^+ is a pharmaceutically acceptable cation;

a is an integers from 0-2, b is an integer from 0-3; and,

Cy is an optionally substituted 5-membered heterocyclic ring bearing an N heteroatom, preferably Cy is



17. The compound of claim 8 or 16, wherein W' is $-N(R^e)-$.

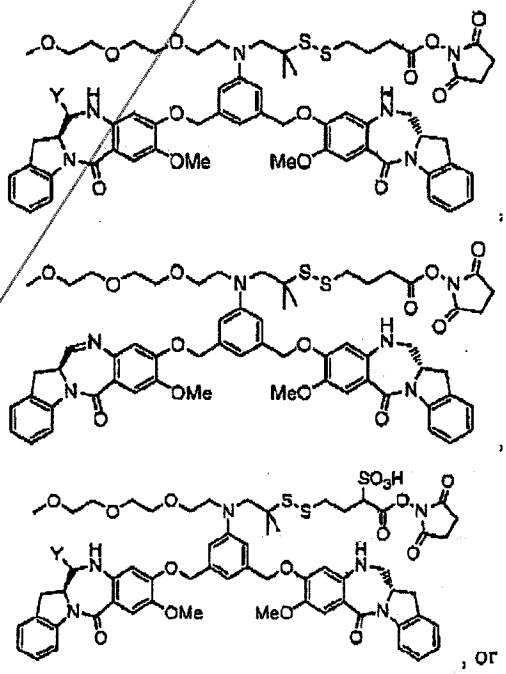
18. The compound of claim 8, 16, or 17, wherein R^e is $-(CH_2-CH_2-O)_{2-6}-R^k$, wherein R^k is a -H, a linear, branched cyclic alkyl having 1 to 6 carbon atoms.

19. The compound to claim 8, 16, 17, or 18, wherein V is -S- or -SS-.

20. The compound of claim 8, 16, 17, 18, or 19, wherein L' is represented by the following formula:

$$-NR^{e}-[CR_{1''}R_{2''}]_a-S-[CR_{3''}R_{4''}]_b-COE.$$

21. The compound to claim 8, 16, 17, 18, or 19, which is:



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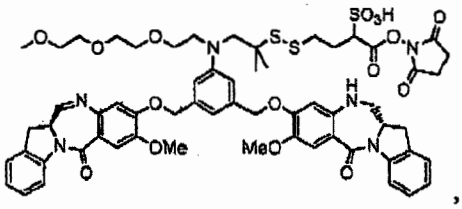
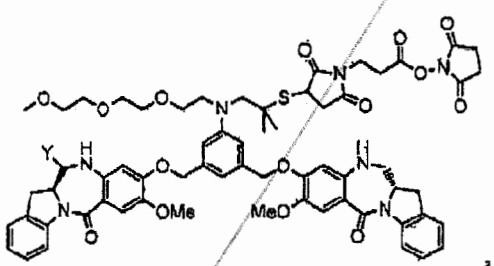


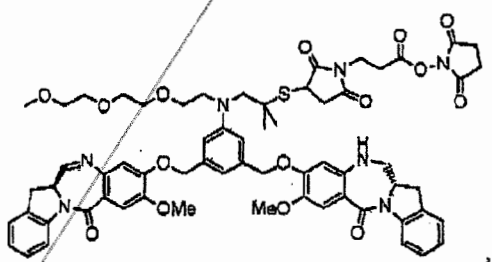
wherein Y is -H or -SO_3M (*e.g.*, Y is -SO_3M), and M is -H or a pharmaceutically acceptable cation.

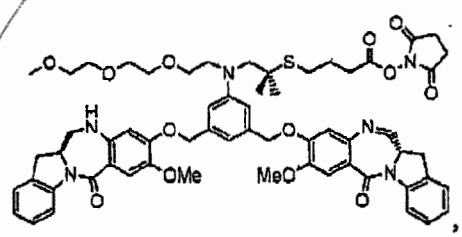
22. The compound of claim 8, 16, 17, 18, or 19, wherein L' is represented by the following formula:

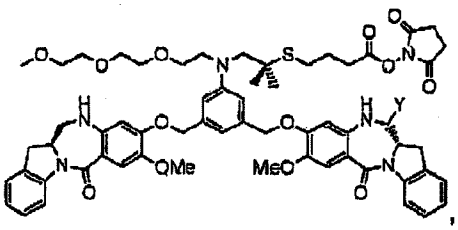
$$-NR^{6}-[CR_{1''}R_{2''}]_{a}-S-Cy-[CR_{3''}R_{4''}]_{b}-COE.$$

23. The compound of claim 8, 16, 17, 18, 19, or 22, which is:



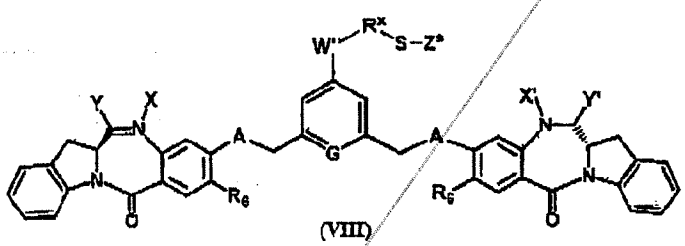




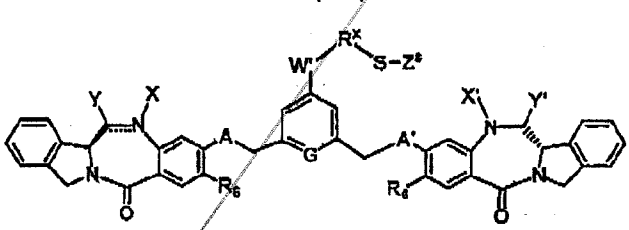


wherein Y is -H or -SO_3M (*e.g.*, Y is -SO_3M), and M is -H or a pharmaceutically acceptable cation.

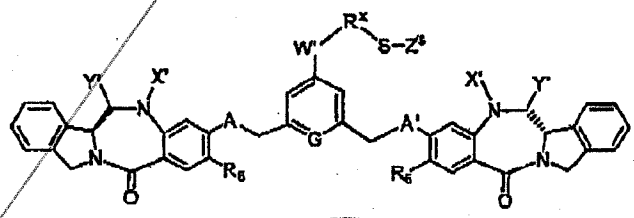
24. The compound of claim 1, 2, 4, or 8, wherein the compound is represented by any one of the following formulas:



(VIII) ;



(X) ; and



(XI) ,

wherein:

the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond, X is absent and Y is -H, and when it is a single bond, X is selected from -H, the linking group with the reactive group bonded thereto, or an amine protecting group (preferably X is -H);

Y is selected from -H, -OR, -OCOR', -SR, -NR'R," -SO_3M, -SO_2M or -OSO_3M, wherein M is -H or a cation such as Na^+ or K^+;

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R is -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms or a PEG group $-(CH_2CH_2O)_n-R^c$, wherein n is an integer from 1 to 24, and R^c is a linear or branched alkyl having 1 to 4 carbon atoms;

R' and R" are the same or different, and are selected from -H, -OH, -OR, -$NRR^{g'}$, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, an optionally substituted aryl having from 6 to 18 carbon atoms, an optionally substituted 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms selected from O, S, N and P, a PEG group $-(CH_2CH_2O)_n-R^c$, wherein n is an integer from 1 to 24, preferably n is 2, 4 or 8; and $R^{g'}$ is -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms or a PEG group $-(CH_2CH_2O)_n-R^c$;

X' is selected from the group consisting of -H, -OH, a substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, phenyl, and an amine-protecting group;

Y' is selected from the group consisting of -H, an oxo group, a substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms;

A and A' are selected from -O- and -S-;

W' is absent, or selected from -O-, $-N(R^c)-$, $-N(R^c)-C(=O)-$, $-N(C(=O)R^c)-$, -S- or $-CH_2-S-$, $-CH_2NR^c-$;

R^x is absent or selected from a linear, branched or cyclic alkyl having 1 to 10 carbon atoms;

R^c is -H, a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms or $-(CH_2-CH_2-O)_n-R^k$, wherein R^k is a -H, a linear, branched cyclic alkyl having 1 to 6 carbon atoms, optionally bearing a secondary amino (*e.g.*, -NHR^{101}) or tertiary amino ($-NR^{101}R^{102}$) group or a 5- or 6-membered nitrogen containing heterocycle, such as piperidine or morpholine, wherein R^{101} and R^{102} are each independently a linear, branched, or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms;

G is selected from -CH- or -N-;

Z^s is -H, or is selected from any one of the following formulas:

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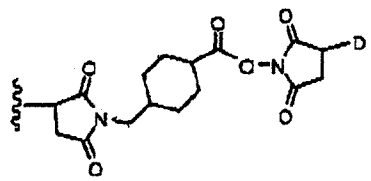
Replacement Sheet



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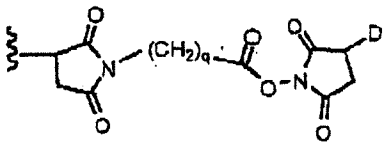
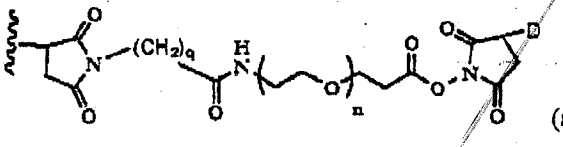


(a2);



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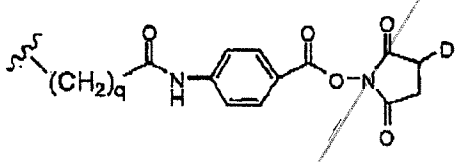
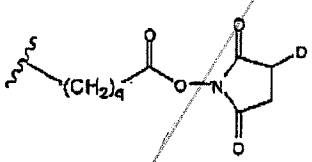
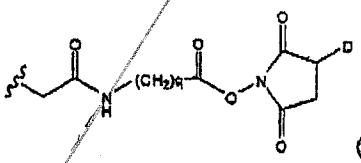


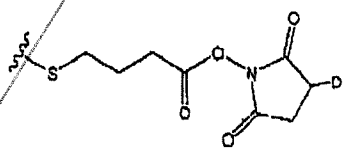
(a4);



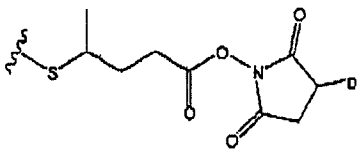
(a5);



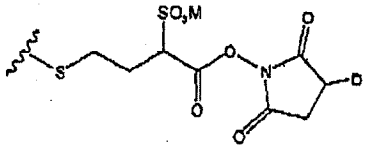
(a6);



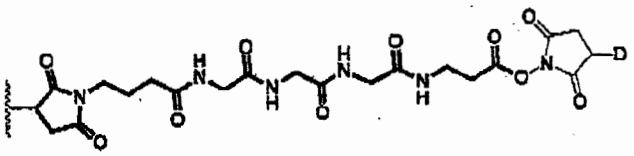
(a7);



(a8);



(a9), and,



(a10),

wherein:

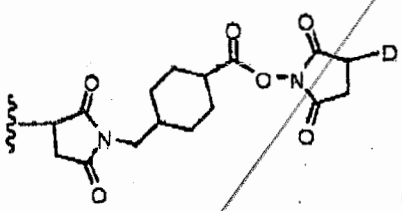
q is an integer from 1 to 5;

r is an integer from 2 to 6;

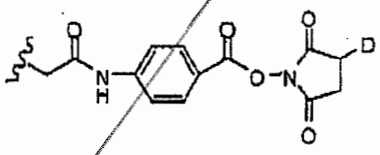
D is -H or $-SO_3M$;

M is -H or a cation, such as Na^+ or K^+.

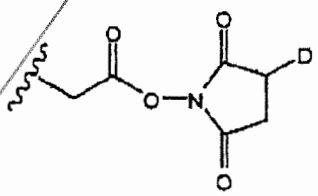
25. The compound of claim 24, wherein Z^5 is represented by any one of the following formulas:



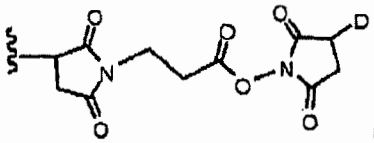
(a1);



(a4');



(a5');



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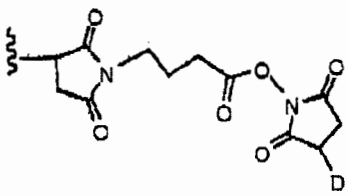


(a13).

26. The compound of claim 24 or 25, wherein W' is $-N(R^6)-$.

27. The compound of claim 26, wherein R^e is $-(CH_2-CH_2-O)_n-R^k$, wherein R^k is a -H, a linear, branched cyclic alkyl having 1 to 6 carbon atoms.

28. The compound of claim 27, wherein R^k is -H or -Me, n is 4, and q is 2.

29. The compound of claim 28, wherein R^x is a linear or branched alkyl having 1 to 6 carbon atoms.

30. The compound of claim 28, wherein R^x is $-(CH_2)_p-(CR^fR^g)-$, wherein R^f and R^g are each independently selected from -H or a linear or branched alkyl having 1 to 4 carbon atoms; and p is 0, 1, 2 or 3.

31. The compound of claim 30, wherein R^f and R^g are the same or different, and are selected from -H and -Me; and p is 1.

32. The compound of any one of claims 24-31, wherein:

the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond X is absent and Y is -H, and when it is a single bond, X is -H; Y is -OH or $-SO_3M$;

M is -H or a pharmaceutically acceptable cation (*e.g.*, Na^+);

X' and Y' are both -H;

A and A' are both -O-;

R_6 is -OMe; and

R^x is a linear or branched alkyl having 1 to 6 carbon atoms.

33. The compound of any one of claims 1-32, wherein the double line == between N and C represents a double bond.

34. The compound of any one of claims 1-31, wherein the double line == between N and C represents a single bond, X is -H, the linking group with the reactive group bonded thereto, or an amine protecting group; and Y is selected from -H, -OR, -OCOR', -SR, -NR'R," an optionally substituted 5- or 6-membered nitrogen-containing heterocycle, $-SO_3M$, $-SO_2M$ and a sulfate $-OSO_3M$.

35. The compound of claim 34, wherein Y is selected from -H, $-SO_3M$, -OH, -OMe, -OEt or -NHOH.

36. The compound of claim 35, wherein Y is -H, $-SO_3M$ or -OH.

37. The compound of any one of claims 34-36, wherein M is -H, Na^+ or K^+.

38. The compound of any one of claims 1-37, wherein W, when present, is C=O.

39. The compound of any one of claims 1-38, wherein Z and Z', when present, are -CH_2-.

40. The compound of any one of claims 1-39, wherein X' is selected from the group consisting of -H, -OH, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, phenyl, the linking group with the reactive group bounded thereto, and an amine-protecting group.

41. The compound of claim 40, wherein X' is -H, -OH, -Me or the linking group with the reactive group bounded thereto.

42. The compound of claim 41, wherein X' is -H.

43. The compound of any one of claims 1-42, wherein Y' is selected from the group consisting of -H, an oxo group, a substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms.

44. The compound of claim 43, wherein Y' is -H or oxo.

45. The compound of claim 44, wherein Y' is -H.

46. The compound of any one of claims 1-45, wherein A and A' are the same or different, and are selected from -O-, -S-, -NR_5-, and oxo -(C=O)-.

47. The compound of claim 46, wherein A and A' are the same or different, and are selected from -O- and -S-.

48. The compound of claim 47, wherein A and A' are -O-.

49. The compound of any one of claims 1-48, wherein D and D', when present, are the same or different, and are independently selected from a polyethylene glycol unit (-$OCH_2CH_2)_n$, wherein n is an integer from 1 to 24, an amino acid, a peptide bearing 2 to 6 amino acids, or a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, wherein the alkyl, alkenyl and alkynyl are optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OR, -NR'COR'', -SR and -COR'.

50. The compound of claim 49, wherein D and D' are linear or branched alkyl bearing 1 to 4 carbon atoms.

51. The compound of claim 1, 2, 4, or 24, wherein:

the double line == between N and C represents a double bond;

Y is -H;

W is C=O;

R_1, R_2, R_1', R_2', R_4 and R_4' are -H;

one of R_3, or R_3' is optionally the linking group with the reactive group bounded thereto and the other is -H;

R_6 is -OMe;

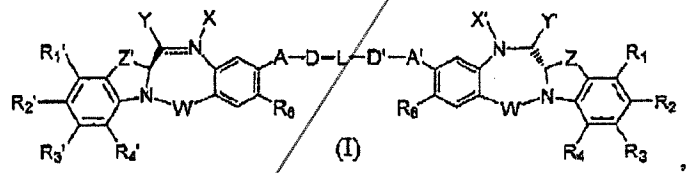
Z and Z' are -CH_2;

X' is -H;

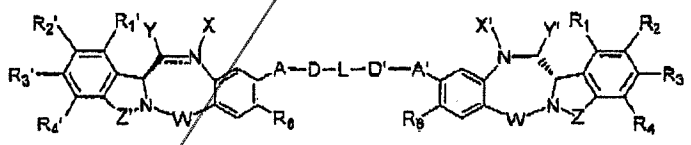
Y' is -H; and

A and A' are -O-.

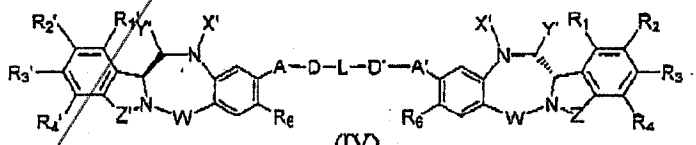
52. A conjugate comprising: a cytotoxic compound and a cell binding agent (CBA), wherein the cytotoxic compound comprises a linking group which covalently links the cytotoxic compound to the CBA, and wherein said cytotoxic compound is represented by any one of the following formulas:



(I)



(III)



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond X is absent and Y is -H, or a linear or branched alkyl having 1 to 4 carbon atoms, and when it is a single bond, X is -H, the linking group, or an amine protecting moiety;

Y is -H or a leaving group selected from -OR, -OCOR', -OCOOR', -

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OCONR'R'', -NR'R'', -NR'COR'', -NR'NR'R'', an optionally substituted 5- or 6-membered nitrogen-containing heterocycle (*e.g.*, piperidine, tetrahydropyrrole, pyrazole, morpholine), a guanidinum represented by -NR'(C=NH)NR'R'', an amino acid, or a peptide represented by -NRCOP', wherein P' is an amino acid or a polypeptide containing between 2 to 20 amino acid units, -SR, -SOR', $-SO_2M$, $-SO_3M$, $-OSO_3M$, halogen, cyano and an azido; or,

Y is a sulfite (HSO_3, HSO_2 or a salt of HSO_3^-, SO_3^{2-} or HSO_2^- formed with a cation), metabisulfite ($H_2S_2O_5$ or a salt of $S_2O_5^{2-}$ formed with a cation), mono-, di-, tri-, and tetra- thiophosphate (PO_3SH_3, $PO_2S_2H_2$, POS_3H_2, PS_4H_2 or a salt of PO_3S^{3-}, $PO_2S_2^{3-}$, POS_3^{3-} or PS_4^{3-} formed with a cation), thio phosphate ester $(R^iO)_2PS(OR^i)$, R^iS-, R^iSO, R^iSO_2, R^iSO_3, thiosulfate (HS_2O_3 or a salt of $S_2O_3^{2-}$ formed with a cation), dithionite (HS_2O_4 or a salt of $S_2O_4^{2-}$ formed with a cation), phosphorodithioate $(P(=S)(OR^{k'})(S)(OH)$ or a salt thereof formed with a cation), hydroxamic acid ($R^{k'}C(=O)NOH$ or a salt formed with a cation), formaldehyde sulfoxylate ($HOCH_2SO_2^-$ or a salt of $HOCH_2SO_2^-$ formed with a cation, such as $HOCH_2SO_2^-Na^+$) or a mixture thereof, wherein R^i is a linear or branched alkyl having 1 to 10 carbon atoms and is substituted with at least one substituent selected from $-N(R^j)_2$, $-CO_2H$, $-SO_3H$, and $-PO_3H$; R^i can be further optionally substituted with a substituent for an alkyl described herein; R^j is a linear or branched alkyl having 1 to 6 carbon atoms; $R^{k'}$ is a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, aryl, heterocyclyl or heteroaryl;

M is -H or a cation;

R, for each occurrence, is independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R^c$, an optionally substituted aryl having 6 to 18 carbon atoms, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an optionally substituted 3- to 18-membered heterocyclic ring containing 1 to 6 heteroatoms independently selected from O, S, N and P;

R' and R'' are each independently selected from -H, -OH, -OR, -NHR, $-NR_2$, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-$

R^c, and an optionally substituted 3-18-membered heterocyclic ring having 1 to 6 heteroatoms independently selected from O, S, N and P;

R^c is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms, or the linking group;

n is an integer from 1 to 24;

W is selected from C=O, C=S, CH_2, BH, SO and SO_2;

X' is selected from -H, an amine-protecting group, the linking group, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R^c$, an optionally substituted aryl having 6 to 18 carbon atoms, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, and an optionally substituted 3- to 18-membered heterocyclic ring containing 1 to 6 heteroatoms independently selected from O, S, N and P;

Y' is selected from -H, an oxo group, the linking group, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, an optionally substituted 6- to 18-membered aryl, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 3 to 18-membered heterocyclic ring having 1 to 6 heteroatoms;

R_1, R_2, R_3, R_4, R_1', R_2', R_3' and R_4' are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-R^c$, halogen, guanidinium [-NH(C=NH)NH_2], -OR, -NR'R'', $-NO_2$, -NCO, -NR'COR'', -SR, a sulfoxide represented by -SOR', a sulfone represented by $-SO_2R'$, a sulfonate $-SO_3^-M^+$, a sulfate $-OSO_3^-M^+$, a sulfonamide represented by $-SO_2NR'R''$, cyano, an azido, -COR', -OCOR', -OCONR'R'' and the linking group;

R_6 is -H, -R, -OR, -SR, -NR'R'', $-NO_2$, halogen or the linking group;

Z and Z' are independently selected from $-(CH_2)_{n'}-$, $-(CH_2)_{n'}-CR_7R_8-(CH_2)_{na'}-$, $-(CH_2)_{n'}-NR_9-(CH_2)_{na'}-$, $-(CH_2)_{n'}-O-(CH_2)_{na'}-$ and $-(CH_2)_{n'}-S-(CH_2)_{na'}-$;

n' and na' are the same or different, and are selected from 0, 1, 2 and 3;

R_7 and R_8 are the same or different, and are each independently selected from -H, -OH, -SH, -COOH, -NHR', a polyethylene glycol unit $-(OCH_2CH_2)_n-$, an

amino acid, a peptide unit bearing 2 to 6 amino acids, an optionally substituted linear, branched or cyclic alkyl having from 1 to 10 carbon atoms;

R_9 is independently selected from -H, an optionally substituted linear, branched or cyclic alkyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-$;

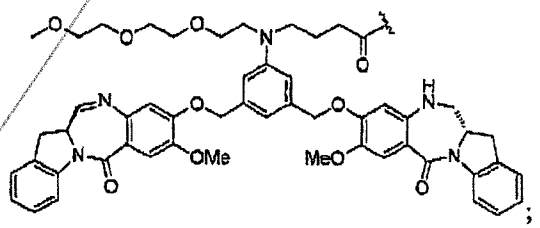
A and A' are the same or different, and are independently selected from -O-, oxo (-C(=O)-), -CRR'O-, -CRR'-, -S-, -CRR'S-, $-N(R_5)-$ and $-CRR'N(R_5)-$,

R_5 for each occurrence is independently -H or an optionally substituted linear or branched alkyl having 1 to 10 carbon atoms;

D and D' are the same or different, and are independently absent or selected from the group consisting of an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, an amino acid, a peptide bearing 2 to 6 amino acids, and a polyethylene glycol unit $(-OCH_2CH_2)_n-$;

L is absent, the linking group, a polyethylene glycol unit $(-OCH_2CH_2)_n-$, a linear, branched or cyclic alkyl or alkenyl having 1 to 10 carbon atoms, a phenyl group, a 3- to 18-membered heterocyclic ring or a 5- to 18-membered heteroaryl ring having 1 to 6 heteroatoms independently selected from O, S, N and P, wherein the alkyl or alkenyl is optionally substituted with the linking group; phenyl or heterocyclic or heteroaryl ring can be optionally substituted, wherein the substituent can be the linking group;

wherein the compound is not:



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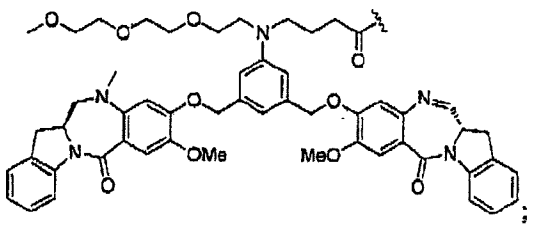

;

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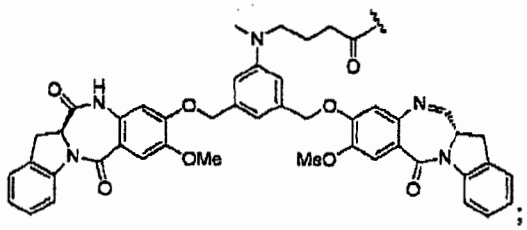
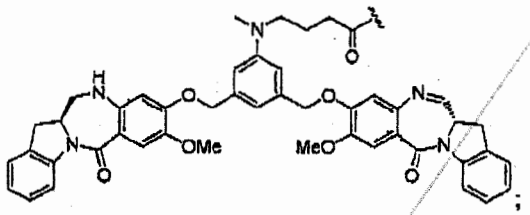
Received at the EPO on May 01, 2013 21:10:19. Page 72 of 97


OMe
MeO
;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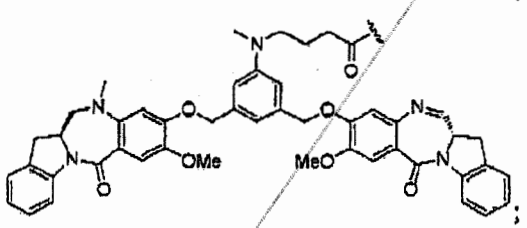
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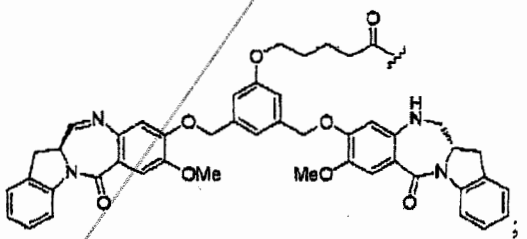
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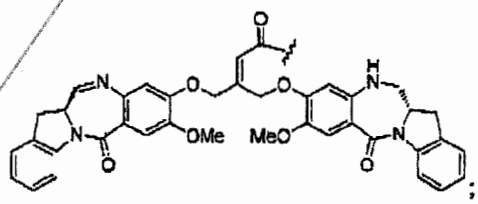
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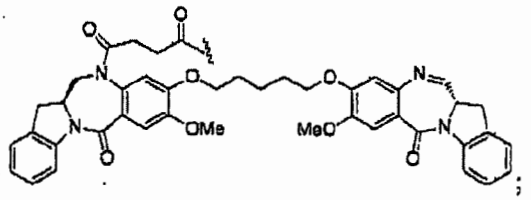
OMe
MeO
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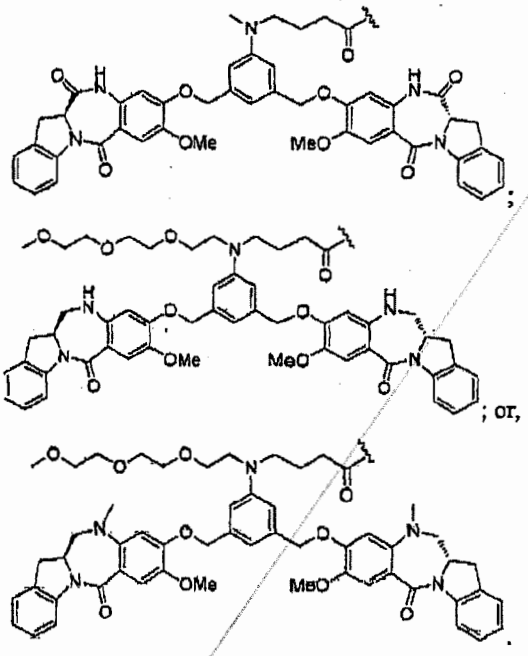
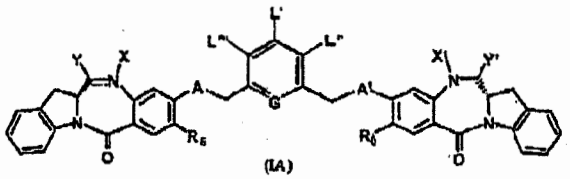


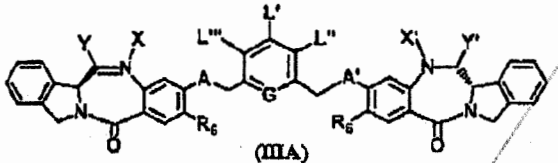
53. The conjugate of claim 52, wherein Y is a leaving group selected from -OR, -OCOR', -OCOOR', -OCONR'R'', -NR'R'', -NR'COR'', -NR'NR'R'', an optionally substituted 5- or 6-membered nitrogen-containing heterocycle (*e.g.*, piperidine, tetrahydropyrrole, pyrazole, morpholine, *etc.*), a guanidinum represented by -NR'(C=NH)NR'R'', an amino acid, or a peptide represented by -NRCOP', wherein P' is an amino acid or a polypeptide containing between 2 to 20 amino acid units, -SR, -SOR', $-SO_2M$, $-SO_3M$, $-OSO_3M$, halogen, cyano and an azido.

54. The conjugate of claim 52 or 53, wherein L is absent, or is selected from an optionally substituted phenyl group and an optionally substituted pyridyl group, wherein the phenyl and the pyridyl group bears the linking group, or L is an amine group bearing the linking group (*i.e.*, -N(linking group)-), or L is a linear, branched or cyclic alkyl or alkenyl having from 1 to 6 carbon atoms and bearing the linking group.

55. The conjugate of claim 52 or 53, wherein the compound is represented by any one of the following formulas:



(IA)



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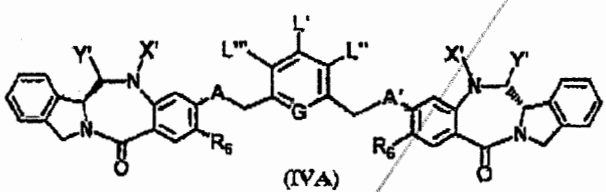

(IVA)

wherein:

L', L'', and L''' are the same or different, and are independently selected from -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-R^c$, halogen, guanidinium [$-NH(C=NH)NH_2$], -OR, -NR'R'', $-NO_2$, -NR'COR'', -SR, a sulfoxide represented by -SOR', a sulfone represented by $-SO_2R'$, a sulfonate $-SO_3M$, a sulfate $-OSO_3M$, a sulfonamide represented by $-SO_2NR'R''$, cyano, an azido, -COR', -OCOR', -OCONR'R'' and the linking group, provided only one of L', L'', and L''' is the linking group; and

G is selected from -CH- or -N-.

56. The conjugate of claim 55, wherein one of L', L'', or L''' is the linking group, while the others are -H.

57. The conjugate of claim 56, wherein L' is the linking group, and L'' and L''' are -H.

58. The conjugate of claim 56 or 57, wherein A and A' are both -O-, R_6 is -OMe, and G is -CH-.

59. The conjugate of claim 56, 57, or 58, wherein L' is represented by the following formula:

$$-W'-R^x-V-R^y-J,$$

wherein:

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W' and V are the same or different, and are each independently absent, or selected from -$CR^eR^{e'}$-, -O-, -O-C(=O)-, -C(=O)-O-, -S-, -SO-, -SO_2-, -CH_2-S-, -CH_2O-, -CH_2NR^e-, -O-(C=O)O-, -O-(C=O)N(R^e)-, -N(R^e)-, -N(R^e)-C(=O)-, -C(=O)-N(R^e)-, -N(R^e)-C(=O)O-, -N(C(=O)R^e)C(=O)-, -N(C(=O)R^e)-, -(O-CH_2-CH_2)$_n$-, -SS-, or -C(=O)-, or an amino acid, or a peptide having 2 to 8 amino acids;

R^x and R^y are the same or different, and are each independently absent or an optionally substituted linear, branched or cyclic alkyl, alkenyl, or alkynyl having 1 to 10 carbon atoms, an aryl bearing 6 to 10 carbon atoms or a 3- to 8-membered hetereocyclic ring bearing 1 to 3 heteroatoms selected from O, N or S;

R^e and $R^{e'}$ are the same or different, and are selected from -H, a linear, branched or cyclic alkyl, alkenyl, or alkynyl having 1 to 10 carbon atoms or -(CH_2-CH_2-O)$_n$-R^k, wherein R^k is a -H, a linear, branched cyclic alkyl having 1 to 6 carbon atoms, optionally bearing a secondary amino (*e.g.*, -NHR^{101}) or tertiary amino (-$NR^{101}R^{102}$) group or a 5- or 6-membered nitrogen containing heterocycle, such as piperidine or morpholine, wherein R^{101} and R^{102} are each independently a linear, branched, or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms; preferably, R^{101} and R^{102} are each independently a linear or branched alkyl having 1 to 6 carbon atoms;

n is an integer from 1 to 24; and

J is covalently linked to the CBA, and is selected from a succinimide, a acetamido, -S-, -SS-, -CH_2S-, -CH(Me)S-, -$C(Me)_2$S-, -NR^{e1}-, -CH_2NR^{e1}-, -NR^{e1}N-, and -C(=O)-, wherein R^{e1} is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms.

60. The conjugate of claim 59, wherein J is -S-, -SS-, a succinimide, or -C(=O)-.

61. The conjugate of claim 59 or 60, wherein:

$R^{e'}$ is -H or -Me;

R^e is a linear or branched alkyl having 1 to 6 carbon atoms or -(CH_2-CH_2-O)$_n$-R^k;

n is an integer from 2 to 8; and

R^k is -H, -Me or -CH_2CH_2-NMe_2.

62. The conjugate of any one of claims 59-61, wherein V is an amino acid or a peptide having 2 to 8 amino acids.

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63. The conjugate of claim 62, wherein V is valine-citrulline, gly-gly-gly, or ala-leu-ala-leu.

64. The conjugate of claim 59, wherein:

W' is -O-, -N(R^e)- or -N(R^e)-C(=O)-;

R^e is -H, a linear or branched alkyl having 1 to 4 carbon atoms, or -(CH_2-CH_2-O)$_n$-R^k;

R^x is a linear or branched alkyl having 1 to 6 carbon atoms;

V is absent, -(O-CH_2-CH_2)$_n$-, -C(=O)-NH-, -S-, -NH-C(=O)-;

R^y is absent or a linear or branched alkyl having 1 to 4 carbon atoms; and

J is -S-, -SS-, or -C(=O)-.

65. The conjugate of claim 59, wherein:

W' is -O-, -N(R^e)- or -N(R^e)-C(=O)-;

R^e is -H, -Me, or -(CH_2-CH_2-O)$_n$-Me;

n is an integer from 2 to 6;

R^x is linear or branched alkyl bearing 1 to 6 carbon atoms;

V and R^y are absent; and

J is -C(=O)-.

66. The conjugate of claim 59, wherein L' is represented by the following formula:

$$-W'-[CR_{1''}R_{2''}]_a-V-[Cy]_{0-1}-[CR_{3''}R_{4''}]_b-C(=O)-,$$

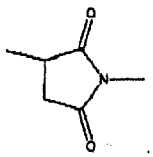
wherein:

$R_{1''}$, $R_{2''}$, and $R_{3''}$ are each independently -H or -Me;

$R_{4''}$ is -H, -Me, -SO_3H, or -$SO_3^-M^+$, wherein M^+ is a pharmaceutically acceptable cation;

a is an integers from 0-2, b is an integer from 0-3; and,

Cy is an optionally substituted 5-membered heterocyclic ring bearing an N heteroatom, preferably Cy is



67. The conjugate of claim 59 or 66, wherein W' is -N(R^e)-.

68. The conjugate of claim 59, 66, or 67, wherein R^e is -(CH_2-CH_2-O)$_{2-6}$-R^k, wherein R^k

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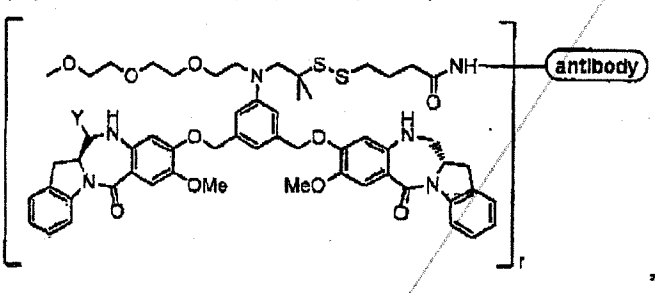
is a linear or branched alkyl having 1 to 6 carbon atoms.

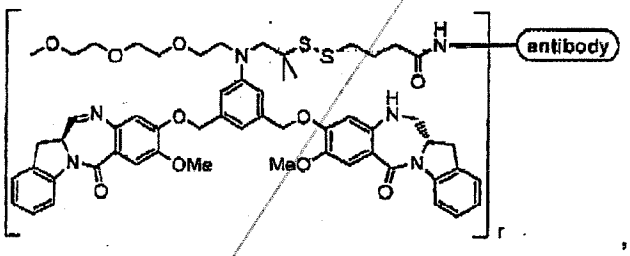
69. The conjugate to claim 59, 66, 67, or 68, wherein V is -S- or -SS-.

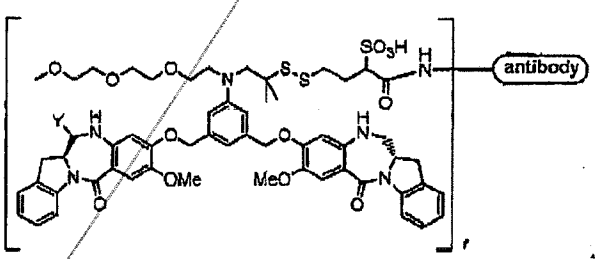
70. The conjugate of claim 59, 66, 67, 68, or 69, wherein L' is represented by the following formula:

$$-NR^{c}-[CR_{1''}R_{2''}]_{a}-S-[CR_{3''}R_{4''}]_{b}-C(=O)-.$$

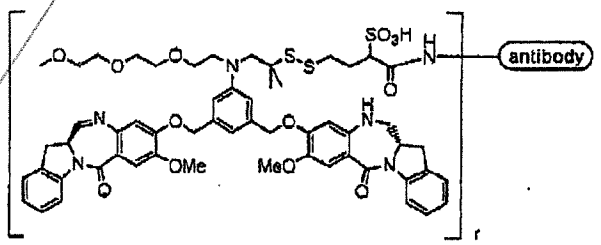
71. The conjugate to claim 59, 66, 67, 68, 69, or 70, which is:







, or



wherein r is an integer from 1 to 10, Y is -H or $-SO_3M$ (*e.g.*, Y is $-SO_3M$), and M is -H or a pharmaceutically acceptable cation.

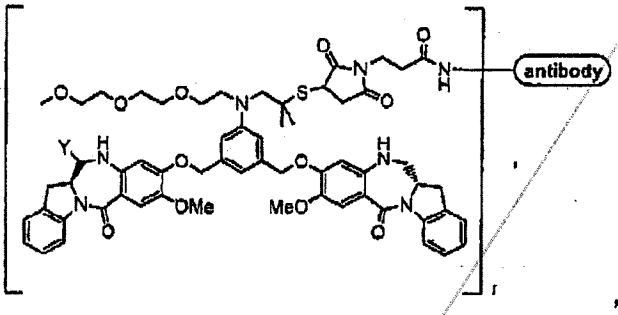
72. The conjugate of claim 59, 66, 67, 68, 69, 70, or 71, wherein the antibody is

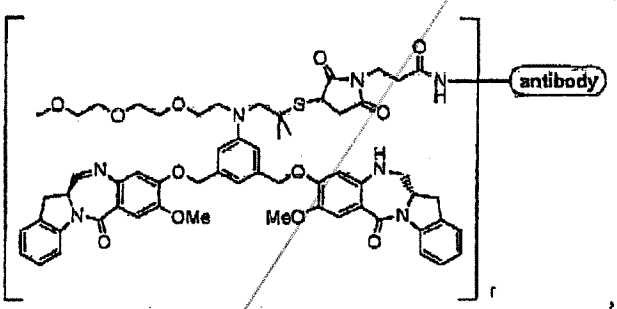
huMy9-6.

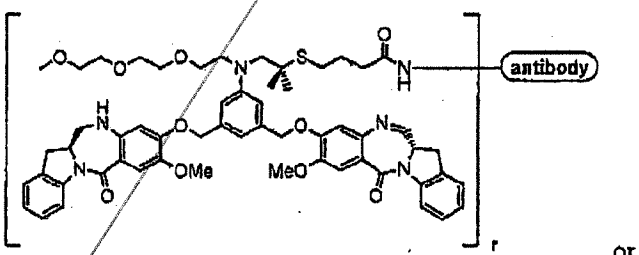
73. The conjugate of claim 59, 66, 67, 68, or 69, wherein L' is represented by the following formula:

$$-NR^e-[CR_1{=}R_{2'}]_a-S-Cy-[CR_3{=}R_{4'}]_b-C(=O)-.$$

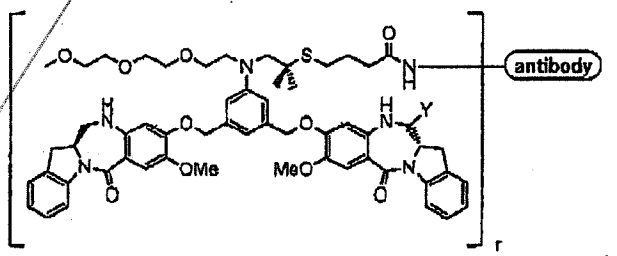
74. The conjugate of claim 59, 66, 67, 68, 69, or 73, which is:







, or,



wherein r is an integer from 1 to 10, Y is -H or $-SO_3M$ (*e.g.*, Y is $-SO_3M$), and M is -H or a pharmaceutically acceptable cation.

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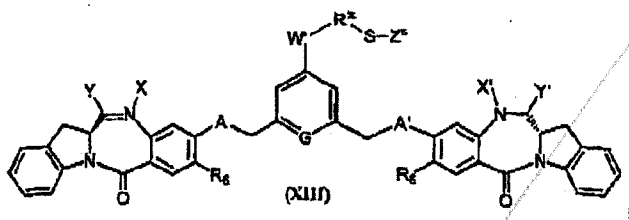
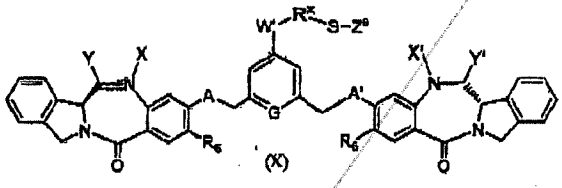
Replacement Sheet

75. The conjugate of claim 59, 66, 67, 68, 69, 73, or 74, wherein the antibody is huMy9-6.

76. The conjugate of claim 55, wherein the compound is represented by the following formula:



(XIII)



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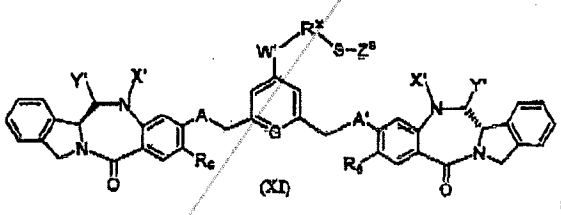


(XI)

wherein:

W' is absent, or selected from -O-, -N(R^6)-, -N(R^6)-C(=O)-, -N(C(=O)R^6)-, -S-, -CH_2-S-, or -CH_2NR^e-;

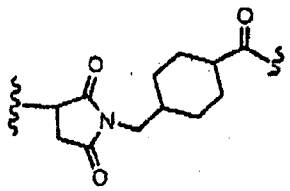
R^x is absent or selected from a linear, branched or cyclic alkyl having 1 to 10 carbon atoms;

R^e is -H, a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms or -(CH_2-CH_2-O)$_n$-R^k, wherein R^k is a -H, a linear, branched cyclic alkyl having 1 to 6 carbon atoms, optionally bearing a secondary amino (*e.g.*, -NHR^{101}) or tertiary amino (-$NR^{101}R^{102}$) group or a 5 or 6-membered nitrogen containing heterocycle, such as piperidine or morpholine, wherein R^{101} and R^{102} are each independently a linear, branched, or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms;

n is an integer from 2 to 6;

Z^6 is linked to the CBA, and is selected from:

a bond;



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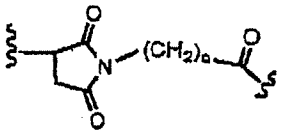

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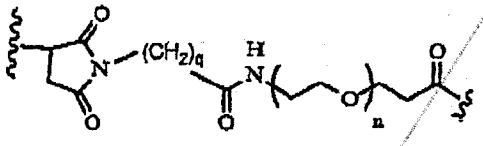

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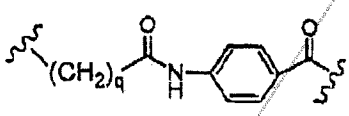
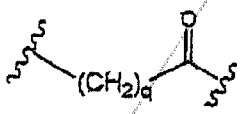
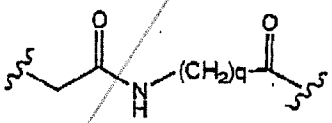


(b4);



(b5);



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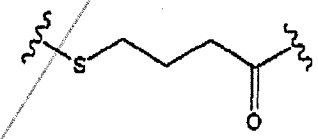
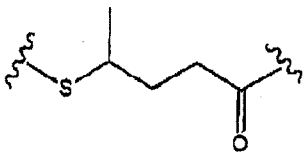
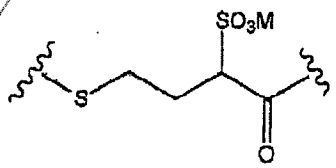


(b7);



(b8);



(b9), and,

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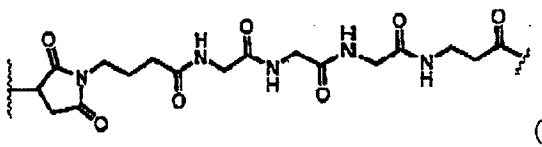


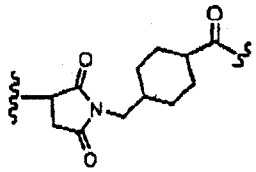
(b10),

wherein:

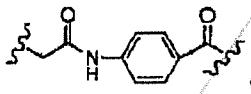
q is an integer from 1 to 5; and,

M is -H or a cation, such as Na^+ or K^+.

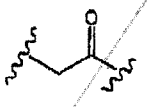
77. The conjugate of claim 76, wherein Z^5 is:



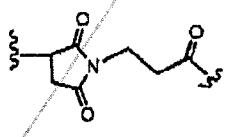
(b1);



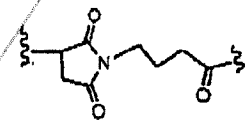
(b4');



(b5');



(b12);



(b13).

78. The conjugate of claim 76 or 77, wherein W' is $-N(R^6)-$.

79. The conjugate of claim 78, wherein R^6 is $-(CH_2-CH_2-O)_n-R^k$, wherein R^k is a -H, a linear, branched cyclic alkyl having 1 to 6 carbon atoms.

80. The conjugate of claim 79, wherein R^k is -H or -Me, n is 4, and q is 2.

81. The conjugate of claim 80, wherein R^x is a linear or branched alkyl having 1 to 6 carbon atoms.

82. The conjugate of claim 80, wherein R^x is $-(CH_2)_p-(CR^fR^g)-$, wherein R^f and R^g are each independently selected from H or a linear or branched alkyl having 1 to 4 carbon atoms; and p is 0, 1, 2 or 3.

83. The conjugate of claim 82, wherein R^f and R^g are the same or different, and are selected from H and Me; and p is 1.

84. The conjugate of any of claims 76-83, wherein:

the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond X is absent and Y is -H, and when it is a single bond, X is -H; Y is -OH or $-SO_3M$;

M is -H or a pharmaceutically acceptable cation (*e.g.*, Na^+);

X' and Y' are both -H;

A and A' are both -O-;

R_6 is -OMe; and

R^x is a linear or branched alkyl having 1 to 6 carbon atoms.

85. The conjugate of any one of claims 52-84, wherein the double line == between N and C represents a double bond.

86. The conjugate of any one of claims 52-83, wherein the double line == between N and C represents a single bond, X is -H, the linking group, or an amine protecting group; and Y is selected from -H, -OR, -OCOR', -SR, -NR'R," an optionally substituted 5 or 6-membered nitrogen-containing heterocycle, $-SO_3M$, $-SO_2M$ and a sulfate $-OSO_3M$.

87. The conjugate of claim 86, wherein Y is selected from -H, $-SO_3M$, -OH, -OMe, -OEt or -NHOH.

88. The conjugate of claim 87, wherein Y is -H, $-SO_3M$ or -OH.

89. The conjugate of any one of claims 86-88, wherein M is -H, Na^+ or K^+.

90. The conjugate of any one of claims 52-89, wherein W, when present, is C=O.

91. The conjugate of any one of claims 52-90, wherein Z and Z', when present, are $-CH_2-$.

92. The conjugate of any one of claims 52-91, wherein X' is selected from the group consisting of -H, -OH, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, phenyl, the linking group, and an amine-protecting group.

93. The conjugate of claim 92, wherein X' is -H, -OH, -Me or the linking group.

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94. The conjugate of claim 93, wherein X' is -H.

95. The conjugate of any one of claims 52-94, wherein Y' is selected from the group consisting of -H, an oxo group, a substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms.

96. The conjugate of claim 95, wherein Y' is -H or oxo.

97. The conjugate of claim 96, wherein Y' is -H.

98. The conjugate of any one of claims 52-97, wherein A and A' are the same or different, and are selected from -O-, -S-, -N(R_5)-, and oxo (C=O).

99. The conjugate of claim 98, wherein A and A' are the same or different, and are selected from -O- and -S-.

100. The conjugate of claim 99, wherein A and A' are -O-.

101. The conjugate of any one of claims 52-100, wherein D and D', when present, are the same or different, and are independently selected from a polyethylene glycol unit (-$OCH_2CH_2)_n$, wherein n is an integer from 1 to 24, an amino acid, a peptide bearing 2 to 6 amino acids, or a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, wherein the alkyl, alkenyl and alkynyl are optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OR, -NR'COR'', -SR and -COR'.

102. The conjugate of claim 101, wherein D and D' are linear or branched alkyl bearing 1 to 4 carbon atoms.

103. The conjugate of claim 52, 53, 55, or 76, wherein:

the double line == between N and C represents a double bond;

Y is -H;

W is C=O;

R_1, R_2, R_1', R_2', R_4 and R_4' are -H;

one of R_3, or R_3' is optionally the linking group and the other is -H;

R_6 is -OMe;

Z and Z' are -CH_2-;

X' is -H;

Y' is -H; and

A and A' are -O-.

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104. The conjugate of any one of claims 52-103, wherein the conjugate comprises 1-10 cytotoxic compounds, each cytotoxic compound comprising the linking group linking the cytotoxic compound to the CBA, and each cytotoxic compound on the conjugate is the same.

105. The conjugate of any one of claims 52-104, wherein the cell-binding agent binds to target cells selected from tumor cells, virus infected cells, microorganism infected cells, parasite infected cells, autoimmune cells, activated cells, myeloid cells, activated T-cells, B cells, or melanocytes; cells expressing the CD4, CD6, CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD40, CD44, CD56, EpCAM, CanAg, CALLA, or Her-2 antigens; Her-3 antigens; or cells expressing insulin growth factor receptor, epidermal growth factor receptor, and folate receptor.

106. The conjugate of claim 105, wherein the cell-binding agent is an antibody, a single chain antibody, an antibody fragment that specifically binds to the target cell, a monoclonal antibody, a single chain monoclonal antibody, or a monoclonal antibody fragment that specifically binds to a target cell, a chimeric antibody, a chimeric antibody fragment that specifically binds to the target cell, a domain antibody, a domain antibody fragment that specifically binds to the target cell, a lymphokine, a hormone, a vitamin, a growth factor, a colony stimulating factor, or a nutrient-transport molecule.

107. The conjugate of claim 106, wherein the antibody is a resurfaced antibody, a resurfaced single chain antibody, or a resurfaced antibody fragment.

108. The conjugate of claim 106, wherein the antibody is a monoclonal antibody, a single chain monoclonal antibody, or a monoclonal antibody fragment thereof.

109. The conjugate of claim 106, wherein the antibody is a humanized antibody, a humanized single chain antibody, or a humanized antibody fragment.

110. A pharmaceutical composition comprising the conjugate of any one of claims 52-109 and a pharmaceutically acceptable carrier.

111. A method of inhibiting abnormal cell growth or treating a proliferative disorder, an autoimmune disorder, destructive bone disorder, infectious disease, viral disease, fibrotic disease, neurodegenerative disorder, pancreatitis or kidney disease in a mammal comprising administering to said mammal a therapeutically effective

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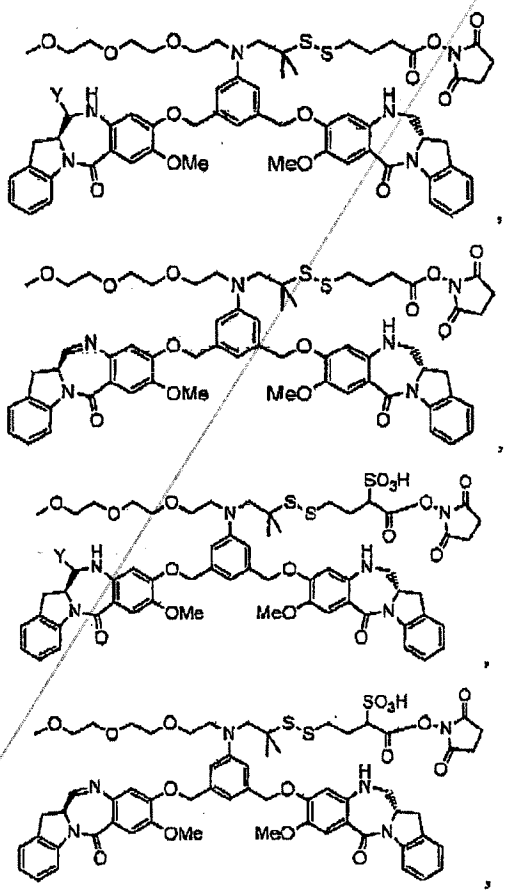
amount of a compound of any one of claims 1-51 or a conjugate of any one of claims 52-109 and, optionally, a chemotherapeutic agent.

112. A method of inhibiting abnormal cell growth or treating a proliferative disorder, an autoimmune disorder, destructive bone disorder, infectious disease, viral disease, fibrotic disease, neurodegenerative disorder, pancreatitis or kidney disease in a mammal comprising administering to said mammal a therapeutically effective amount of a compound or a conjugated, and, optionally, a chemotherapeutic agent, wherein the compound or the conjugate is selected from:



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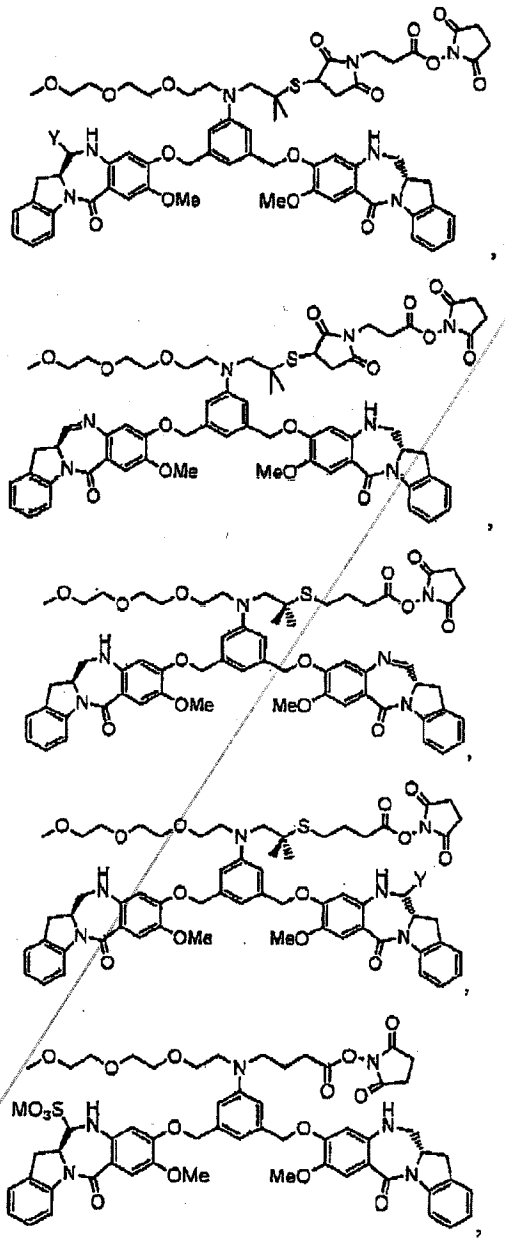

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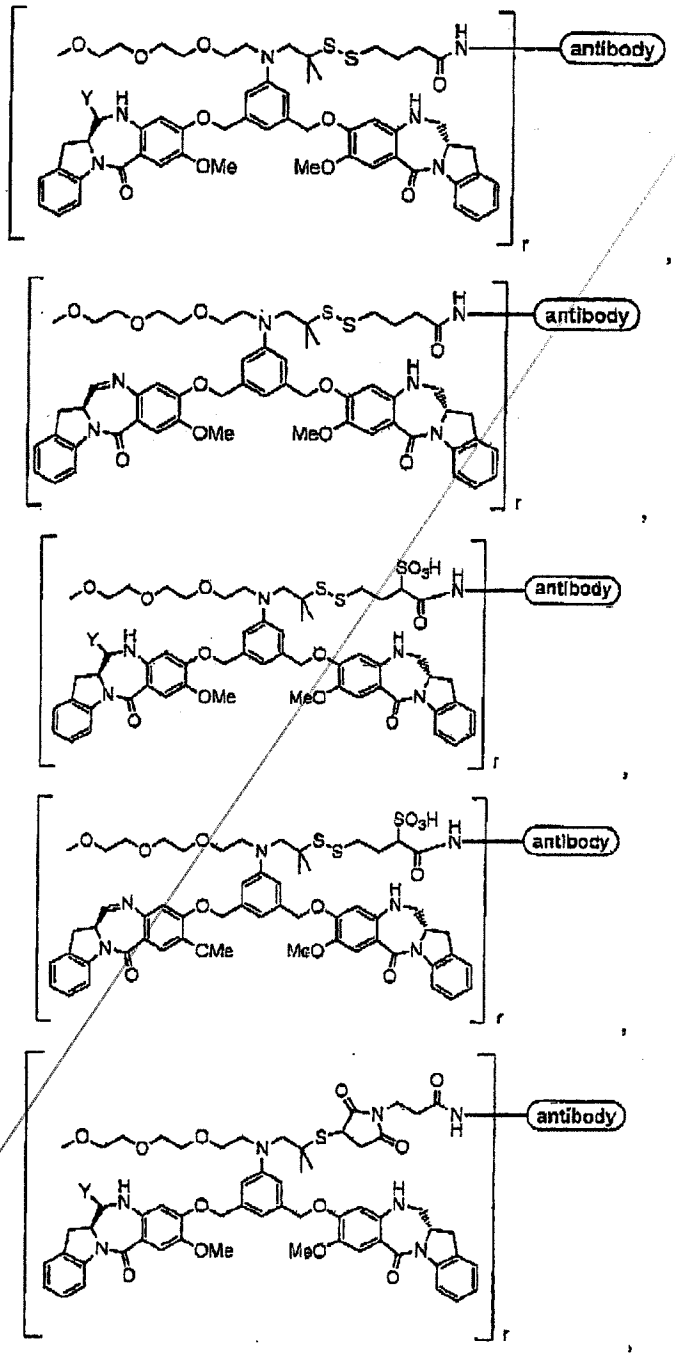
antibody
antibody
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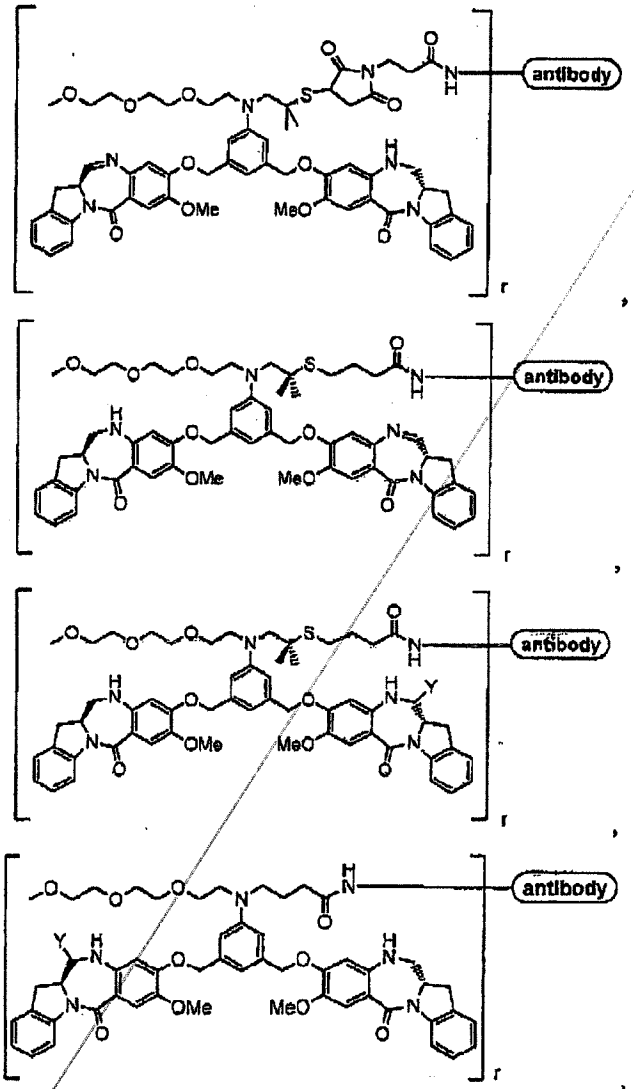
antibody
antibody
OMe
MeO
SO3H



wherein r is an integer from 1 to 10, Y is -H or $-SO_3M$ (*e.g.*, Y is $-SO_3M$), and M is -H or a pharmaceutically acceptable cation.

113. A method of inhibiting abnormal cell growth or treating a proliferative disorder, an autoimmune disorder, destructive bone disorder, infectious disease, viral disease, fibrotic disease, neurodegenerative disorder, pancreatitis or kidney disease in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of the following formula and, optionally, a chemotherapeutic agent:

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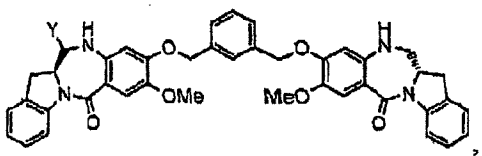

wherein Y is -H or -SO_3M (*e.g.*, Y is -SO_3M), and M is -H or a pharmaceutically acceptable cation.

114. The method of any one of claims 111-113, wherein said second chemotherapeutic agent is administered to said mammal sequentially or consecutively.

115. The method of any one of claims 111-114, wherein the method is for treating a condition selected from cancer, rheumatoid arthritis, multiple sclerosis, graft versus host disease (GVHD), transplant rejection, lupus, myositis, infection, and immune deficiency.

116. The method of any one of claims 111-115, wherein the method is for treating a cancer.

117. The method of claim 115 or 116, wherein the cancer is selected from breast cancer, colon cancer, brain cancer, prostate cancer, kidney cancer, pancreatic cancer, ovarian cancer, head and neck cancer, melanoma, colorectal cancer, gastric cancer, squamous cancer, small-cell lung cancer, non small-cell lung cancer, testicular cancer, Merkel cell carcinoma, glioblastoma, neuroblastoma, cancers of lymphatic organs and hematological malignancy including Leukemia (Acute lymphoblastic leukemia (ALL), Acute myelogenous leukemia (AML), Chronic lymphocytic leukemia (CLL), Chronic myelogenous leukemia (CML), Acute monocytic leukemia (AMOL), Hairy cell leukemia (HCL), T-cell prolymphocytic leukemia (T-PLL), Large granular lymphocytic leukemia, Adult T-cell leukemia), Lymphoma (small lymphocytic lymphoma (SLL), Hodgkin's lymphomas (Nodular sclerosis, Mixed cellularity, Lymphocyte-rich, Lymphocyte depleted or not depleted, and Nodular lymphocyte-predominant Hodgkin lymphoma), Non-Hodgkin's lymphomas (all subtypes), Chronic lymphocytic leukemia/Small lymphocytic lymphoma, B-cell prolymphocytic leukemia, Lymphoplasmacytic lymphoma (such as Waldenström macroglobulinemia), Splenic marginal zone lymphoma, Plasma cell neoplasms (Plasma cell myeloma, Plasmacytoma, Monoclonal immunoglobulin deposition diseases, Heavy chain diseases), Extranodal marginal zone B cell lymphoma (MALT lymphoma), Nodal marginal zone B cell lymphoma (NMZL), Follicular

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lymphoma, Mantle cell lymphoma, Diffuse large B cell lymphoma, Mediastinal (thymic) large B cell lymphoma, Intravascular large B cell lymphoma, Primary effusion lymphoma, Burkitt lymphoma/leukemia, T cell prolymphocytic leukemia, T cell large granular lymphocytic leukemia, Aggressive NK cell leukemia, Adult T cell leukemia/lymphoma, Extranodal NK/T cell lymphoma (nasal type), Enteropathy-type T cell lymphoma, Hepatosplenic T cell lymphoma, Blastic NK cell lymphoma, Mycosis fungoides / Sezary syndrome, Primary cutaneous CD30-positive T cell lymphoproliferative disorders, Primary cutaneous anaplastic large cell lymphoma, Lymphomatoid papulosis, Angioimmunoblastic T cell lymphoma, Peripheral T cell lymphoma (unspecified), Anaplastic large cell lymphoma), multiple myeloma (plasma cell myeloma or Kahler's disease).

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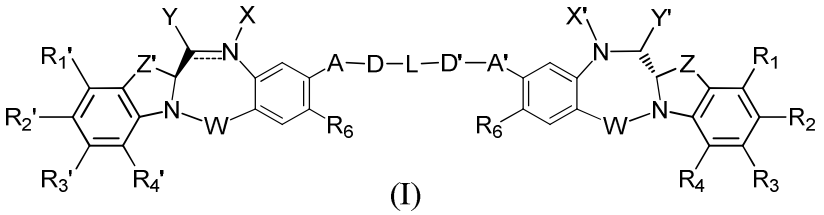
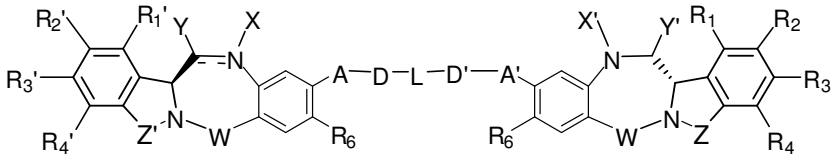
CLAIMS

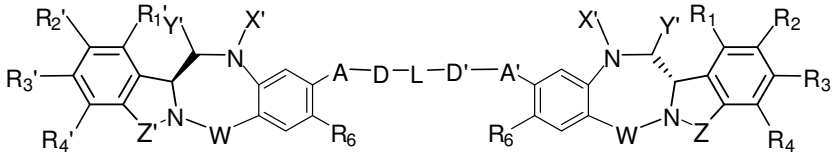
1. A cytotoxic compound comprising a linking group with a reactive group bonded thereto capable of covalently linking the cytotoxic compound to a cell binding agent (CBA), wherein said cytotoxic compound is represented by any one of the following formulas:



(I)



(III)



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond X is absent and Y is -H, or a linear or branched alkyl having 1 to 4 carbon atoms, and when it is a single bond, X is -H, the linking group with the reactive group bonded thereto, or an amine protecting moiety;

Y is -H or a leaving group selected from -OR, -OCOR', -OCOOR', -OCONR'R'', -NR'R'', -NR'COR'', -NR'NR'R'', an optionally substituted 5- or 6-membered nitrogen-containing heterocycle (*e.g.*, piperidine, tetrahydropyrrole, pyrazole, morpholine, *etc*.), a guanidinum represented by -NR'(C=NH)NR'R'', an amino acid, or a peptide represented by -NRCOP', wherein P' is an amino acid or a

polypeptide containing between 2 to 20 amino acid units, -SR, -SOR', -SO_2M, -SO_3M, -OSO_3M, halogen, cyano and an azido; or,

Y is a sulfite (HSO_3, HSO_2 or a salt of HSO_3^-, SO_3^{2-} or HSO_2^- formed with a cation), metabisulfite ($H_2S_2O_5$ or a salt of $S_2O_5^{2-}$ formed with a cation), mono-, di-, tri-, and tetra- thiophosphate (PO_3SH_3, $PO_2S_2H_2$, POS_3H_2, PS_4H_2 or a salt of PO_3S^{3-}, $PO_2S_2^{3-}$, POS_3^{3-} or PS_4^{3-} formed with a cation), thio phosphate ester $(R^iO)_2PS(OR^i)$, R^iS-, R^iSO, R^iSO_2, R^iSO_3, thiosulfate (HS_2O_3 or a salt of $S_2O_3^{2-}$ formed with a cation), dithionite (HS_2O_4 or a salt of $S_2O_4^{2-}$ formed with a cation), phosphorodithioate ($P(=S)(OR^{k'})(S)(OH)$ or a salt thereof formed with a cation), hydroxamic acid ($R^{k'}C(=O)NOH$ or a salt formed with a cation), formaldehyde sulfoxylate ($HOCH_2SO_2^-$ or a salt of $HOCH_2SO_2^-$ formed with a cation, such as $HOCH_2SO_2^-Na^+$) or a mixture thereof, wherein R^i is a linear or branched alkyl having 1 to 10 carbon atoms and is substituted with at least one substituent selected from -$N(R^j)_2$, -CO_2H, -SO_3H, and -PO_3H; R^i can be further optionally substituted with a substituent for an alkyl described herein; R^j is a linear or branched alkyl having 1 to 6 carbon atoms; $R^{k'}$ is a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, aryl, heterocyclyl or heteroaryl;

M is -H or a cation;

R, for each occurrence, is independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -$(CH_2CH_2O)_n$-R^c, an optionally substituted aryl having 6 to 18 carbon atoms, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an optionally substituted 3- to 18-membered heterocyclic ring containing 1 to 6 heteroatoms independently selected from O, S, N and P;

R' and R'' are each independently selected from -H, -OH, -OR, -NHR, -NR_2, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -$(CH_2CH_2O)_n$-R^c, and an optionally substituted 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms independently selected from O, S, N and P;

R^c is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms, or the linking group with the reactive group bonded thereto;

n is an integer from 1 to 24;

W is selected from C=O, C=S, CH_2, BH, SO and SO_2;

X' is selected from -H, an amine-protecting group, the linking group with the reactive group bonded thereto, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R^c$, an optionally substituted aryl having 6 to 18 carbon atoms, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, and an optionally substituted 3- to 18-membered heterocyclic ring containing 1 to 6 heteroatoms independently selected from O, S, N and P;

Y' is selected from -H, an oxo group, the linking group with the reactive group bonded thereto, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, an optionally substituted 6- to 18-membered aryl, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms;

R_1, R_2, R_3, R_4, R_1', R_2', R_3' and R_4' are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-R^c$, halogen, guanidinium [$-NH(C=NH)NH_2$], -OR, -NR'R'', $-NO_2$, -NCO, -NR'COR'', -SR, a sulfoxide represented by -SOR', a sulfone represented by $-SO_2R$', a sulfonate $-SO_3^-M^+$, a sulfate $-OSO_3^-M^+$, a sulfonamide represented by $-SO_2NR'R''$, cyano, an azido, -COR', -OCOR', -OCONR'R'', and the linking group with the reactive group bonded thereto;

R_6 is -H, -R, -OR, -SR, -NR'R'', $-NO_2$, halogen or the linking group with the reactive group bonded thereto;

Z and Z' are independently selected from $-(CH_2)_{n'}-$, $-(CH_2)_{n'}-CR_7R_8-(CH_2)_{na'}-$, $-(CH_2)_{n'}-NR_9-(CH_2)_{na'}-$, $-(CH_2)_{n'}-O-(CH_2)_{na'}-$ and $-(CH_2)_{n'}-S-(CH_2)_{na'}-$;

n' and na' are the same or different, and are selected from 0, 1, 2 and 3;

R_7 and R_8 are the same or different, and are each independently selected from -H, -OH, -SH, -COOH, -NHR', a polyethylene glycol unit $-(OCH_2CH_2)_n-$, an amino acid, a peptide unit bearing 2 to 6 amino acids, an optionally substituted linear, branched or cyclic alkyl having from 1 to 10 carbon atoms;

R_9 is independently selected from -H, an optionally substituted linear, branched or cyclic alkyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-$;

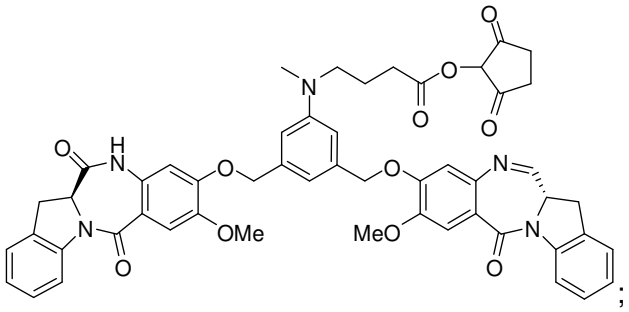
A and A' are the same or different, and are independently selected from -O-, oxo (-C(=O)-), -CRR'O-, -CRR'-, -S-, -CRR'S-, $-NR_5$ and -CRR'N(R_5)-,

R_5 for each occurrence is independently -H or an optionally substituted linear or branched alkyl having 1 to 10 carbon atoms;

D and D' are the same or different, and are independently absent or selected from the group consisting of an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, an amino acid, a peptide bearing 2 to 6 amino acids, and a polyethylene glycol unit $(-OCH_2CH_2)_n-$;

L is absent, the linking group with the reactive group bonded thereto, a polyethylene glycol unit $(-OCH_2CH_2)_n-$, a linear, branched or cyclic alkyl or alkenyl having 1 to 10 carbon atoms, a phenyl group, a 3 to 18-membered heterocyclic ring or a 5- to 18-membered heteroaryl ring having 1 to 6 heteroatoms independently selected from O, S, N and P, wherein the alkyl or alkenyl is optionally substituted with the linking group with the reactive group bonded thereto; phenyl or heterocyclic or heteroaryl ring can be optionally substituted, wherein the substituent can be the linking group with the reactive group bonded thereto;

provided that the compound is not any one of the following compounds:



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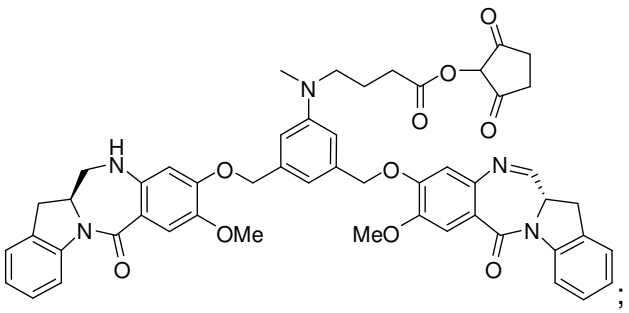
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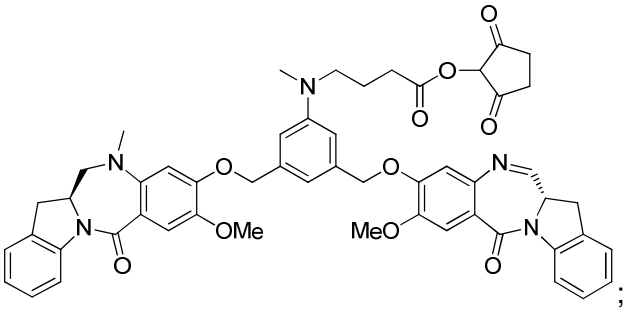
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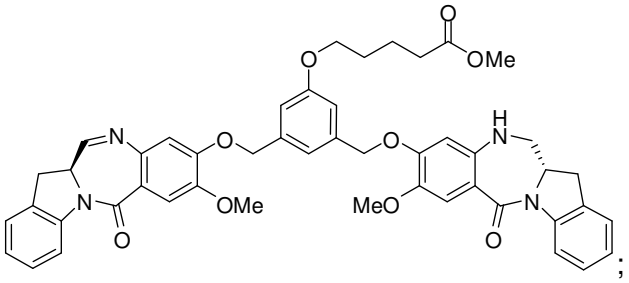
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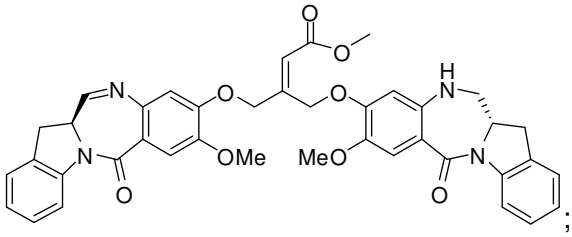
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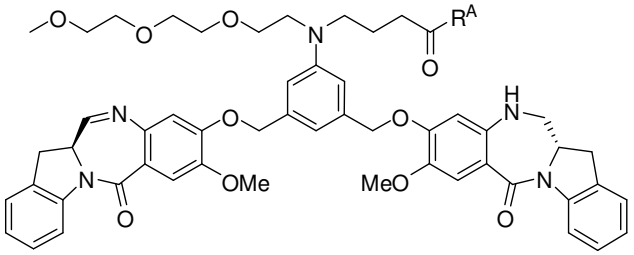
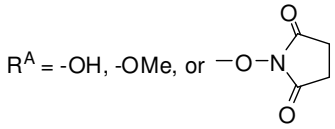
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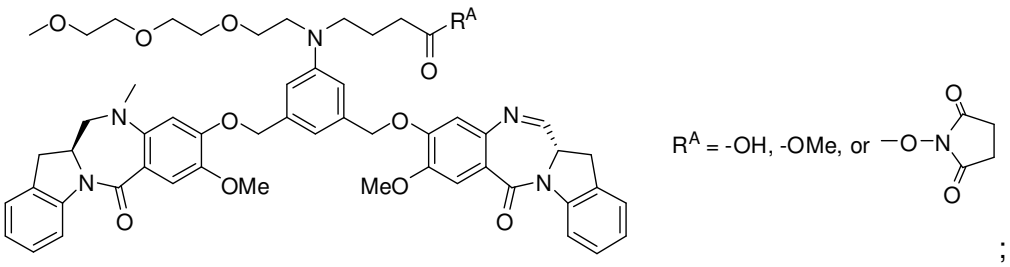

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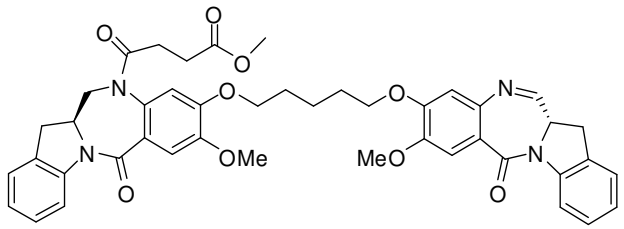

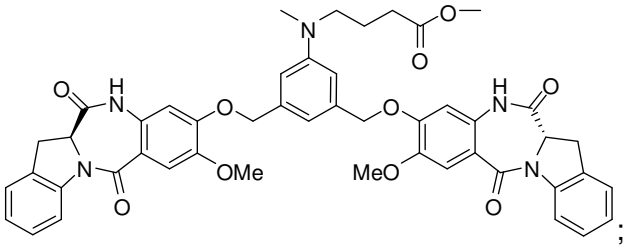

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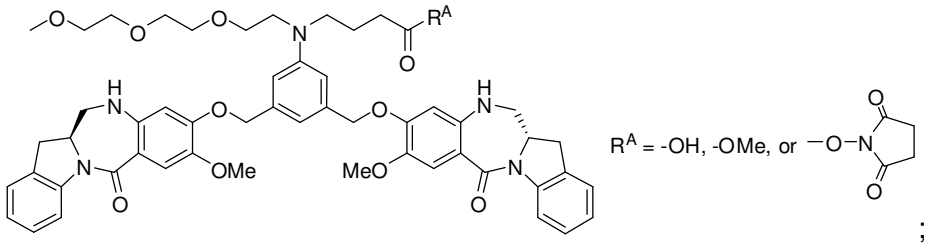

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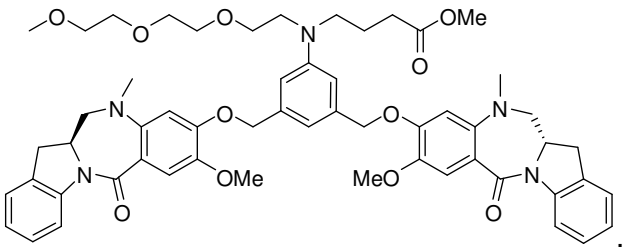

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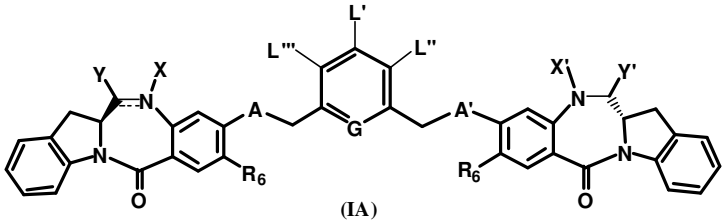
2. The compound of claim 1, wherein the compound is represented by any one of the following formulas:



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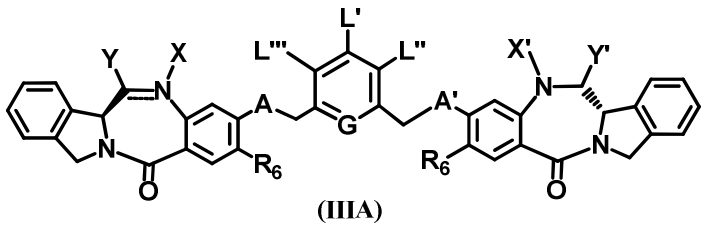

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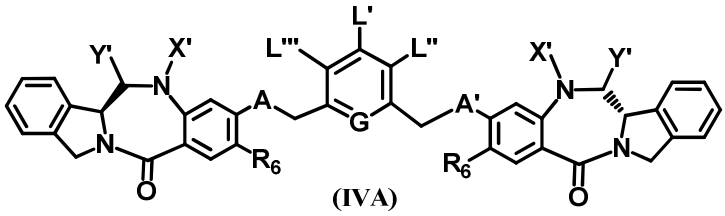


(IVA)

,

or a pharmaceutically acceptable salt thereof, wherein:

L', L'', and L''' are the same or different, and are independently selected from -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-R^c$, halogen, guanidinium [$-NH(C=NH)NH_2$], -OR, -NR'R'', $-NO_2$, -NR'COR'', -SR, a sulfoxide represented by -SOR', a sulfone represented by $-SO_2R'$, a sulfonate $-SO_3M$, a sulfate $-OSO_3M$, a sulfonamide represented by $-SO_2NR'R''$, cyano, an azido, -COR', -OCOR', -OCONR'R'' and the linking group with the reactive group bonded thereto, provided only one of L', L'', and L''' is the linking group with the reactive group bonded thereto; and

G is selected from -CH- or -N-.

3. The compound of claim 2, wherein L'' and L''' are -H; and L' is represented by the following formula:

$$-W'-R^x-V-R^y-J,$$

wherein:

W' and V are the same or different, and are each independently absent, or selected from $-CR^eR^{e'}-$, -O-, -O-C(=O)-, -C(=O)-O-, -S-, -SO-, $-SO_2-$, $-CH_2-S-$, $-CH_2O-$, $-CH_2NR^e-$, -O-(C=O)O-, -O-(C=O)N(R^e)-, -N(R^e)-, -N(R^e)-C(=O)-, -C(=O)-N(R^e)-, -N(R^e)-C(=O)O-, -N(C(=O)R^e)C(=O)-, -N(C(=O)R^e)-, $-(O-CH_2-CH_2)_n-$, -SS-, or -C(=O)-, or an amino acid, or a peptide having 2 to 8 amino acids;

R^x and R^y are the same or different, and are each independently absent or an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to

10 carbon atoms, an aryl bearing 6 to 10 carbon atoms or a 3- to 8-membered hetereocyclic ring bearing 1 to 3 heteroatoms selected from O, N or S;

R^e and $R^{e'}$ are the same or different, and are selected from -H, a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms or -$(CH_2$-CH_2-$O)_n$-R^k, wherein R^k is a -H, a linear, branched cyclic alkyl having 1 to 6 carbon atoms, optionally bearing a secondary amino (*e.g.*, -NHR^{101}) or tertiary amino (-$NR^{101}R^{102}$) group or a 5- or 6-membered nitrogen containing heterocycle, such as piperidine or morpholine, wherein R^{101} and R^{102} are each independently a linear, branched, or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms; preferably, R^{101} and R^{102} are each independently a linear or branched alkyl having 1 to 6 carbon atoms;

n is an integer from 1 to 24;

J comprises the reactive group bonded thereto, and is selected from a maleimide, a haloacetamido, -SH, -SSR^d, -CH_2SH, -CH(Me)SH, -$C(Me)_2SH$, -NHR^{c1}, -CH_2NHR^{c1}, -$NR^{c1}NH_2$, -COOH, and -COE, wherein -COE represents a reactive ester selected from, but not limited to, N-hydroxysuccinimde ester, N-hydroxy sulfosuccinimide ester, nitrophenyl (*e.g.*, 2 or 4-nitrophenyl) ester, dinitrophenyl (*e.g.*, 2,4-dinitrophenyl) ester, sulfo-tetraflurophenyl (*e.g.*, 4-sulfo-2,3,5,6-tetrafluorophenyl) ester, and pentafluorophenyl ester, and wherein R^{c1} is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms, and,

R^d is selected from phenyl, nitrophenyl (*e.g.*, 2 or 4-nitrophenyl), dinitrophenyl (*e.g.*, 2 or 4-nitrophenyl), carboxynitrophenyl (*e.g.*, 3-carboxy-4-nitrophenyl), pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

4. The compound of claim 3, wherein:

(i) W' is -O-, -$N(R^e)$- or -$N(R^e)$-C(=O)-;

R^e is -H, a linear or branched alkyl having 1 to 4 carbon atoms, or -$(CH_2$-CH_2-$O)_n$-R^k;

R^x is a linear or branched alkyl having 1 to 6 carbon atoms;

V is absent, -$(O$-CH_2-$CH_2)_n$-, -C(=O)-NH-, -S-, -NH-C(=O)-;

R^y is absent or a linear or branched alkyl having 1 to 4 carbon atoms; and

J is -SH, -SSR^{d} or -COE, wherein -COE is preferably N-hydroxysuccinimide ester; or

(ii) W' is -O-, -N(R^{e})- or -N(R^{e})-C(=O)-;

R^{e} is -H, -Me, or -(CH$_2$-CH$_2$-O)$_n$-Me;

n is an integer from 2 to 6;

R^{x} is linear or branched alkyl bearing 1 to 6 carbon atoms;

V and R^{y} are absent; and

J is -COE, preferably N-hydroxysuccinimide ester.

5. The compound of claim 3, wherein L' is represented by any of the following formulas:

$$-W'-[CR_{1''}R_{2''}]_a-V-[Cy]_{0-1}-[CR_{3''}R_{4''}]_b-COE;$$

$$-NR^{e}-[CR_{1''}R_{2''}]_a-S-[CR_{3''}R_{4''}]_b-COE; \text{ or}$$

$$-NR^{e}-[CR_{1''}R_{2''}]_a-S-Cy-[CR_{3''}R_{4''}]_b-COE,$$

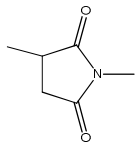
wherein:

$R_{1''}$, $R_{2''}$, and $R_{3''}$ are each independently -H or -Me;

$R_{4''}$ is -H, -Me, $-SO_3H$, or $-SO_3^-M^+$, wherein M^+ is a pharmaceutically acceptable cation;

a is an integers from 0-2, b is an integer from 0-3; and,

Cy is an optionally substituted 5-membered heterocyclic ring bearing an N heteroatom, preferably Cy is



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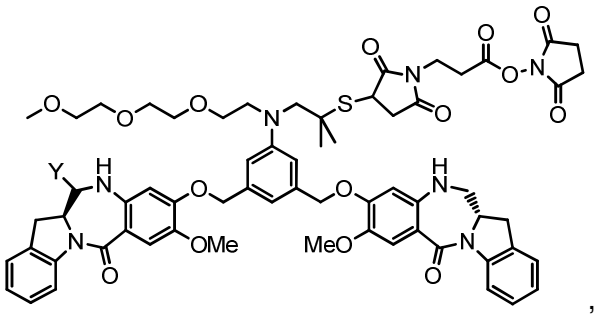
6. The compound of any one of claims 1 to 5, wherein, where the double line == between N and C represents a single bond, Y is a leaving group selected from -OR, -OCOR', -OCOOR', -OCONR'R'', -NR'R'', -NR'COR'', -NR'NR'R'', an optionally substituted 5- or 6-membered nitrogen-containing heterocycle (*e.g.*, piperidine, tetrahydropyrrole, pyrazole, morpholine, *etc*.), a guanidinum represented by -NR'(C=NH)NR'R'', an amino acid, or a peptide represented by -NRCOP', wherein P' is an amino acid or a polypeptide containing between 2 to 20 amino acid

units, -SR, -SOR', $-SO_2M$, $-SO_3M$, $-OSO_3M$, halogen, cyano and an azido.

7. The compound of claim 6, wherein said cytotoxic compound is of formula (I).

8. The compound of claim 1, wherein the compound is: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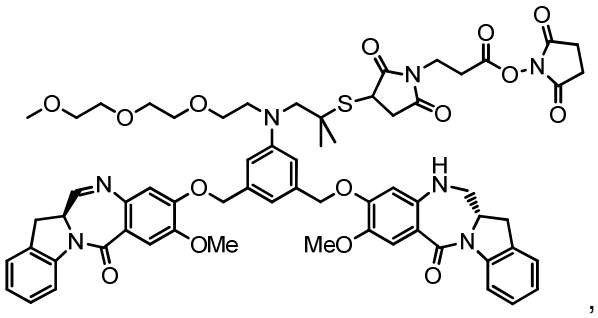
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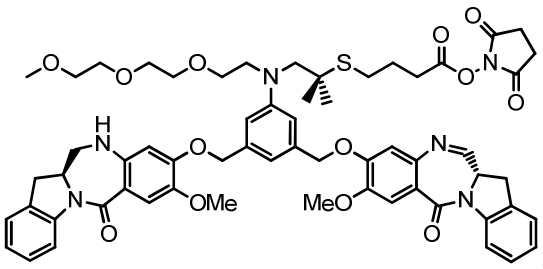
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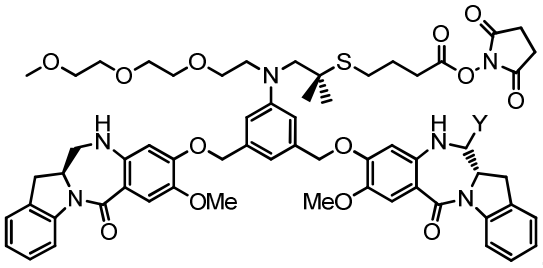
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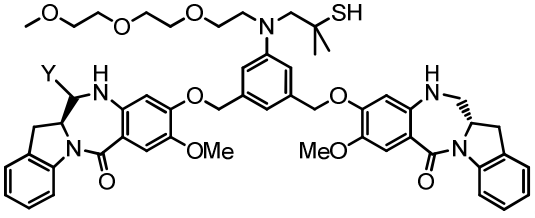
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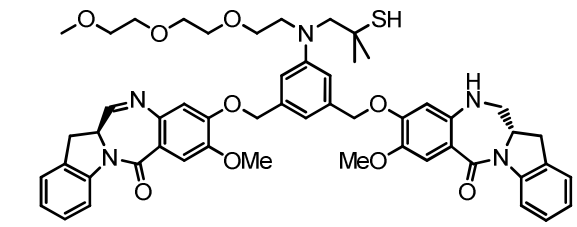

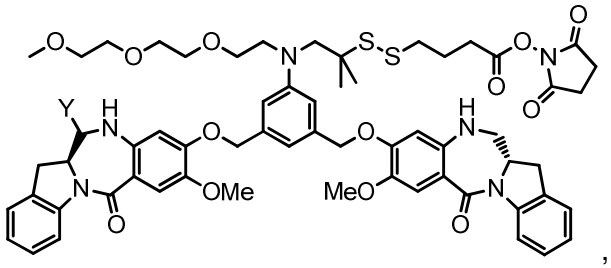
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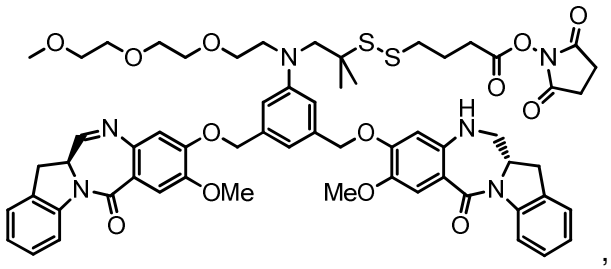
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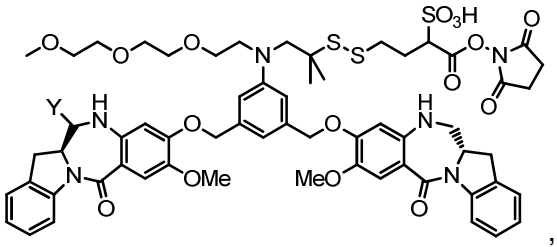
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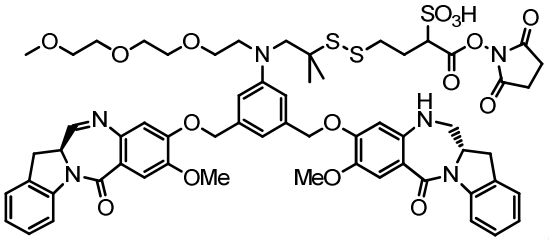
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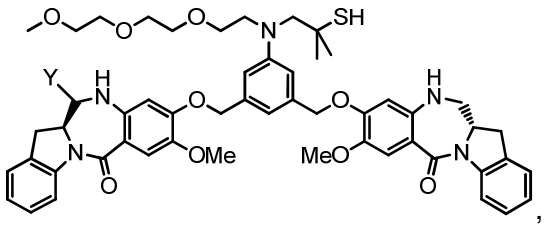
or a pharmaceutically acceptable salt thereof, wherein Y is -H or -SO_3M (*e.g.*, Y is -SO_3M), and M is -H or a pharmaceutically acceptable cation.

9. The compound of claim 1, wherein the compound is: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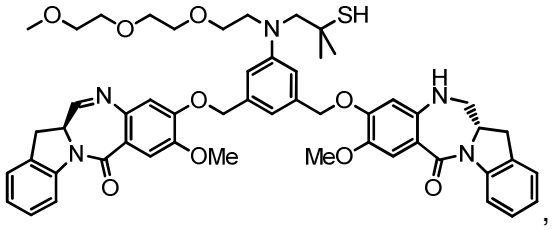
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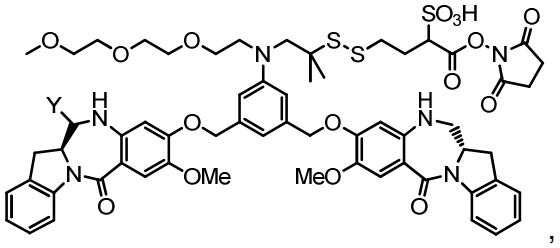
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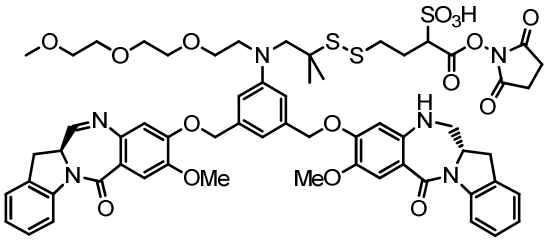
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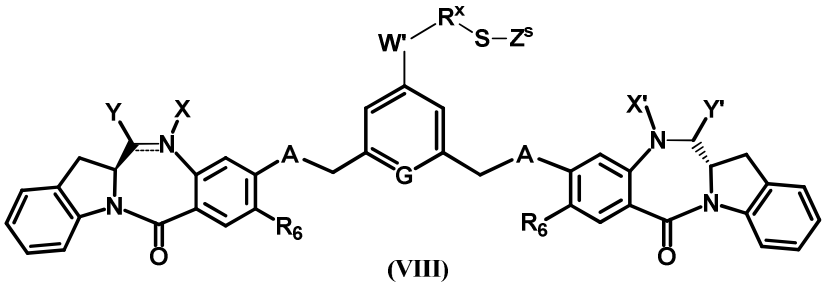
or a pharmaceutically acceptable salt thereof, wherein Y is $-SO_3M$ and M is -H or a pharmaceutically acceptable cation.

10. The compound of any one of claims 1 to 3, wherein the compound is represented by any one of the following formulas:



(VIII)

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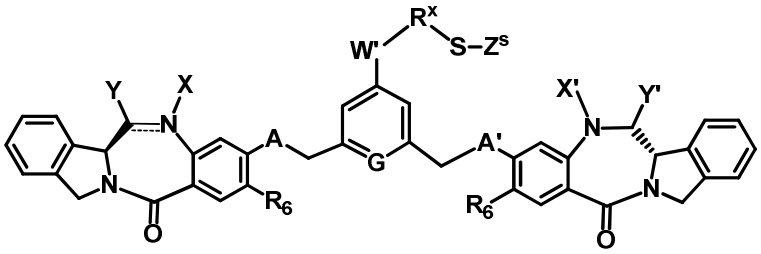
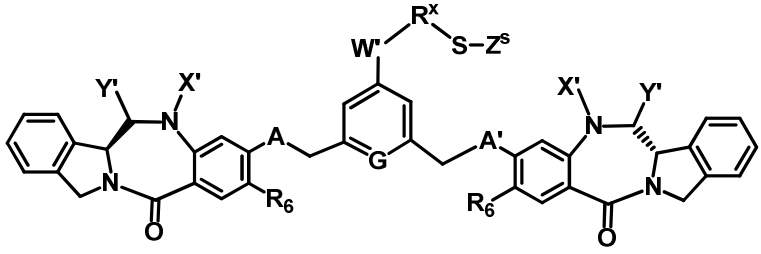


(X)

; and



(XI)

,

or a pharmaceutically acceptable salt thereof, wherein:

the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond, X is absent and Y is -H, and when it is a single bond, X is selected from -H, the linking group with the reactive group bonded thereto, or an amine protecting group (preferably X is -H);

Y is selected from -H, -OR, -OCOR', -SR, -NR'R," $-SO_3M$, $-SO_2M$ or $-OSO_3M$, wherein M is -H or a cation such as Na^+ or K^+;

R is -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms or a PEG group $-(CH_2CH_2O)_n-R^c$, wherein n is an integer from 1 to 24, and R^c is a linear or branched alkyl having 1 to 4 carbon atoms;

R' and R" are the same or different, and are selected from -H, -OH, -OR, $-NRR^{g'}$, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, an optionally substituted aryl having from 6 to 18 carbon atoms**,** an optionally substituted 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms selected from O, S, N and P, a PEG group $-(CH_2CH_2O)_n-R^c$, wherein n is an integer from 1 to 24, preferably n is 2, 4 or 8; and $R^{g'}$ is -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms or a PEG group $-(CH_2CH_2O)_n-R^c$;

X' is selected from the group consisting of -H, -OH, a substituted or

unsubstituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, phenyl, and an amine-protecting group;

Y' is selected from the group consisting of -H, an oxo group, a substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms;

A and A' are selected from -O- and -S-;

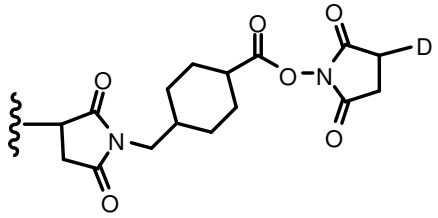
W' is absent, or selected from -O-, -N(R^e)-, -N(R^e)-C(=O)-, -N(C(=O)R^e)-, -S- or -CH_2-S-, -CH_2NR^e-;

R^x is absent or selected from a linear, branched or cyclic alkyl having 1 to 10 carbon atoms;

R^e is -H, a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms or -$(CH_2$-CH_2-$O)_n$-R^k, wherein R^k is a -H, a linear, branched cyclic alkyl having 1 to 6 carbon atoms, optionally bearing a secondary amino (*e.g.*, -NHR^{101}) or tertiary amino (-$NR^{101}R^{102}$) group or a 5- or 6-membered nitrogen containing heterocycle, such as piperidine or morpholine, wherein R^{101} and R^{102} are each independently a linear, branched, or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms;

G is selected from -CH- or -N-;

Z^s is -H, or is selected from any one of the following formulas: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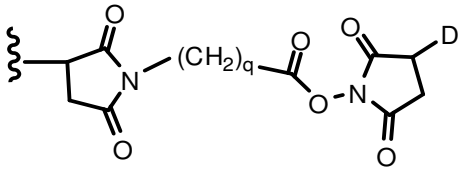
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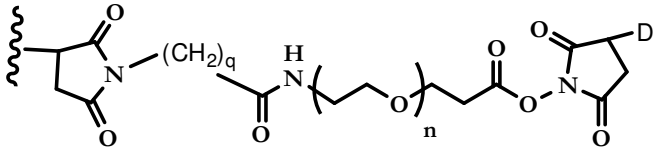
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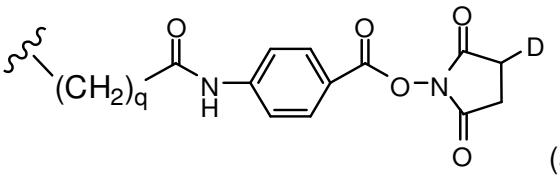

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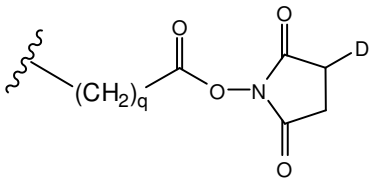

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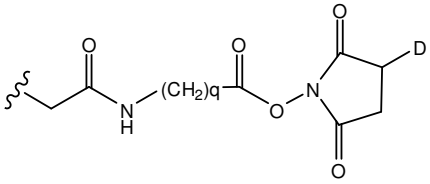

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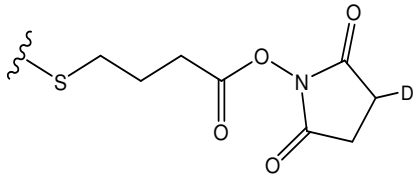

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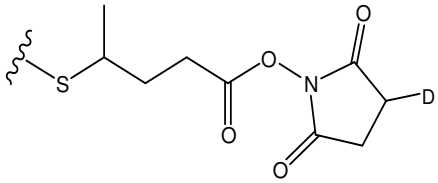

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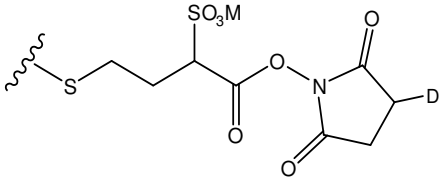

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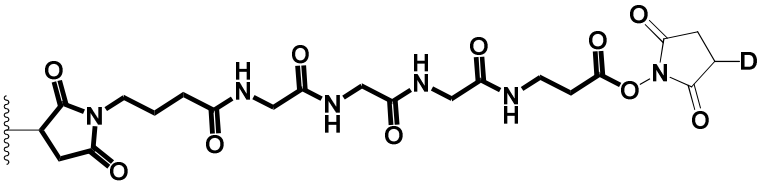

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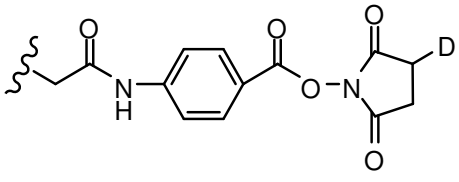
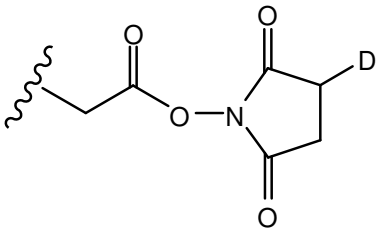


(a4');



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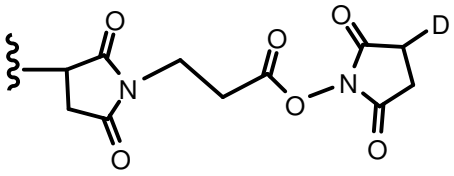
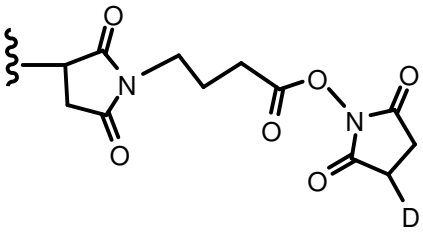


(a12); and



(a13)

wherein:

q is an integer from 1 to 5;

n is an integer from 2 to 6;

D is -H or -SO_3M;

M is -H or a cation, such as Na^+ or K^+.

11. The compound of claim 10, wherein W' is -$N(R^e)$-; and R^e is -$(CH_2$-CH_2-$O)_n$-R^k, wherein (i) R^k is a -H, a linear, branched, or cyclic alkyl having 1 to 6 carbon atoms; or (ii) R^k is -H or -Me, n is 4, and q is 2.

12. The compound of claim 10 or 11, wherein:

the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond X is absent and Y is -H, and when it is a single bond, X is -H; Y is -OH or -SO_3M;

M is -H or a pharmaceutically acceptable cation (*e.g.*, Na^+);

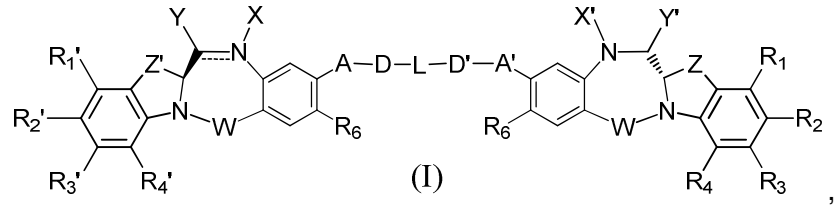
X' and Y' are both -H;

A and A' are both -O-;

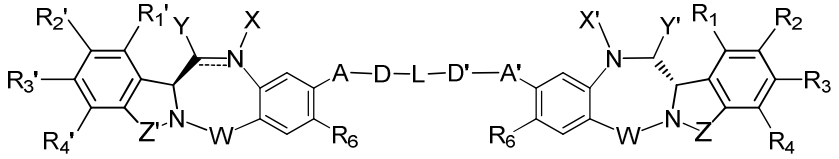
R_6 is -OMe; and

R^x is a linear or branched alkyl having 1 to 6 carbon atoms.

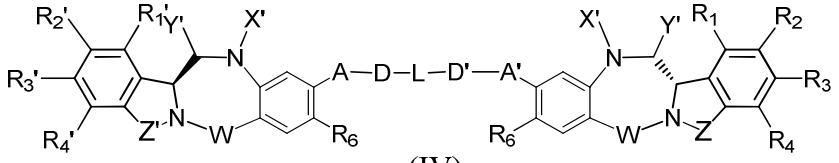
13. A conjugate comprising: a cytotoxic compound and a cell binding agent (CBA), wherein the cytotoxic compound comprises a linking group which covalently links the cytotoxic compound to the CBA, and wherein said cytotoxic compound is represented by any one of the following formulas:



(I) ,



(III) ,



(IV) ,

or a pharmaceutically acceptable salt thereof, wherein:

the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond X is absent and Y is -H, or a linear or branched alkyl having 1 to 4 carbon atoms, and when it is a single bond, X is -H, the linking group, or an amine protecting moiety;

Y is -H or a leaving group selected from -OR, -OCOR', -OCOOR', -OCONR'R'', -NR'R'', -NR'COR'', -NR'NR'R'', an optionally substituted 5- or 6-membered nitrogen-containing heterocycle (*e.g.*, piperidine, tetrahydropyrrole, pyrazole, morpholine), a guanidinum represented by -NR'(C=NH)NR'R'', an amino acid, or a peptide represented by -NRCOP', wherein P' is an amino acid or a polypeptide containing between 2 to 20 amino acid units, -SR, -SOR', $-SO_2M$, $-SO_3M$, $-OSO_3M$, halogen, cyano and an azido; or,

Y is a sulfite (HSO_3, HSO_2 or a salt of HSO_3^-, SO_3^{2-} or HSO_2^- formed with a cation), metabisulfite ($H_2S_2O_5$ or a salt of $S_2O_5^{2-}$ formed with a cation), mono-, di-, tri-, and tetra- thiophosphate (PO_3SH_3, $PO_2S_2H_2$, POS_3H_2, PS_4H_2 or a salt of PO_3S^{3-},

$PO_2S_2^{3-}$, POS_3^{3-} or PS_4^{3-} formed with a cation), thio phosphate ester $(R^iO)_2PS(OR^i)$, R^iS-, R^iSO, R^iSO_2, R^iSO_3, thiosulfate (HS_2O_3 or a salt of $S_2O_3^{2-}$ formed with a cation), dithionite (HS_2O_4 or a salt of $S_2O_4^{2-}$ formed with a cation), phosphorodithioate ($P(=S)(OR^{k'})(S)(OH)$ or a salt thereof formed with a cation), hydroxamic acid ($R^{k'}C(=O)NOH$ or a salt formed with a cation), formaldehyde sulfoxylate ($HOCH_2SO_2^-$ or a salt of $HOCH_2SO_2^-$ formed with a cation, such as $HOCH_2SO_2^-Na^+$) or a mixture thereof, wherein R^i is a linear or branched alkyl having 1 to 10 carbon atoms and is substituted with at least one substituent selected from $-N(R^j)_2$, $-CO_2H$, $-SO_3H$, and $-PO_3H$; R^i can be further optionally substituted with a substituent for an alkyl described herein; R^j is a linear or branched alkyl having 1 to 6 carbon atoms; $R^{k'}$ is a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, aryl, heterocyclyl or heteroaryl;

M is -H or a cation;

R, for each occurrence, is independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R^c$, an optionally substituted aryl having 6 to 18 carbon atoms, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an optionally substituted 3- to 18-membered heterocyclic ring containing 1 to 6 heteroatoms independently selected from O, S, N and P;

R' and R'' are each independently selected from -H, -OH, -OR, -NHR, $-NR_2$, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R^c$, and an optionally substituted 3-18-membered heterocyclic ring having 1 to 6 heteroatoms independently selected from O, S, N and P;

R^c is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms, or the linking group;

n is an integer from 1 to 24;

W is selected from C=O, C=S, CH_2, BH, SO and SO_2;

X' is selected from -H, an amine-protecting group, the linking group, an

optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R^c$, an optionally substituted aryl having 6 to 18 carbon atoms, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, and an optionally substituted 3- to 18-membered heterocyclic ring containing 1 to 6 heteroatoms independently selected from O, S, N and P;

Y' is selected from -H, an oxo group, the linking group, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, an optionally substituted 6- to 18-membered aryl, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 3 to 18-membered heterocyclic ring having 1 to 6 heteroatoms;

R_1, R_2, R_3, R_4, R_1', R_2', R_3' and R_4' are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-R^c$, halogen, guanidinium [$-NH(C=NH)NH_2$], -OR, -NR'R'', $-NO_2$, -NCO, -NR'COR'', -SR, a sulfoxide represented by -SOR', a sulfone represented by $-SO_2R'$, a sulfonate $-SO_3^-M^+$, a sulfate $-OSO_3^-M^+$, a sulfonamide represented by $-SO_2NR'R''$, cyano, an azido, -COR', -OCOR', -OCONR'R'' and the linking group;

R_6 is -H, -R, -OR, -SR, -NR'R'', $-NO_2$, halogen or the linking group;

Z and Z' are independently selected from $-(CH_2)_{n'}-$, $-(CH_2)_{n'}-CR_7R_8-(CH_2)_{na'}-$, $-(CH_2)_{n'}-NR_9-(CH_2)_{na'}-$, $-(CH_2)_{n'}-O-(CH_2)_{na'}-$ and $-(CH_2)_{n'}-S-(CH_2)_{na'}-$;

n' and na' are the same or different, and are selected from 0, 1, 2 and 3;

R_7 and R_8 are the same or different, and are each independently selected from -H, -OH, -SH, -COOH, -NHR', a polyethylene glycol unit $-(OCH_2CH_2)_n-$, an amino acid, a peptide unit bearing 2 to 6 amino acids, an optionally substituted linear, branched or cyclic alkyl having from 1 to 10 carbon atoms;

R_9 is independently selected from -H, an optionally substituted linear, branched or cyclic alkyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-$;

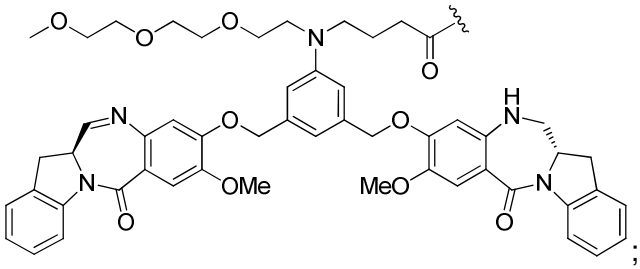
A and A' are the same or different, and are independently selected from -O-, oxo (-C(=O)-), -CRR'O-, -CRR'-, -S-, -CRR'S-, -N(R_5)- and -CRR'N(R_5)-,

R_5 for each occurrence is independently -H or an optionally substituted linear or branched alkyl having 1 to 10 carbon atoms;

D and D' are the same or different, and are independently absent or selected from the group consisting of an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, an amino acid, a peptide bearing 2 to 6 amino acids, and a polyethylene glycol unit (-$OCH_2CH_2)_n$-;

L is absent, the linking group, a polyethylene glycol unit (-$OCH_2CH_2)_n$-, a linear, branched or cyclic alkyl or alkenyl having 1 to 10 carbon atoms, a phenyl group, a 3- to 18-membered heterocyclic ring or a 5- to 18-membered heteroaryl ring having 1 to 6 heteroatoms independently selected from O, S, N and P, wherein the alkyl or alkenyl is optionally substituted with the linking group; phenyl or heterocyclic or heteroaryl ring can be optionally substituted, wherein the substituent can be the linking group;

wherein the compound is not:



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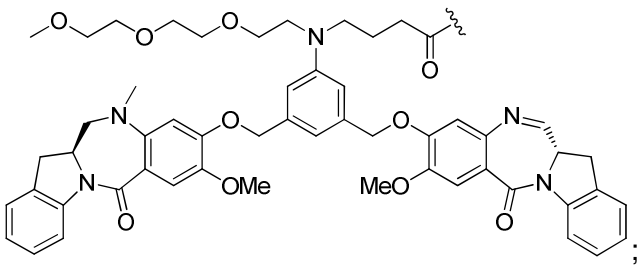

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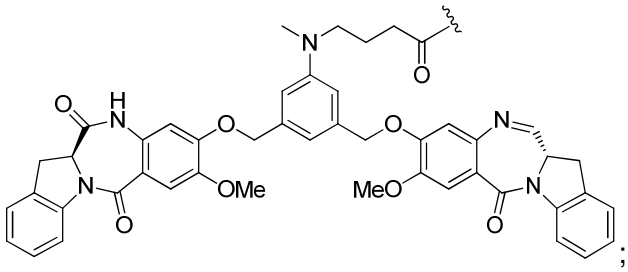

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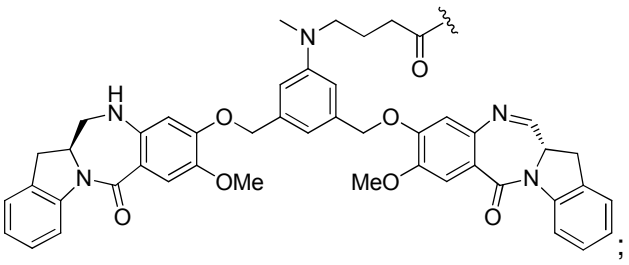
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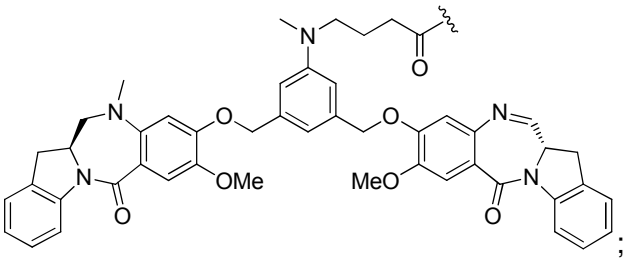
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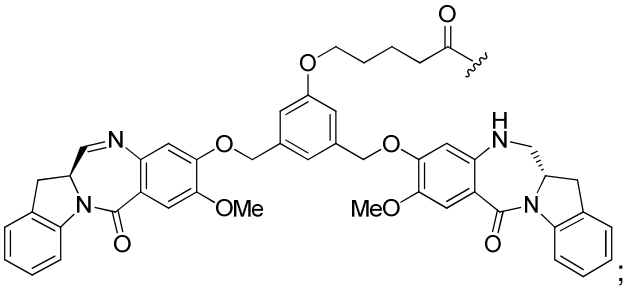
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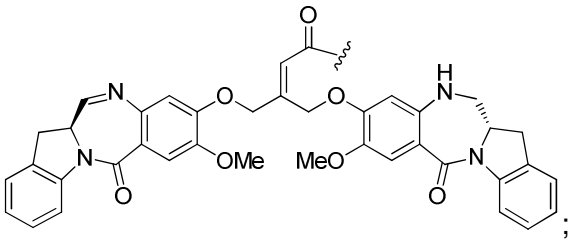
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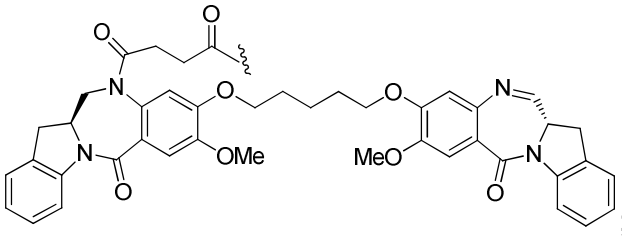
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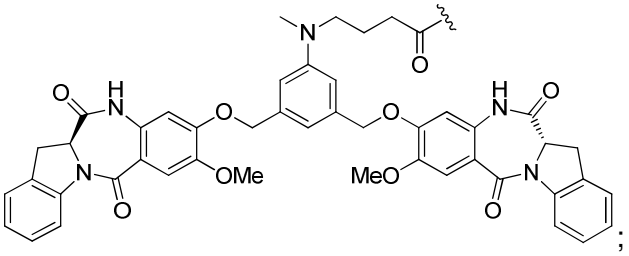
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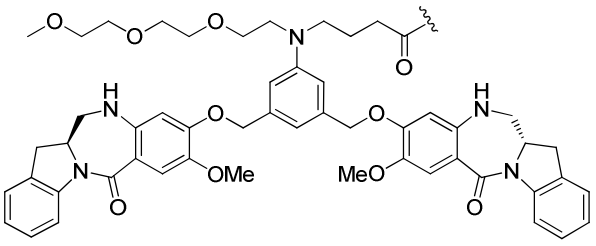
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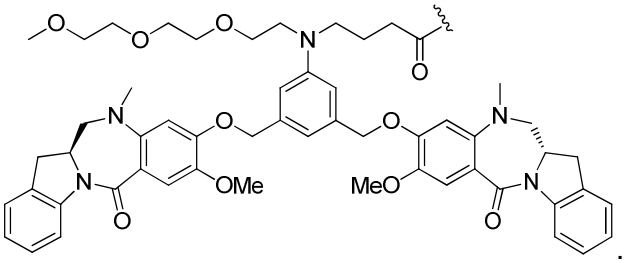
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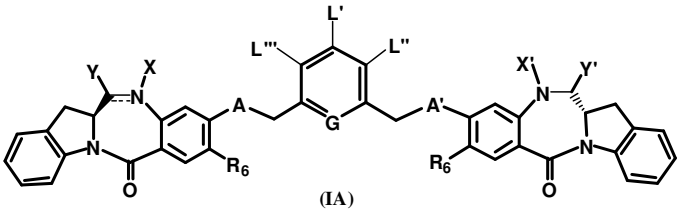
14. The conjugate of claim 12, wherein the compound is represented by any one of the following formulas: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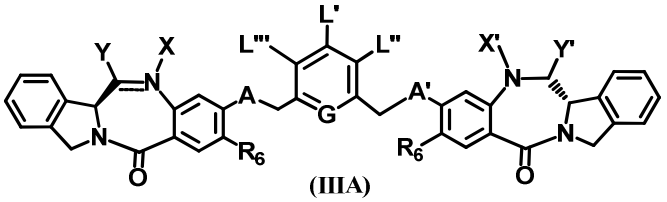
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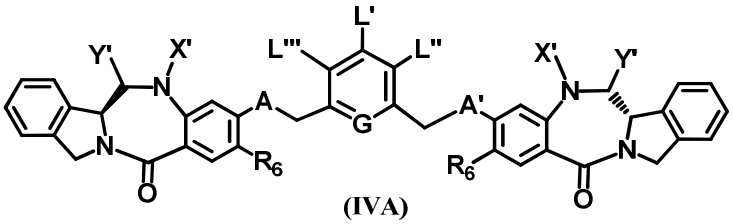
(IVA)
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or a pharmaceutically acceptable salt thereof, wherein:

L', L'', and L''' are the same or different, and are independently selected from -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-R^c$, halogen, guanidinium [$-NH(C=NH)NH_2$], -OR, -NR'R'', $-NO_2$, -NR'COR'', -SR, a sulfoxide represented by -SOR', a sulfone represented by $-SO_2R'$, a sulfonate -

SO_3M, a sulfate $-OSO_3M$, a sulfonamide represented by $-SO_2NR'R''$, cyano, an azido, -COR', -OCOR', -OCONR'R'' and the linking group, provided only one of L', L'', and L''' is the linking group; and

G is selected from -CH- or -N-.

15. The conjugate of claim 14, wherein L'' and L''' are –H; and L' is represented by the following formula:

$$-W'-R^x-V-R^y-J,$$

wherein:

W' and V are the same or different, and are each independently absent, or selected from $-CR^eR^{e'}-$, -O-, -O-C(=O)-, -C(=O)-O-, -S-, -SO-, $-SO_2-$, $-CH_2-S-$, $-CH_2O-$, $-CH_2NR^e-$, -O-(C=O)O-, -O-(C=O)N(R^e)-, -N(R^e)-, -N(R^e)-C(=O)-, -C(=O)-N(R^e)-, -N(R^e)-C(=O)O-, -N(C(=O)R^e)C(=O)-, -N(C(=O)R^e)-, $-(O-CH_2-CH_2)_n-$, -SS-, or -C(=O)-, or an amino acid, or a peptide having 2 to 8 amino acids;

R^x and R^y are the same or different, and are each independently absent or an optionally substituted linear, branched or cyclic alkyl, alkenyl, or alkynyl having 1 to 10 carbon atoms, an aryl bearing 6 to 10 carbon atoms or a 3- to 8-membered hetereocyclic ring bearing 1 to 3 heteroatoms selected from O, N or S;

R^e and $R^{e'}$ are the same or different, and are selected from -H, a linear, branched or cyclic alkyl, alkenyl, or alkynyl having 1 to 10 carbon atoms or $-(CH_2-CH_2-O)_n-R^k$, wherein R^k is a -H, a linear, branched cyclic alkyl having 1 to 6 carbon atoms, optionally bearing a secondary amino (*e.g.*, $-NHR^{101}$) or tertiary amino ($-NR^{101}R^{102}$) group or a 5- or 6-membered nitrogen containing heterocycle, such as piperidine or morpholine, wherein R^{101} and R^{102} are each independently a linear, branched, or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms; preferably, R^{101} and R^{102} are each independently a linear or branched alkyl having 1 to 6 carbon atoms;

n is an integer from 1 to 24; and

J is covalently linked to the CBA, and is selected from a succinimide, a acetamido, -S-, -SS-, $-CH_2S-$, -CH(Me)S-, $-C(Me)_2S-$, $-NR^{c1}-$, $-CH_2NR^{c1}-$, $-NR^{c1}N-$, and -C(=O)-, wherein R^{c1} is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms.

16. The conjugate of claim 15, wherein:

(i) W' is -O-, -N(R^e)- or -N(R^e)-C(=O)-;

R^e is -H, a linear or branched alkyl having 1 to 4 carbon atoms, or -(CH_2-CH_2-O)$_n$-R^k;

R^x is a linear or branched alkyl having 1 to 6 carbon atoms;

V is absent, -(O-CH_2-CH_2)$_n$-, -C(=O)-NH-, -S-, -NH-C(=O)-;

R^y is absent or a linear or branched alkyl having 1 to 4 carbon atoms; and

J is -S-, -SS-, or -C(=O)-; or

(ii) W' is -O-, -N(R^e)- or -N(R^e)-C(=O)-;

R^e is -H, -Me, or -(CH_2-CH_2-O)$_n$-Me;

n is an integer from 2 to 6;

R^x is linear or branched alkyl bearing 1 to 6 carbon atoms;

V and R^y are absent; and

J is -C(=O)-.

17. The conjugate of claim 14, wherein L' is represented by any of the following formulas:

$$-W'-[CR_{1''}R_{2''}]_a-V-[Cy]_{0-1}-[CR_{3''}R_{4''}]_b-C(=O)-;$$

$$-NR^e-[CR_{1''}R_{2''}]_a-S-[CR_{3''}R_{4''}]_b-C(=O)-; \text{ or}$$

$$-NR^e-[CR_{1''}R_{2''}]_a-S-Cy-[CR_{3''}R_{4''}]_b-C(=O)-,$$

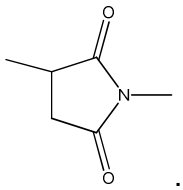
wherein:

$R_{1''}$, $R_{2''}$, and $R_{3''}$ are each independently -H or -Me;

$R_{4''}$ is -H, -Me, -SO_3H, or -$SO_3^-M^+$, wherein M^+ is a pharmaceutically acceptable cation;

a is an integers from 0-2, b is an integer from 0-3; and,

Cy is an optionally substituted 5-membered heterocyclic ring bearing an N heteroatom, preferably Cy is



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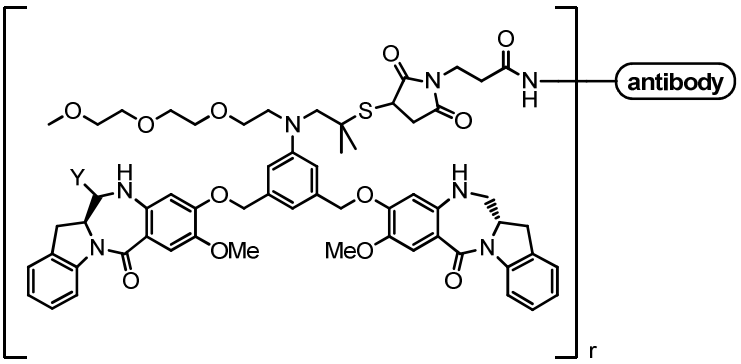
18. The conjugate of any one of claims 13 to 17, wherein, where the double line ==

between N and C represents a single bond, Y is a leaving group selected from -OR, -OCOR', -OCOOR', -OCONR'R'', -NR'R'', -NR'COR'', -NR'NR'R'', an optionally substituted 5- or 6-membered nitrogen-containing heterocycle (*e.g.*, piperidine, tetrahydropyrrole, pyrazole, morpholine, *etc*.), a guanidinum represented by -NR'(C=NH)NR'R'', an amino acid, or a peptide represented by -NRCOP', wherein P' is an amino acid or a polypeptide containing between 2 to 20 amino acid units, -SR, -SOR', $-SO_2M$, $-SO_3M$, $-OSO_3M$, halogen, cyano and an azido.

19. The conjugate of claim 18, wherein said cytotoxic compound is of formula (I).

20. The conjugate of claim 14, wherein the conjugate is:



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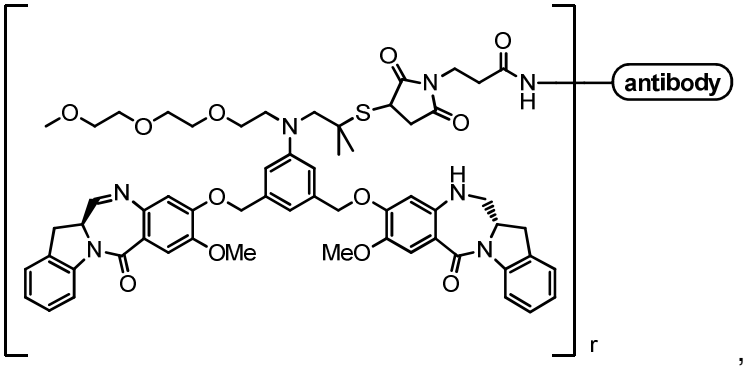

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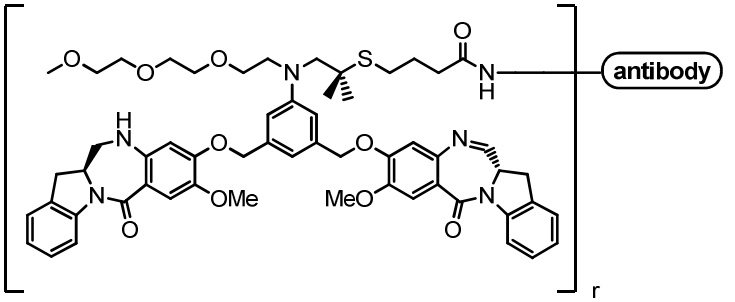

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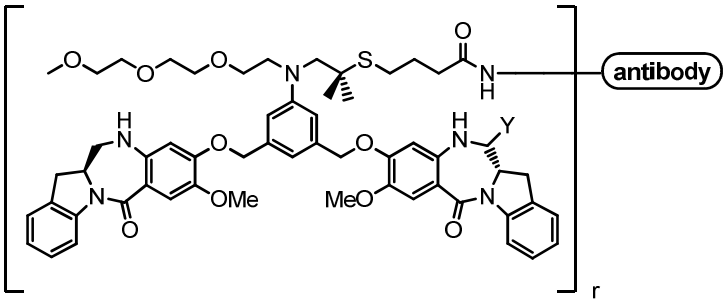

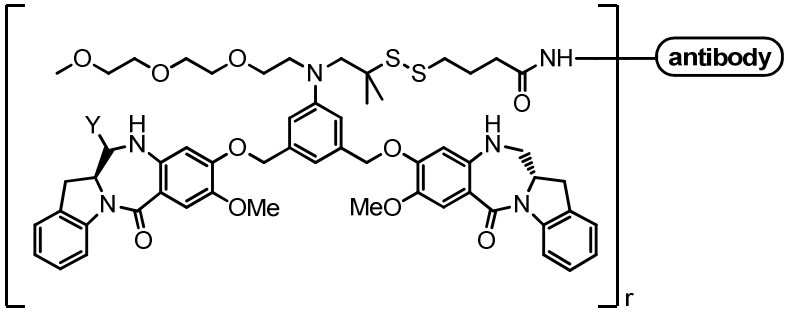

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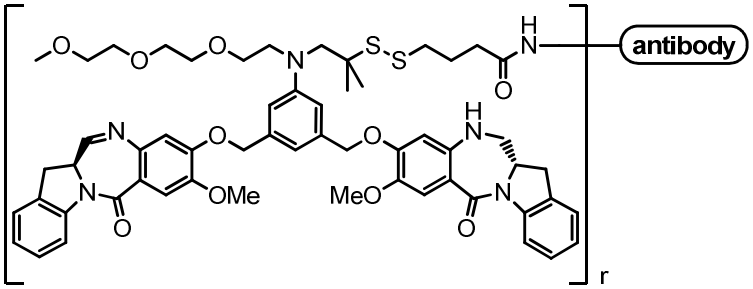

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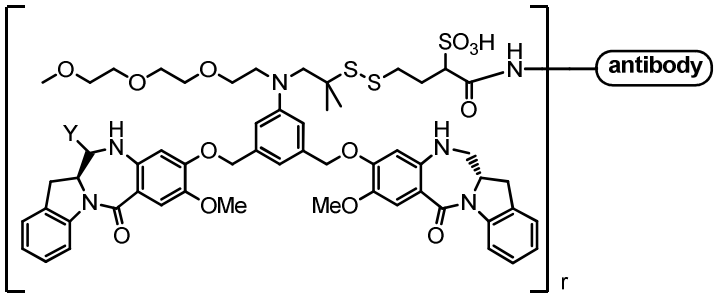

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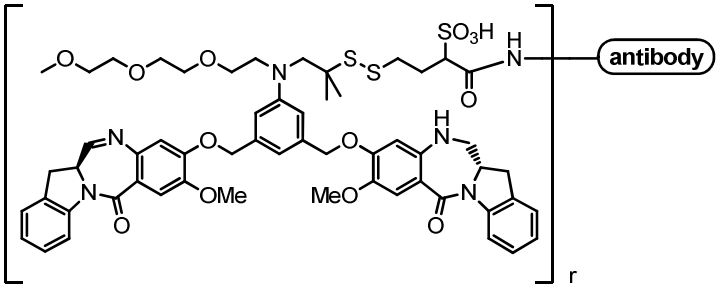
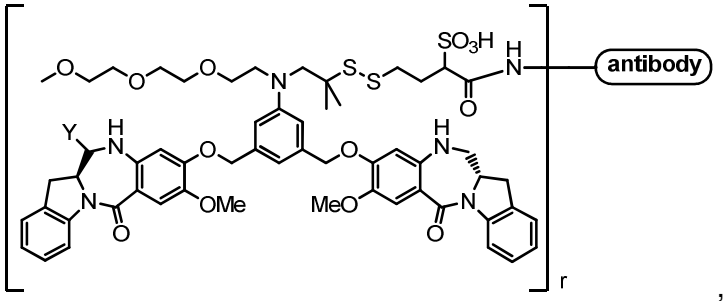


,

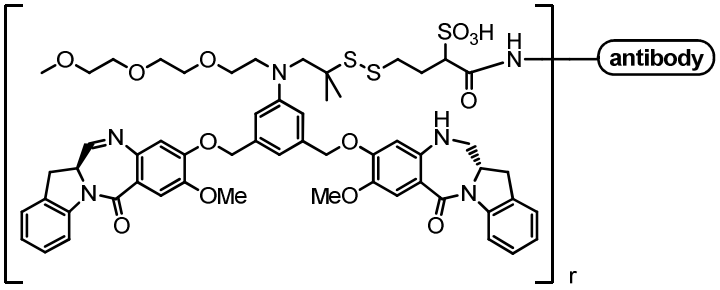
or a pharmaceutically acceptable salt thereof, wherein r is an integer from 1 to 10, Y is -H or -SO_3M (*e.g.*, Y is -SO_3M), and M is -H or a pharmaceutically acceptable

cation.

21. The conjugate of claim 14, wherein the conjugate is:



, or

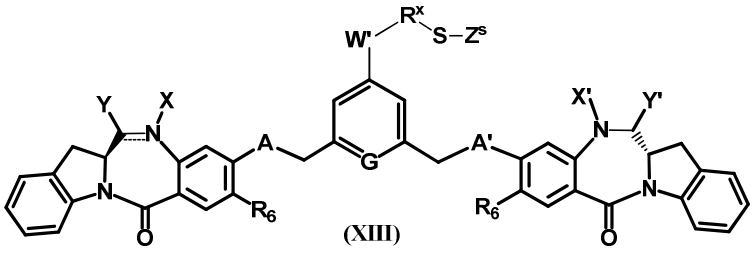


,

or a pharmaceutically acceptable salt thereof, wherein r is an integer from 1 to 10, Y is -SO_3M, and M is -H or a pharmaceutically acceptable cation.

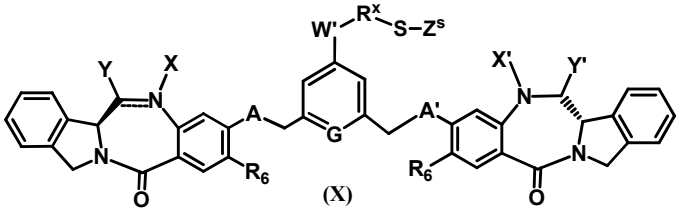
22. The conjugate of any one of claims 13 - 21, wherein the antibody is huMy9-6.

23. The conjugate of claim 14, wherein the compound is represented by the following formula:



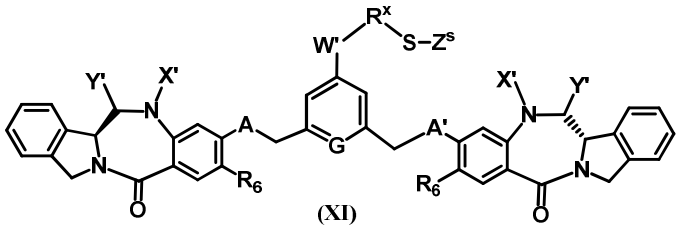
(XIII)

,



(X)

,



(XI)

,

or a pharmaceutically acceptable salt thereof, wherein:

W' is absent, or selected from -O-, -N(R^e)-, -N(R^e)-C(=O)-, -N(C(=O)R^e)-, -S-, -CH_2-S-, or -CH_2NR^e-;

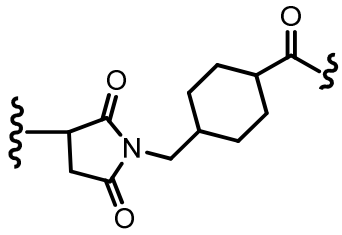
R^x is absent or selected from a linear, branched or cyclic alkyl having 1 to 10 carbon atoms;

R^e is -H, a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms or -$(CH_2$-CH_2-$O)_n$-R^k, wherein R^k is a -H, a linear, branched cyclic alkyl having 1 to 6 carbon atoms, optionally bearing a secondary amino (*e.g.*, -NHR^{101}) or tertiary amino (-$NR^{101}R^{102}$) group or a 5 or 6-membered nitrogen containing heterocycle, such as piperidine or morpholine, wherein R^{101} and R^{102} are each independently a linear, branched, or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms;

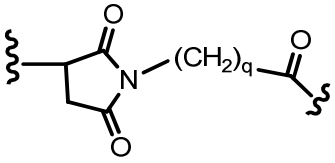
n is an integer from 2 to 6;

Z^s is linked to the CBA, and is selected from:

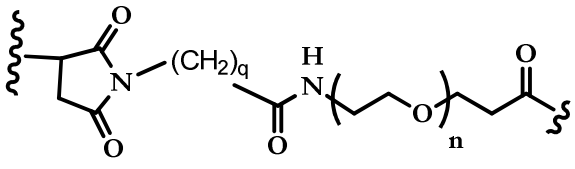
a bond;



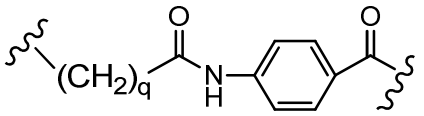
(b1);

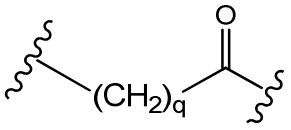


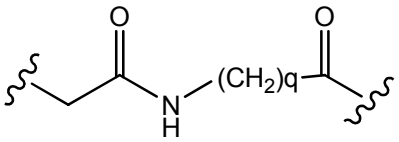
(b2);

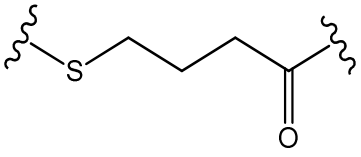


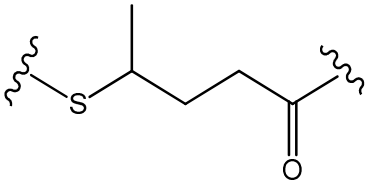
(b3);

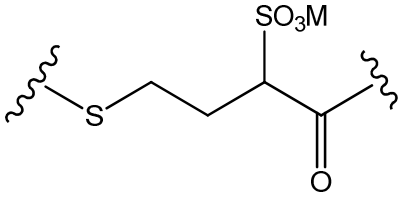

(b4);

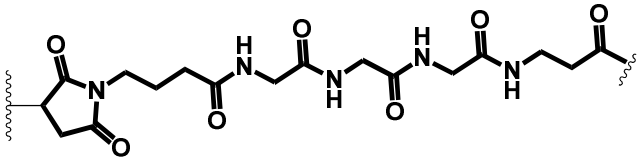

(b5);

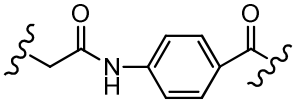

(b6);

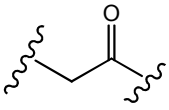

(b7);

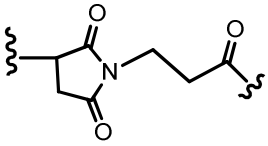

(b8);

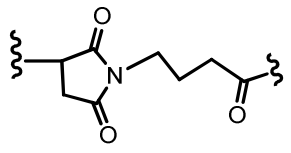

(b9),


(b10),


(b4');


(b5');


(b12); and



(b13)

wherein:

q is an integer from 1 to 5; and,

M is -H or a cation, such as Na^+ or K^+.

24. The conjugate of claim 23, wherein W' is $-N(R^e)-$; R^e is $-(CH_2-CH_2-O)_n-R^k$, wherein (i) R^k is a -H, a linear, branched, or cyclic alkyl having 1 to 6 carbon atoms; or (ii) R^k is -H or -Me, n is 4, and q is 2.

25. The conjugate of claim 23 or 24, wherein:

the double line == between N and C represents a single bond or a double bond, provided that when it is a double bond X is absent and Y is -H, and when it is a single bond, X is -H; Y is -OH or $-SO_3M$;

M is -H or a pharmaceutically acceptable cation (*e.g.*, Na^+);

X' and Y' are both -H;

A and A' are both -O-;

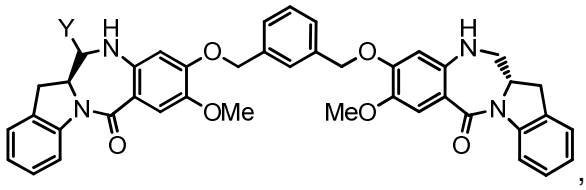
R_6 is -OMe; and

R^x is a linear or branched alkyl having 1 to 6 carbon atoms.

26. The conjugate of any one of claims 13 - 25, wherein the cell-binding agent is an antibody, a single chain antibody, an antibody fragment that specifically binds to the target cell, a monoclonal antibody, a single chain monoclonal antibody, or a monoclonal antibody fragment that specifically binds to a target cell, a chimeric antibody, a chimeric antibody fragment that specifically binds to the target cell, a domain antibody, a domain antibody fragment that specifically binds to the target cell, a resurfaced antibody, a resurfaced single chain antibody, or a resurfaced antibody fragment, a monoclonal antibody, a single chain monoclonal antibody, or a monoclonal antibody fragment thereof, a humanized antibody, a humanized single chain antibody, or a humanized antibody fragment, a lymphokine, a hormone, a vitamin, a growth factor, a colony stimulating factor, or a nutrient-transport molecule.

27. A pharmaceutical composition comprising the conjugate of any one of claims 13 - 25 and a pharmaceutically acceptable carrier.

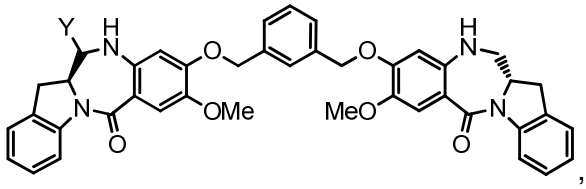
28. A compound as defined in of any one of claims 1- 12, a conjugate as defined in any one of claims 13 - 26, or a compound represented by the following formula:



,

or a pharmaceutically acceptable salt thereof, wherein Y is -H or -SO_3M (*e.g.*, Y is -SO_3M), and M is -H, or a pharmaceutically acceptable cation thereof, for use as a medicament.

29. A compound as defined in of any one of claims 1- 12, a conjugate as defined in any one of claims 13 - 26, or a compound represented by the following formula:



,

or a pharmaceutically acceptable salt thereof, wherein Y is -H or -SO_3M (*e.g.*, Y is -SO_3M), and M is -H, or a pharmaceutically acceptable cation thereof, for use in a method of inhibiting abnormal cell growth or treating a proliferative disorder, an autoimmune disorder, destructive bone disorder, infectious disease, viral disease, fibrotic disease, neurodegenerative disorder, pancreatitis or kidney disease in a mammal, comprising administering to said mammal a therapeutically effective amount of the compound or the conjugate and, optionally, a chemotherapeutic agent.

30. The compound or conjugate for the use of claim 29, which is for treating:

(i) a condition selected from the group consisting of: cancer, rheumatoid arthritis, multiple sclerosis, graft versus host disease (GVHD), transplant rejection, lupus, myositis, infection, and immune deficiency; or

(ii) a cancer,

optionally wherein the cancer is selected from the group consisting of: breast cancer,

colon cancer, brain cancer, prostate cancer, kidney cancer, pancreatic cancer, ovarian cancer, head and neck cancer, melanoma, colorectal cancer, gastric cancer, squamous cancer, small-cell lung cancer, non small-cell lung cancer, testicular cancer, Merkel cell carcinoma, glioblastoma, neuroblastoma, cancers of lymphatic organs and hematological malignancy including Leukemia (Acute lymphoblastic leukemia (ALL), Acute myelogenous leukemia (AML), Chronic lymphocytic leukemia (CLL), Chronic myelogenous leukemia (CML), Acute monocytic leukemia (AMOL), Hairy cell leukemia (HCL), T-cell prolymphocytic leukemia (T-PLL), Large granular lymphocytic leukemia, Adult T-cell leukemia), Lymphoma (small lymphocytic lymphoma (SLL), Hodgkin's lymphomas (Nodular sclerosis, Mixed cellularity, Lymphocyte-rich, Lymphocyte depleted or not depleted, and Nodular lymphocyte-predominant Hodgkin lymphoma), Non-Hodgkin's lymphomas (all subtypes), Chronic lymphocytic leukemia/Small lymphocytic lymphoma, B-cell prolymphocytic leukemia, Lymphoplasmacytic lymphoma (such as Waldenström macroglobulinemia), Splenic marginal zone lymphoma, Plasma cell neoplasms (Plasma cell myeloma, Plasmacytoma, Monoclonal immunoglobulin deposition diseases, Heavy chain diseases), Extranodal marginal zone B cell lymphoma (MALT lymphoma), Nodal marginal zone B cell lymphoma (NMZL), Follicular lymphoma, Mantle cell lymphoma, Diffuse large B cell lymphoma, Mediastinal (thymic) large B cell lymphoma, Intravascular large B cell lymphoma, Primary effusion lymphoma, Burkitt lymphoma/leukemia, T cell prolymphocytic leukemia, T cell large granular lymphocytic leukemia, Aggressive NK cell leukemia, Adult T cell leukemia/lymphoma, Extranodal NK/T cell lymphoma (nasal type), Enteropathy-type T cell lymphoma, Hepatosplenic T cell lymphoma, Blastic NK cell lymphoma, Mycosis fungoides / Sezary syndrome, Primary cutaneous CD30-positive T cell lymphoproliferative disorders, Primary cutaneous anaplastic large cell lymphoma, Lymphomatoid papulosis, Angioimmunoblastic T cell lymphoma, Peripheral T cell lymphoma (unspecified), Anaplastic large cell lymphoma), and multiple myeloma (plasma cell myeloma or Kahler's disease).

31. The compound or conjugate for the use of claim 29, which is for treating acute myelogenous leukaemia (AML).