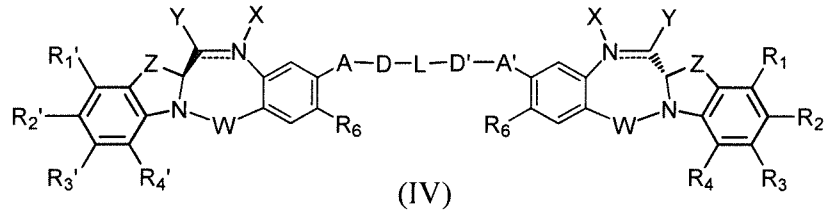
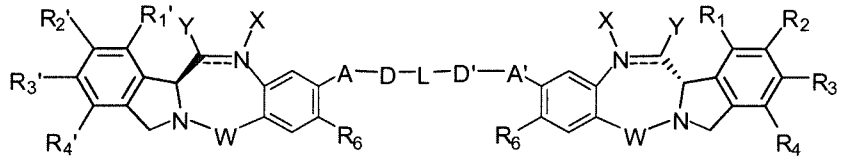
Claims

1. A conjugate comprising a cell binding agent (CBA) covalently linked, through a linking group, to a compound represented by formula (IV) or (V):



(IV)



(V)

or a pharmaceutically acceptable salt, optical isomer, racemate, diastereomer, or enantiomer of the compound, 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 or an amine protecting moiety that is capable of being enzymatically or hydrolytically cleaved;

Y is selected from the group consisting of -OR, -OCOR', -OCOOR', -OCONR'R'', -NR'R'', -NRCOR', -NRCOP, wherein P is an amino acid or a polypeptide containing between 2 to 20 amino acid units, -SR', -SOR', $-SO_2R'$, $-SO_3$, $-OSO_3$, a halogen, a cyano, and an azido, wherein R, R' and R'' are the same or different and are 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 $(-OCH_2CH_2)_n$, wherein n is an integer from 1 to 2000, a 5- or 6-membered heteroaryl ring containing one or more heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, a 5- to 18-membered fused ring system, wherein at least one of the rings is aromatic, containing one or more heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, an aryl having from 6 to 18 carbon atoms, and a 3- to 18-membered heterocyclic ring having 1 to

6 heteroatoms selected from the group consisting of O, S, N and P, wherein the optional substituent is selected from the group consisting of halogen, $-OR_7$, $-NR_8R_9$, $-NO_2$, -NRCOR', $-SR_{10}$, -SOR', $-SO_2R'$, $-SO_3$, $-OSO_3$, $-SO_2NRR'$, a cyano, an azido, $-COR_{11}$, $-OCOR_{11}$ or $-OCONR_{11}R_{12}$, wherein R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are each independently selected from the group consisting of -H, a linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $(-OCH_2CH_2)_n$, wherein n is an integer from 1 to 2000, a 5- or 6-membered heteroaryl ring containing one or more heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, a 5- to 18-membered fused ring system, wherein at least one of the rings is aromatic, containing one or more heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, an aryl having from 6 to 18 carbon atoms, and a 3- to 10-membered heterocyclic ring having 1 to 6 heteroatoms selected from O, S, N and P, and R_{10} is $-SR_{13}$ or $-COR_{13}$, wherein R_{13} is selected from the group consisting of a linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a 5- or 6-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5- to 18-membered fused ring system, wherein at least one of the rings is aromatic, containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, an aryl having from 6 to 18 carbon atoms, and a 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms selected from O, S, N and P, optionally R_{11} is $-OR_{14}$, wherein R_{14} has the same definition as R, optionally R'' is -OH;

W is C=O;

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, and a polyethylene glycol unit $(-OCH_2CH_2)_n$, wherein n is an integer from 1 to 2000, wherein the optional substituent is selected from the group consisting of halogen, $-NH(C=NH)NH_2$, $-OR_7$, $-NR_8R_9$, $-NO_2$, -NRCOR', $-SR_{10}$, -SOR', $-SO_2R'$, $-SO_3$, $-OSO_3$, $-SO_2NRR'$, a cyano, an azido, $-COR_{11}$, $-OCOR_{11}$, $-OCONR_{11}R_{12}$, and a polyethylene glycol unit $(-OCH_2CH_2)_n$, wherein n is an integer from 1 to 2000, optionally, any one of R_1, R_2, R_3, R_4, R_1', R_2', R_3', or R_4' is

covalently linked, through the linking group, to the cell binding agent or is selected from a polypyrrolo, poly-indolyl, poly-imidazolyl, polypyrollo-imidazolyl, poly-pyrollo-indolyl or polyimidazolo-indolyl unit optionally linked to the linking group;

Z is CH_2;

R_6 is -OR, -SR or -NRR', optionally R_6 is linked to the linking group;

A and A' are the same or different and are selected from O, CRR'O, S, CRR'S, NR_{15} or CRR'NHR_{15}, wherein R_{15} has the same definition as R;

D and D' are the same or different and are independently a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms, optionally substituted with any one of halogen, -OR_7, -NR_8R_9, -NO_2, -NRCOR', -SR_{10}, -SOR', -SO_2R', -SO_3, -OSO_3, -SO_2NRR', a cyano, an azido, -COR_{11}, -$OCOR_{11}$ or -$OCONR_{11}R_{12}$, and a polyethylene glycol unit $(-OCH_2CH_2)_n$, wherein n is an integer from 1 to 2000;

L is absent, or is a phenyl group or 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms selected from O, S, N and P, wherein said phenyl group or 3- to 18-membered heterocyclic ring represented by L is optionally linked to the linking group, or is selected from a linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, optionally substituted with any one of halogen, -OR_7, -NR_8R_9, -NO_2, -NRCOR', -SR_{10}, -SOR', -SO_2R', -SO_3, -OSO_3, -SO_2NRR', a cyano, an azido, -COR_{11}, -$OCOR_{11}$, -$OCONR_{11}R_{12}$, and a polyethylene glycol unit $(-OCH_2CH_2)_n$, wherein n is an integer from 1 to 2000; optionally, L itself is the linking group;

provided that the conjugate has no more than one linking group.

2. The conjugate of claim 1, wherein:

Y is selected from the group consisting of -OR, -NR'R", -SO_3, and -OSO_3, wherein R is selected from the group consisting of -H, a linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $(-OCH_2CH_2)_n$, wherein n is an integer from 1 to 2000, an aryl having from 6 to 10 carbon atoms, and a heterocyclic ring having from 3 to 10 carbon atoms;

W is C=O;

R_1, R_2, R_3, R_4, R_1', R_2', R_3' and R_4' are each independently selected from -H, -NO_2 or the linking group;

R_6 is $-OR_{18}$, wherein R_{18} has the same definition as R;

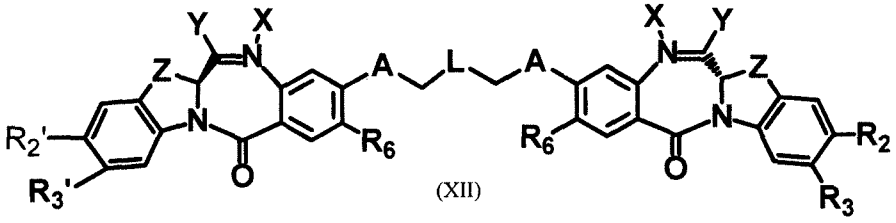
Z is CH_2;

A and A' are each O;

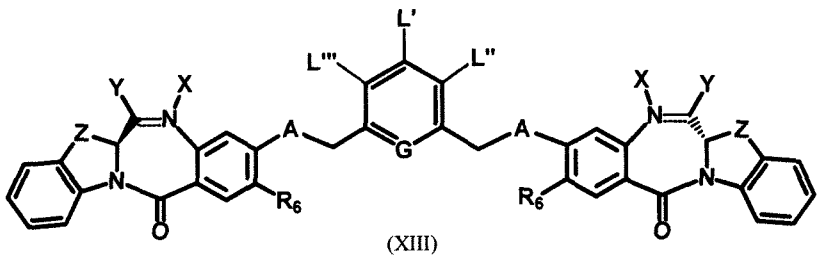
D and D' are the same or different and are independently a linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms;

L is absent, or is a phenyl group or a heterocyclic ring having from 3 to 10 carbon atoms, wherein said phenyl group or heterocyclic ring represented by L is optionally linked to the linking group, or is a linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, optionally substituted with any one of halogen, $-OR_7$, $-NR_8R_9$, $-NO_2$, -NRCOR', $-SR_{10}$, -SOR', $-SO_2R'$, $-SO_3$, $-OSO_3$, $-SO_2NRR'$, a cyano, an azido, $-COR_{11}$, $-OCOR_{11}$ and $-OCONR_{11}R_{12}$, or a polyethylene glycol unit $(-OCH_2CH_2)_n$, wherein n is an integer from 1 to 2000; optionally, L itself is the linking group.

3. The conjugate of claim 1, selected from formulae (XII) and (XIII):



(XII)



(XIII)

or a pharmaceutically acceptable salt, optical isomer, racemate, diastereomer, or enantiomer thereof, wherein

Y is selected from the group consisting of -OH, -OR, -NR'R", $-SO_3$, and $-OSO_3$, wherein R, R' and R" are a linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms;

one of R_2, R_3, R_2' and R_3' is the linking group and the others are -H or $-NO_2$;

R_6 is -OR;

Z is CH_2;

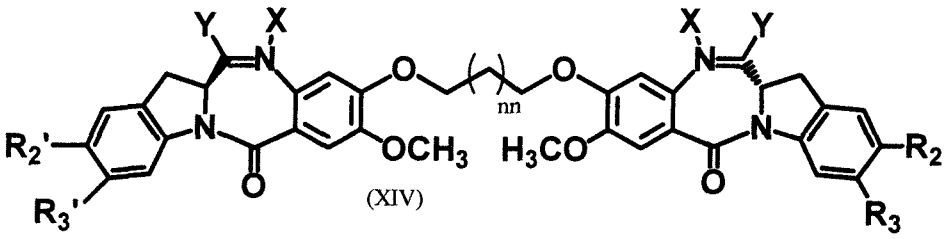
A is O or NR_{15};

L is $(CH_2)_{nn}$, wherein nn is 0 or an integer between 1 and 5, or a substituted or unsubstituted alkyl or alkenyl having from 2 to 4 carbon atoms, wherein the substituent is selected from halogen, $-OR_7$, $-NR_8R_9$, $-NO_2$, -NRCOR', $-SR_{10}$, -SOR', $-SO_2R'$, $-SO_3$, $-OSO_3$, $-SO_2NRR'$, a cyano, an azido, $-COR_{11}$, $-OCOR_{11}$ or $-OCONR_{11}R_{12}$, optionally, L itself is the linking group;

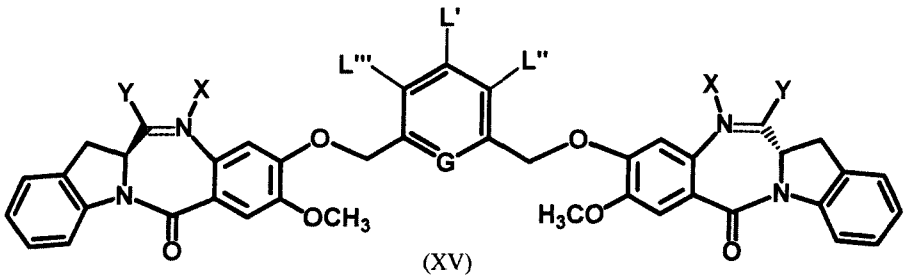
one of L', L'' or L''' is the linking group, while the others are -H; preferably L' is the linking group; and

G is CH or N.

4. The conjugate of claim 1, selected from formulae (XIV) and (XV):



(XIV)



(XV)

or a pharmaceutically acceptable salt, optical isomer, racemate, diastereomer, or enantiomer thereof, wherein

Y is selected from the group consisting of -OH, -OR, $-SO_3$, and $-OSO_3$, wherein R is a linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms;

nn is 0 or an integer from 1 to 5;

one of R_2, R_3, R_2' and R_3' in formula (XIV) is the linking group and the others are -H or $-NO_2$;

one of L', L'' or L''' in formula (XV) is the linking group, and the others are -H; and

G is CH or N.

5. The conjugate of claim 1, wherein one of R_1, R_2, R_3, R_4, R_1', R_2', R_3', R_4', L', L'', L''' is covalently linked to the CBA, and is selected from the group consisting of:

$-O(CR_{20}R_{21})_m(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-O(CR_{20}R_{21})_m(CR_{26}=CR_{27})_{m'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-O(CR_{20}R_{21})_m(alkynyl)_{n'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-O(CR_{20}R_{21})_m(piperazino)_{t'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-O(CR_{20}R_{21})_m(pyrrolo)_{t'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-O(CR_{20}R_{21})_mA''_{m''}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-S(CR_{20}R_{21})_m(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-S(CR_{20}R_{21})_m(CR_{26}=CR_{27})_{m'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-S(CR_{20}R_{21})_m(alkynyl)_{n'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-S(CR_{20}R_{21})_m(piperazino)_{t'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-S(CR_{20}R_{21})_m(pyrrolo)_{t'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-S(CR_{20}R_{21})_mA''_{m''}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-NR_{33}(C=O)_{p''}(CR_{20}R_{21})_m(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-NR_{33}(C=O)_{p''}(CR_{20}R_{21})_m(CR_{26}=CR_{27})_{m'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

$-NR_{33}(C=O)_{p''}(CR_{20}R_{21})_m(alkynyl)_{n'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$,

-$NR_{33}(C=O)_{p''}(CR_{20}R_{21})_m$(piperazino)$_{t'}(CR_{22}R_{23})_n(OCH_2CH_2)_p$ $(CR_{40}R_{41})_pY''(CR_{24}R_{25})_q(CO)_tX''$,

-$NR_{33}(C=O)_{p''}(CR_{20}R_{21})_m$(pyrrolo)$_{t'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''$ $(CR_{24}R_{25})_q(CO)_tX''$,

-$NR_{33}(C=O)_{p''}(CR_{20}R_{21})_mA''_{m''}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''$ $(CR_{24}R_{25})_q(CO)_tX''$,

-$(CR_{20}R_{21})_m(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q$ $(CO)_tX''$,

-$(CR_{20}R_{21})_m(CR_{26}=CR_{27})_{m'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''$ $(CR_{24}R_{25})_q(CO)_tX''$,

-$(CR_{20}R_{21})_m$(alkynyl)$_{n'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q$ $(CO)_tX''$,

-$(CR_{20}R_{21})_m$(piperazino)$_{t'}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''$ $(CR_{24}R_{25})_q(CO)_tX''$,

-$(CR_{20}R_{21})_mA''_{m''}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q$ $(CO)_tX''$,

-$(CR_{20}R_{21})_m(CR_{29}=N\text{-}NR_{30})_{n''}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''$ $(CR_{24}R_{25})_q(CO)_tX''$,

-$(CR_{20}R_{21})_m(CR_{29}=N\text{-}NR_{30})_{n''}(CR_{26}=CR_{27})_{m'}(CR_{22}R_{23})_n(OCH_2CH_2)_p$ $(CR_{40}R_{41})_pY''(CR_{24}R_{25})_q(CO)_tX''$,

-$(CR_{20}R_{21})_m(CR_{29}=N\text{-}NR_{30})_{n''}$(alkynyl)$_{n'}(CR_{22}R_{23})_n(OCH_2CH_2)_p$ $(CR_{40}R_{41})_{p''}Y''(CR_{24}R_{25})_q(CO)_tX''$, and

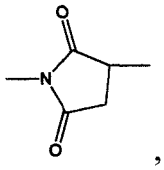
-$(CR_{20}R_{21})_m(CR_{29}=N\text{-}NR_{30})_{n''}A''_{m''}(CR_{22}R_{23})_n(OCH_2CH_2)_p(CR_{40}R_{41})_{p''}Y''$ $(CR_{24}R_{25})_q(CO)_tX''$,

wherein:

m, n, p, q, m', n', t' are integer from 1 to 10, or are optionally 0;

m", n" and p" are 0 or 1;

X'' is covalently linked to the CBA, and when Y" is not S-S and t = 0, X" is



, $-CH_2-CO-$, or -S-; and when t = 1, X'' is -NH-;

Y'' is absent or is selected from O, S, S-S or NR_{32}, wherein R_{32} has the same definition as given above for R;

A" is an amino acid selected from glycine, alanine, leucine, valine, lysine, citrulline, glutamate, or a polypeptide containing between 2 to 20 amino acid units;

R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, and R_{27} are the same or different and are -H or a linear or branched alkyl having from 1 to 5 carbon atoms;

R_{29} and R_{30} are the same or different and are -H or an alkyl from 1 to 5 carbon atoms;

R_{33} is -H or a linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 12 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n$, or R_{33} is $-COR_{34}$, $-CSR_{34}$, $-SOR_{34}$, or $-SO_2R_{34}$, wherein R_{34} is -H or linear, a branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 20 carbon atoms or, a polyethylene glycol unit $-(OCH_2CH_2)_n$; and

one of R_{40} and R_{41} is optionally a negatively or positively charged functional group and the other is -H or an alkyl, alkenyl, alkynyl having 1 to 4 carbon atoms.

6. The conjugate of claim 1, 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.

7. The conjugate of claim 6, wherein the tumor cells are selected from breast cancer cells, prostate cancer cells, ovarian cancer cells, colorectal cancer cells, gastric cancer cells, squamous cancer cells, small-cell lung cancer cells, and testicular cancer cells.

8. The conjugate of claim 1, 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 the 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.

9. The conjugate of claim 8, wherein the antibody is a resurfaced antibody, a resurfaced single chain antibody, or a resurfaced antibody fragment.

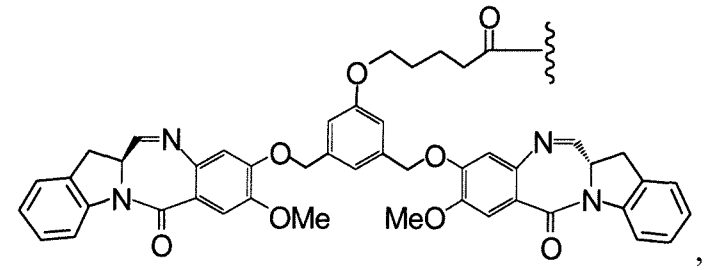
10. The conjugate of claim 8, wherein the antibody is a monoclonal antibody, a single chain monoclonal antibody, or a monoclonal antibody fragment thereof.

11. The conjugate of claim 8, wherein the antibody is a chimeric antibody, a chimeric antibody fragment, a domain antibody, or a domain antibody fragment.

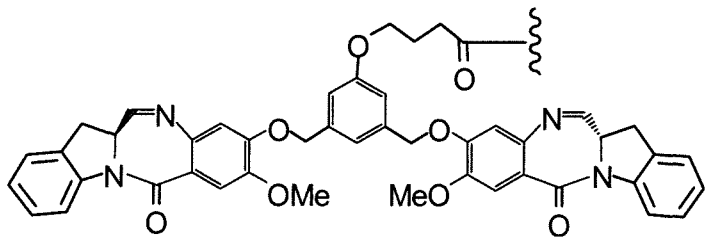
12. The conjugate of claim 8, wherein the antibody is a humanized antibody, a humanized single chain antibody, or a humanized antibody fragment.

13. The conjugate of claim 8, wherein the antibody is humanized or resurfaced MY9, humanized or resurfaced anti-B4, or humanized or resurfaced C242.

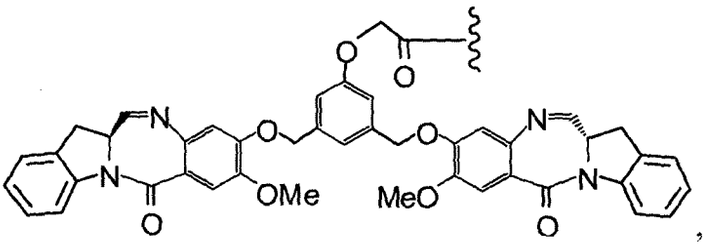
14. The conjugate of claim 1, wherein the compound is selected from the group consisting of:

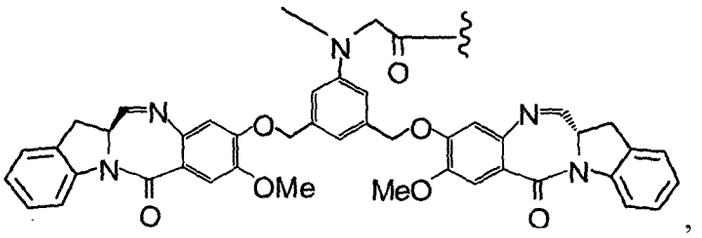


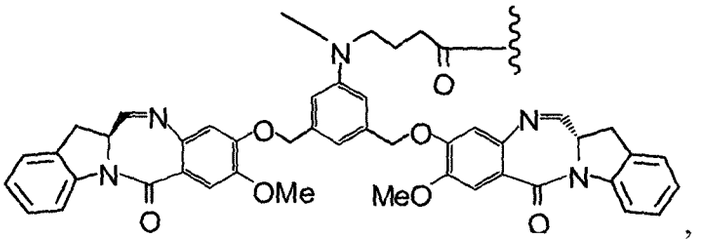
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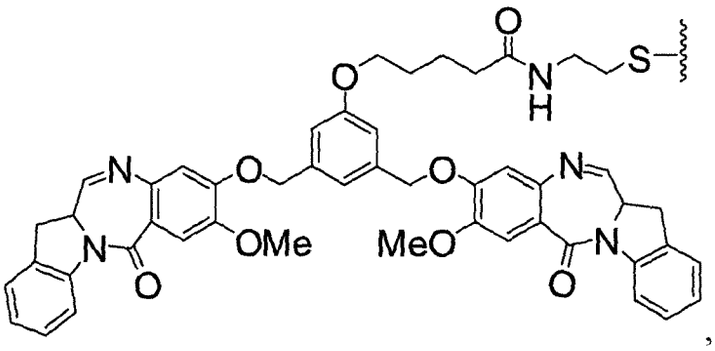


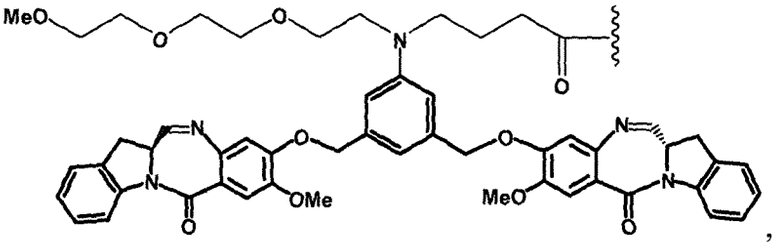
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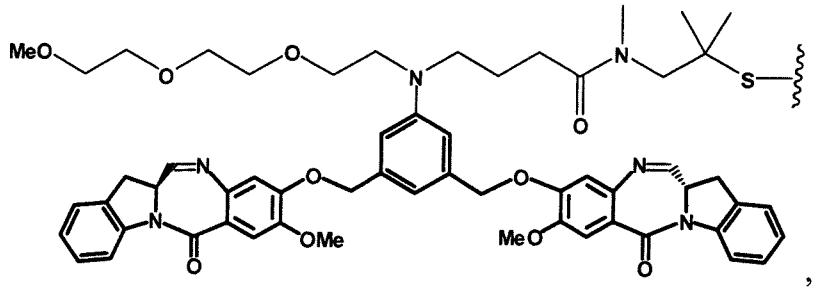

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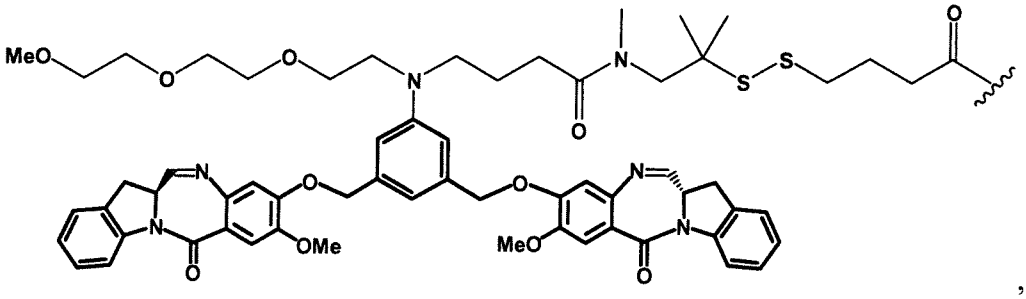

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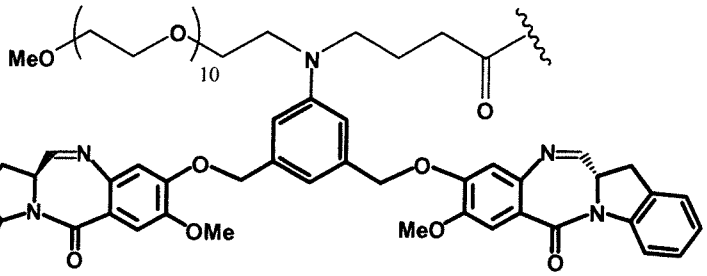

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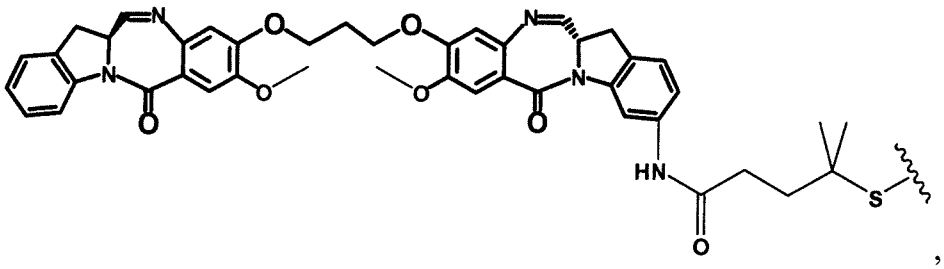

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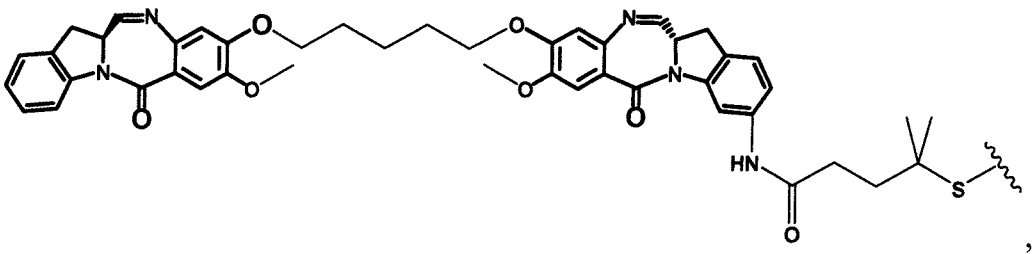

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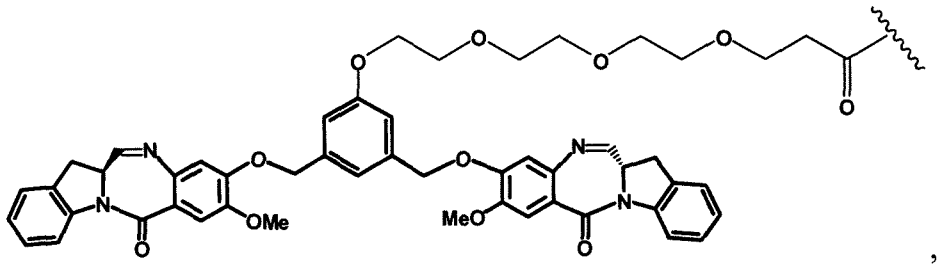

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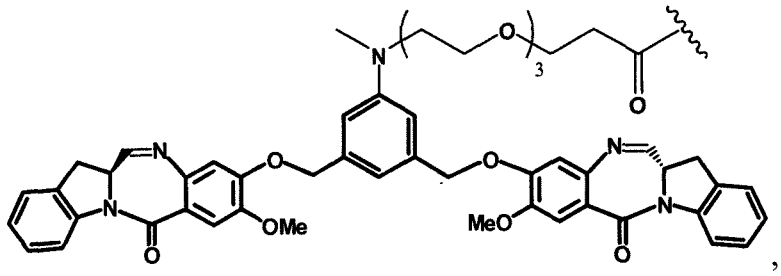

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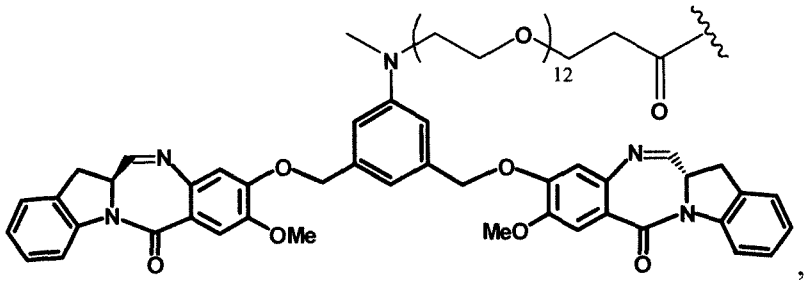

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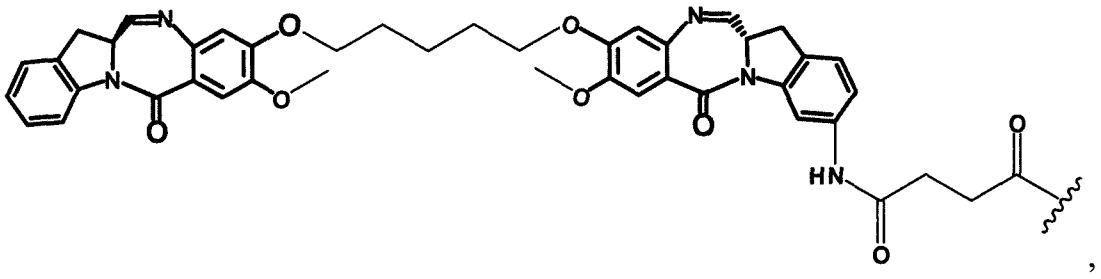

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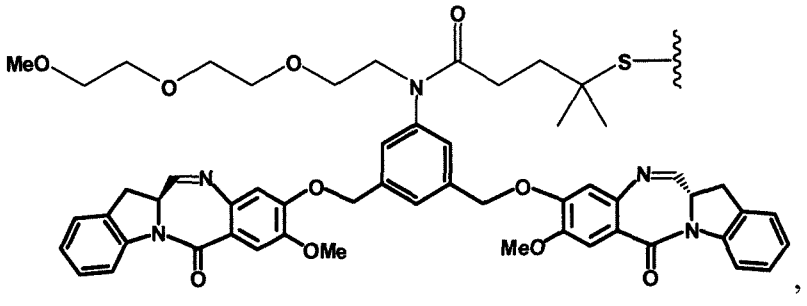

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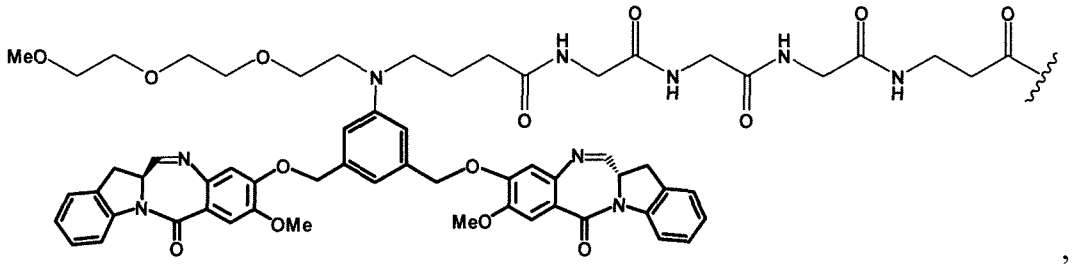

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wherein the wavy line represents a linkage to the cell-binding agent.

15. A pharmaceutical composition comprising a conjugate of claim 1, and a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 15, further comprising a second compound, which is a chemotherapeutic agent.