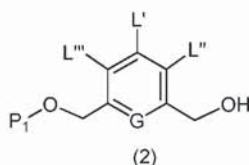
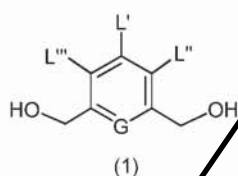


CLAIMS

1. A method of preparing a compound of formula (2),



or a salt thereof, said method comprising introducing an alcohol protecting group onto one of the primary alcohols of a compound of formula (1) by reacting the compound of formula (1) with an alcohol protecting reagent,



wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'' or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -

5 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;
G is selected from -CH- or -N-; and
P₁ is the alcohol protecting group.

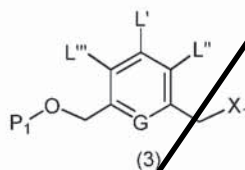
3. The method of claim 1, wherein the alcohol protecting group is sterically hindered.

25 5. The method of claim 4, wherein the alcohol protecting group is methoxymethyl, tetrahydropyranyl, 2-methoxyethoxymethyl, p-methoxybenzyl,

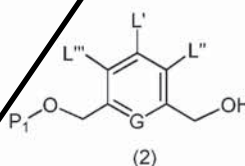
benzyloxymethyl, or 2,2,2-trichloroethoxycarbonyl.

6. The method of claim 5, wherein the alcohol protecting group is 2,2,2-trichloroethoxycarbonyl.
7. The method of claim 1, wherein the alcohol protecting group is a silyl protecting group.
8. The method of claim 7, wherein the silyl protecting group is dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, trimethylsilyl, triisopropylsilyl, tribenzylsilyl, triphenylsilyl, 2-norbornyldimethylsilyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, 2-trimethylethylsilyl (TEOC), or [2-(trimethylsilyl)ethoxy]methyl.
9. The method of claim 8, wherein the silyl protecting group is triethylsilyl, triisopropylsilyl, or *tert*-butyldimethylsilyl.
10. The method of claim 9, wherein the silyl protecting group is *tert*-butyldimethylsilyl.
11. The method of any one of claims 7-10, wherein the silyl protecting group is introduced by reacting the compound of formula (1) with R^3 -Cl, R^3 -Br, R^3 -I or R^3 -OSO₂CF₃ in the presence of a base, wherein R^3 is dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, trimethylsilyl, triisopropylsilyl, tribenzylsilyl, triphenylsilyl, 2-norbornyldimethylsilyl, *tert*-butyldimethylsilyl, or *tert*-butyldiphenylsilyl.
12. The method of claim 11, wherein the base is a non-nucleophilic base.
13. The method of claim 12, wherein the non-nucleophilic base is imidazole, triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, 1,8-diazabicycloundec-7-ene, or tetramethylpiperidine.
14. The method of claim 12, wherein the non-nucleophilic base is imidazole.
15. The method of any one of claims 11-14, wherein the reaction is carried out in the presence of a catalyst.

16. The method of claim 15, wherein the catalyst is 4-dimethylaminopyridine (DMAP), 1,1,3,3-tetramethylguanidine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).
17. The method of any one of claims 1-16, wherein 0.8-1.2, 1-5, 1-2, 1-1.5 or 1-1.2 molar equivalents of the alcohol protecting reagent are used relative to the compound of formula (1).
18. The method of any one of claims 11-17, wherein more than 2 molar equivalents of the non-nucleophilic base are used relative to the compound of formula (1).
19. A method of preparing a compound of formula (3),



or a salt thereof, said method comprising reacting a halogenating reagent, a sulfonating reagent or an esterification reagent with a compound of formula (2),



wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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 -

(CH₂CH₂O)_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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit - (CH₂CH₂O)_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;

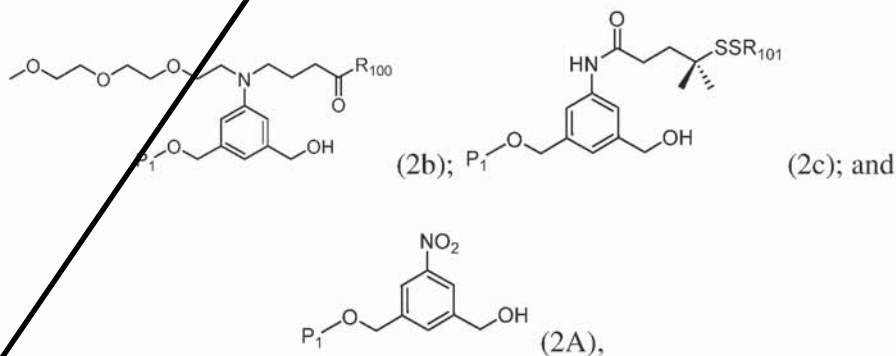
n' is an integer from 1 to 24;

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

P₁ is an alcohol protecting group; and,

X₁ is a leaving group selected from the group consisting of: -Br, -I, -Cl, a sulfonate ester, and an activated ester (preferably, X₁ is -Br, -I, or a sulfonate ester).

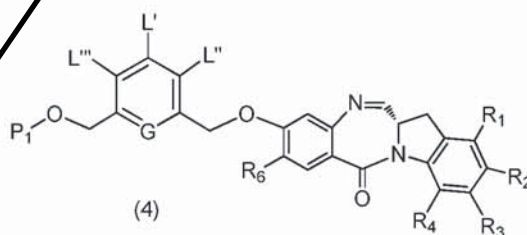
20. The method of claim 19 wherein the compound of formula (2) is represented by a formula selected from the following:



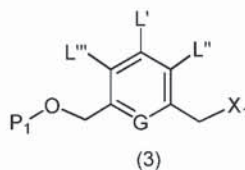
wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

21. The method of claim 19 or 20, wherein the sulfonate ester represented by X₁ is mesylate, tosylate, brosylate, or triflate.

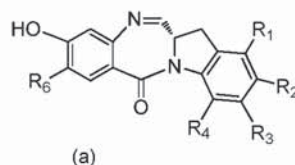
22. The method of claim 21, wherein the sulfonate ester represented by X₁ is mesylate.
23. The method of any one of claims 19-22, wherein the method comprising reacting the compound of formula (2) with a sulfonating reagent in the presence of a non-nucleophilic base.
24. The method of claim 23, wherein the non-nucleophilic base is triethylamine, imidazole, diisopropylethylamine, pyridine, 2,6-lutidine, dimethylformamide, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or tetramethylpiperidine .
25. The method of claim 24, wherein the non-nucleophilic base is triethylamine or diisopropylethylamine.
26. The method of any one of claims 23-25, wherein the sulfonating reagent is methanesulfonic anhydride or methanesulfonyl chloride (MsCl).
27. The method of claim 19 or 20, wherein the method comprising reacting a halogenating reagent with the compound of formula (2) and the halogenating reagent is bromine, hydrobromic acid, carbon tetrabromide, phosphorus tribromide, potassium bromide, hydroiodic acid, iodine, carbon tetraiodide, phosphorus triiodide, sodium iodide, or potassium iodide.
28. A method of preparing a compound of formula (4),



or a salt thereof, said method comprising reacting a compound of formula (3)



with a monomer compound of the formula (a),



wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)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;

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

P₁ is an alcohol protecting group;

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29. The method of claim 28, wherein the compound of formula (3) is represented by a formula selected from the following:

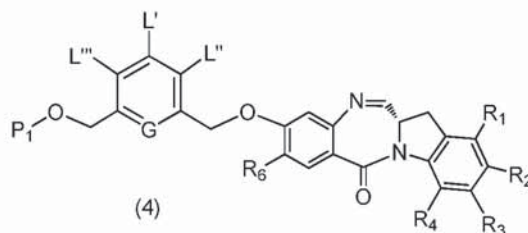


30. The method of claim 28 or 29, wherein the compound of formula (3) is reacted with the monomer compound of formula (a) in the presence of a base.

20



or a salt thereof, said method comprising reacting a compound of formula (4),



with an imine reducing agent, wherein:

5 L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

M is -H or a cation;

15 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;

20 R' and R'' are each independently selected from -H, -OH, -OR, -NHR, -N(R)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;

25 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;

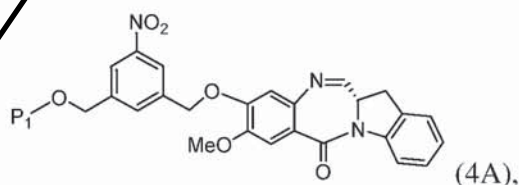
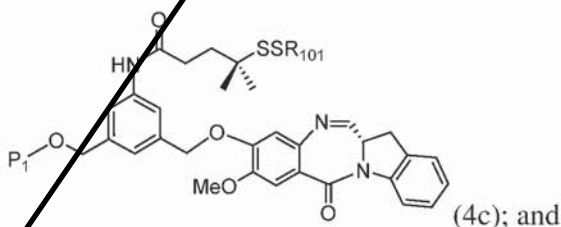
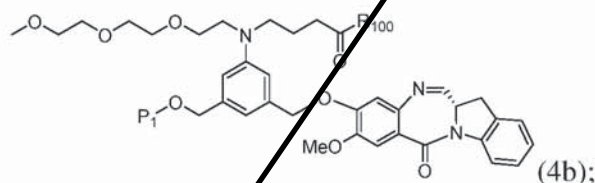
n' is an integer from 1 to 24;

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

P_1 is an alcohol protecting group;

5 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 $-(CH_2CH_2O)_n-R_c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R''; and,
10 R_6 is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen.

33. The method of claim 32, wherein the compound of formula (4) is represented by a formula selected from the following:



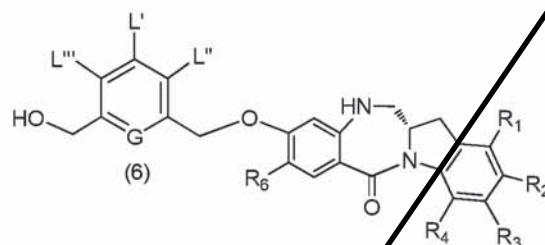
15 wherein R_{100} is a (C₁-C₃)alkoxy; and R_{101} is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

34. The method of claim 32 or 33, wherein the imine reducing reagent is a hydride reducing reagent.

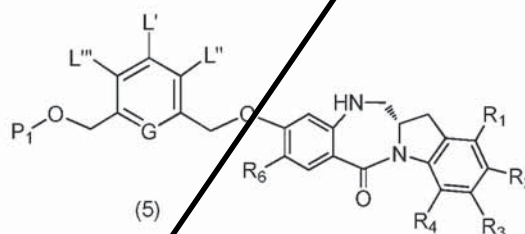
20 35. The method of claim 32 or 33, wherein the imine reducing reagent is sodium borohydride, sodium triacetoxo borohydride, sodium cyanoborohydride, lithium aluminum hydride, hydrogen gas, ammonium formate, borane, 9-

borabicyclo[3.3.1]nonane (9-BBN), diisobutylaluminium hydride (DIBAL), lithium borohydride (LiBH_4), potassium borohydride (KBH_4), or sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al) .

36. The method of claim 35, wherein the imine reducing reagent is sodium triacetox-
 5 borohydride ($\text{NaBH}(\text{OAc})_3$).
37. A method of preparing a compound of formula (6),



or a salt thereof, said method comprising reacting a compound of formula (5),



- 10 with an alcohol deprotecting reagent, wherein:

L' , L'' , and L''' are the same or different, and are independently -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(\text{OCH}_2\text{CH}_2)_n-\text{R}^c$, halogen, guanidinium [$-\text{NH}(\text{C}=\text{NH})\text{NH}_2$], -OR, -NR'R'', -NO₂, -NR'COR'', -
 15 SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L' , L'' , and L''' is the linking group with the reactive group bonded thereto;

20 M is -H or a cation;

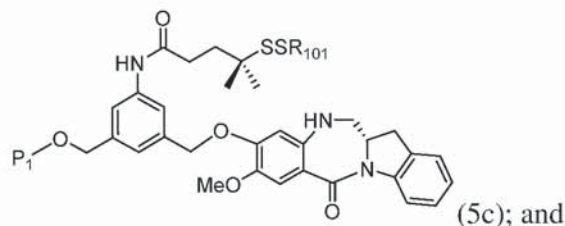
R, for each occurrence, is independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(\text{CH}_2\text{CH}_2\text{O})_n-\text{R}^c$, an optionally substituted aryl having 6 to 18 carbon atoms, an

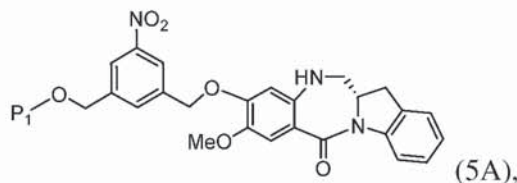
5 R' and R'' are each independently selected from -H, -OH, -OR, -NHR, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit - (CH₂CH₂O)_n - R^c, and an optionally substituted 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms independently selected from O, S, N and P;

n' is an integer from 1 to 24;

P_1 is an alcohol protecting group,

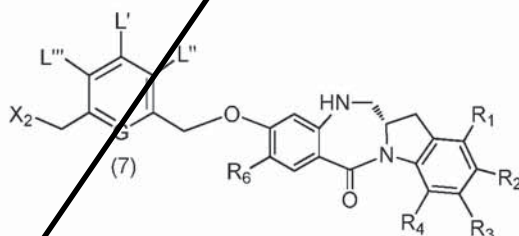
R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen.

COC(=O)CCCCN(CCCOCCOCCOCCOC)Cc1ccc(COc2c3c(c4ccccc4n3C(=O)c2c5c(c1)cc(OC)cc5)O)cc1 (5b)

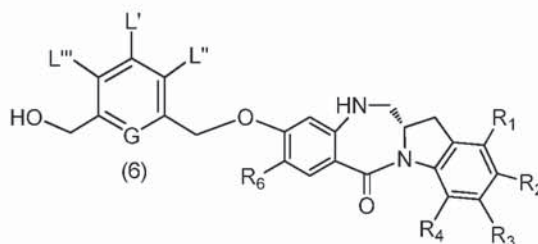


wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

39. The method of claim 37 or 38, wherein the alcohol deprotecting reagent is tetra-
 5 n-butylammonium fluoride, tris(dimethylamino)sulfonium difluorotrimethylsilicate, hydrogen fluoride or a solvate thereof, hydrogen fluoride pyridine, silicon tetrafluoride, hexafluoroantimonic acid, cesium fluoride, hydrochloric acid, acetic acid, trifluoroacetic acid, pyridinium p-toluenesulfonate, p-toluenesulfonic acid (p-TsOH), formic acid, periodic acid.
- 10 40. The method of claim 39, wherein the alcohol deprotecting reagent is hydrochloric acid or tetra-n-butylammonium fluoride.
41. A method of preparing a compound of formula (7),



- 15 or a salt thereof, said method comprising reacting a halogenating reagent, a sulfonating reagent or an esterification reagent with the primary alcohol compound of formula (6),



wherein:

L', L'', and L''' are the same or different, and are independently -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(OCH₂CH₂)_n-R^c,

halogen, guanidinium [$-\text{NH}(\text{C}=\text{NH})\text{NH}_2$], $-\text{OR}$, $-\text{NR}'\text{R}''$, $-\text{NO}_2$, $-\text{NR}'\text{COR}''$, $-\text{SR}$, $-\text{SOR}'$, $-\text{SO}_2\text{R}'$, $-\text{SO}_3\text{M}$, $-\text{OSO}_3\text{M}$, $-\text{SO}_2\text{NR}'\text{R}''$, cyano, an azido, $-\text{COR}'$, $-\text{OCOR}'$, $-\text{OCONR}'\text{R}''$, or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L' , L'' , and L''' is the linking group with the reactive group bonded thereto;

M is $-\text{H}$ or a cation;

R , for each occurrence, is independently selected from the group consisting of $-\text{H}$, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(\text{CH}_2\text{CH}_2\text{O})_n-\text{R}^c$, 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 $-\text{H}$, $-\text{OH}$, $-\text{OR}$, $-\text{NHR}$, $-\text{N}(\text{R})_2$, $-\text{COR}$, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(\text{CH}_2\text{CH}_2\text{O})_n-\text{R}^c$, 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 $-\text{H}$ 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;

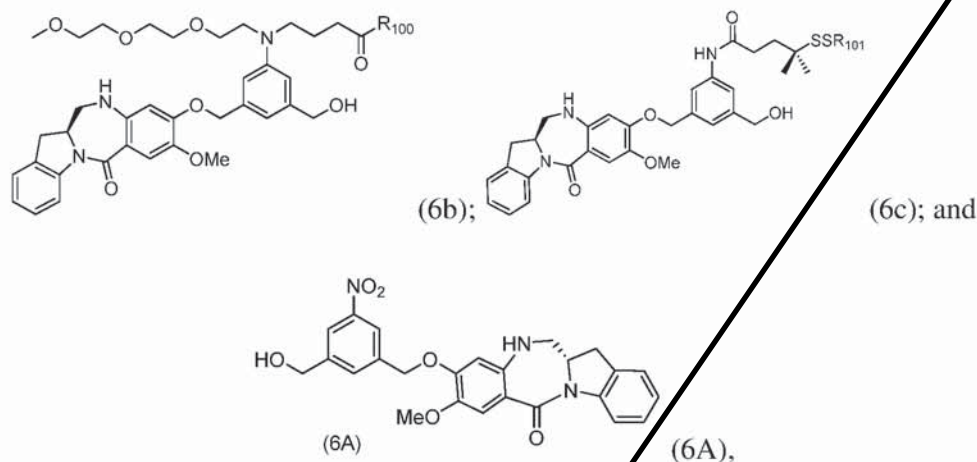
G is selected from $-\text{CH}-$ or $-\text{N}-$;

R_1 , R_2 , R_3 , and R_4 are each independently selected from the group consisting of $-\text{H}$, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(\text{CH}_2\text{CH}_2\text{O})_n-\text{R}^c$, halogen, guanidinium [$-\text{NH}(\text{C}=\text{NH})\text{NH}_2$], $-\text{OR}$, $-\text{NR}'\text{R}''$, $-\text{NO}_2$, $-\text{NCO}$, $-\text{NR}'\text{COR}''$, $-\text{SR}$, $-\text{SOR}'$, $-\text{SO}_2\text{R}'$, $-\text{SO}_3\text{H}$, $-\text{OSO}_3\text{H}$, $-\text{SO}_2\text{NR}'\text{R}''$, cyano, an azido, $-\text{COR}'$, $-\text{OCOR}'$, and $-\text{OCONR}'\text{R}''$;

R_6 is $-\text{H}$, $-\text{R}$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}'\text{R}''$, $-\text{NO}_2$, or halogen; and,

X_2 is a leaving group selected from the group consisting of: $-\text{Br}$, $-\text{I}$, $-\text{Cl}$, a sulfonate ester, and an activated ester (preferably, X_2 is $-\text{Br}$, $-\text{I}$, a sulfonate ester).

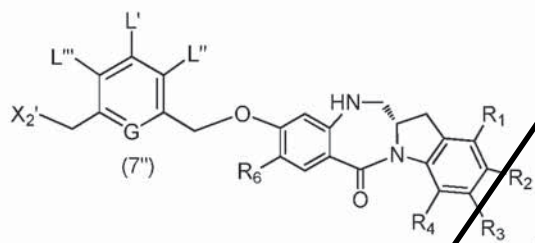
42. The method of claim 41, wherein the compound of formula (6) is represented by a formula selected from the following:



- 5 wherein R_{100} is a (C₁-C₃)alkoxy; and R_{101} is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).
43. The method of claim 41 or 42, wherein the sulfonate ester represented by X_2 is mesylate, tosylate, brosylate, or triflate.
44. The method of claim 43, wherein the sulfonate ester represented by X_2 is
10 mesylate.
45. The method of any one of claims 41-44, wherein the method comprising reacting the compound of formula (6) with the sulfonating reagent in the presence of a non-nucleophilic base.
46. The method of claim 45, wherein the non-nucleophilic base is triethylamine,
15 imidazole, triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or tetramethylpiperidine.
47. The method of claim 45, wherein the non-nucleophilic base is triethylamine or diisopropylethylamine.
48. The method of any one of claims 41-47, wherein the sulfonating reagent is
20 methanesulfonic anhydride or methanesulfonyl chloride (MsCl).
49. The method of claim 41 or 42, wherein the method comprising reacting the compound of formula (6) with a halogenating reagent, wherein the halogenating

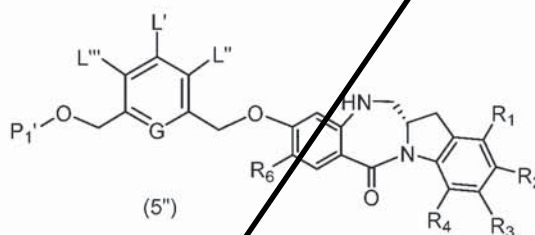
reagent is bromine, hydrobromic acid, carbon tetrabromide, phosphorus tribromide, potassium bromide, hydroiodic acid, iodine, carbon tetraiodide, phosphorus triiodide, sodium iodide, or potassium iodide.

50. A method of preparing a compound of formula (7'')



5

or a salt thereof, said method comprising reacting a compound of formula (5'')



with an alcohol deprotecting reagent and a halogenating reagent, wherein:

10 L' , L'' , and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L' , L'' , and L''' is the linking group with the reactive group bonded thereto;

15

M is -H or a cation;

20

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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -
(CH₂CH₂O)_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;

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

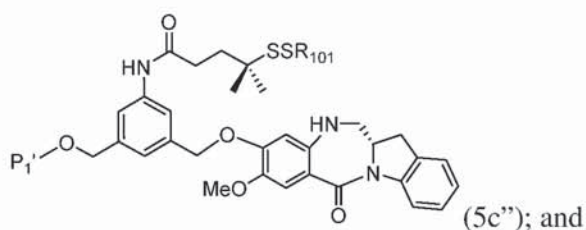
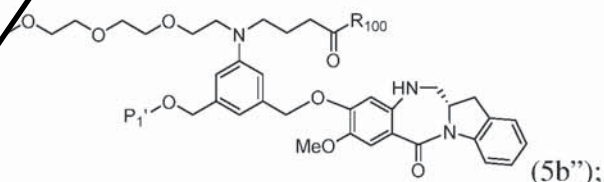
P₁' is an acid labile alcohol protecting group;

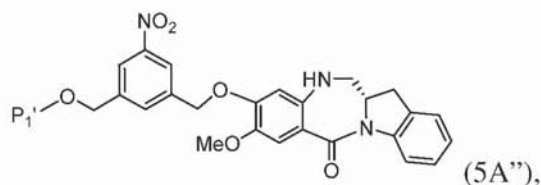
X₂' is -Br or -I;

R₁, R₂, R₃, and R₄ 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 -(CH₂CH₂O)_n-R_c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R''; and

R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen.

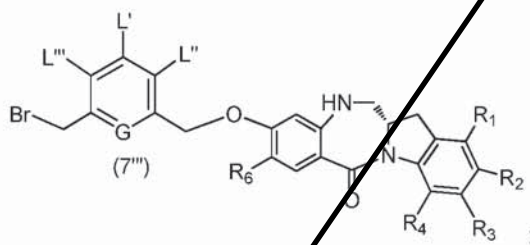
51. The method of claim 50, wherein the compound of formula (5'') is represented by a formula selected from the following:





wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

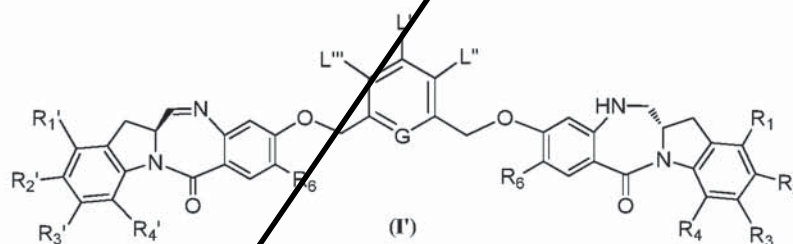
52. The method of claim 51, wherein the compound of formula (7''') is represented by the following:



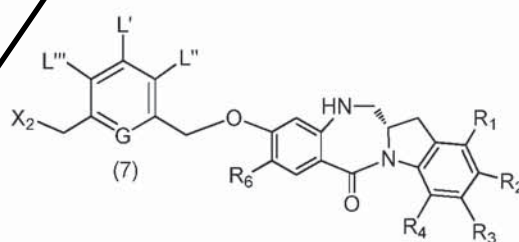
and the method comprising reacting the compound of formula (5'') with an alcohol deprotecting reagent and a bromination reagent.

53. The method of claim 50, 51 or 52, wherein the acid labile alcohol protecting group is acetate, allyl, methoxymethyl, tetrahydrofuranyl, tetrahydropyranyl, 5-dibenzosuberyl, 1-ethoxymethyl, 1-methyl-1-methoxyethyl, 2-(phenylselenyl)ethyl, trityl/triphenylmethyl, or tris(4-*tert*-butylphenyl)methyl.
54. The method of claim 53, wherein the acid labile alcohol protecting group is a silyl protecting group.
55. The method of claim 54, wherein the silyl protecting group is dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, tribenzylsilyl, triphenylsilyl, 2-norbornyldimethylsilyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, 2-trimethylethylsilyl (TEOC), or [2-(trimethylsilyl)ethoxy]methyl.
56. The method of claim 54, wherein the silyl protecting group is triethylsilyl, triisopropylsilyl, or *tert*-butyldimethylsilyl.
57. The method of claim 54, wherein the silyl protecting group is *tert*-butyldimethylsilyl.

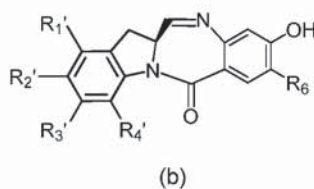
58. The method of any one of claims 50-57, wherein the alcohol deprotecting reagent is tetra-n-butylammonium fluoride, tris(dimethylamino)sulfonium difluorotrimethylsilicate, hydrogen fluoride or a solvate thereof, hydrogen fluoride pyridine, silicon tetrafluoride, hexafluorosilicic acid, cesium fluoride, hydrochloric acid, acetic acid, pyridinium p-toluenesulfonate, formic acid, periodic acid, trifluoroacetic acid, or p-toluenesulfonic acid (p-TsOH).
59. The method of claim 58, wherein the alcohol deprotecting reagent is acetic acid.
60. The method of any one of claims 50-59, wherein the bromination reagent is HBr.
61. The method of any one of claims 50-57, wherein the compound of formula (5'') is reacted with a mixture of acetic acid and HBr.
62. A method of preparing a compound of formula (I'),



or a pharmaceutically acceptable salt thereof, said method comprising reacting a compound of formula (7)



with a monomer compound of the formula (b),



wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)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;

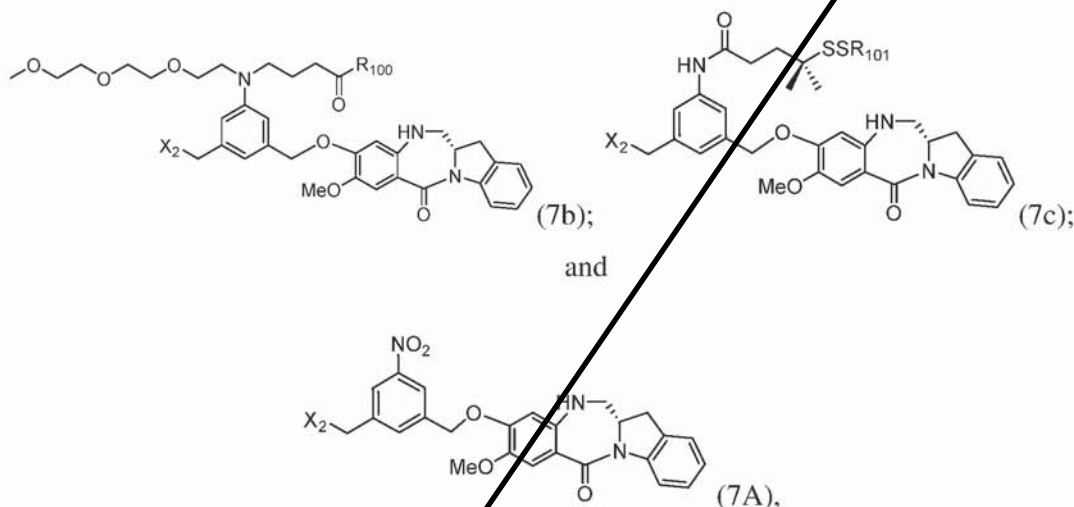
G is selected from -CH- or -N-;

R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' 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 $-(CH_2CH_2O)_n-R^c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

R_6 is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen; and,

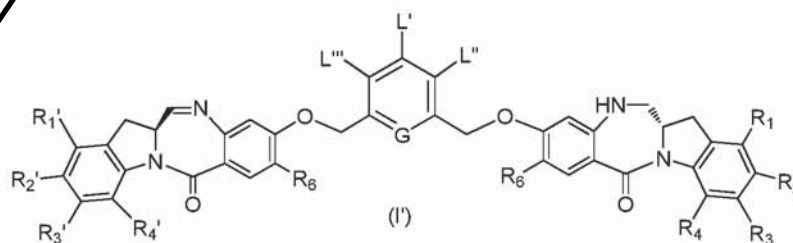
X_2 is a leaving group selected from the group consisting of: -Br, -I, -Cl, a sulfonate ester and an activated ester (preferably, X_2 is -Br, -I, or a sulfonate ester).

- 5 63. The method of claim 62, wherein the compound of formula (7) is represented by a formula selected from the following:



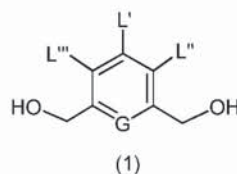
- 10 wherein R_{100} is a (C₁-C₃)alkoxy; and R_{101} is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

64. The method of claim 62 or 63, wherein the compound of formula (7) is reacted with the monomer compound of formula (b) in the presence of a base.
65. The method of claim 64, wherein the base is sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, or potassium hydride.
- 15 66. A method of preparing a compound of formula (I'),

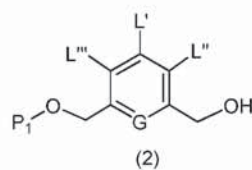


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

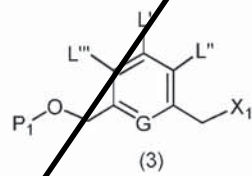
(1) introducing an alcohol protecting group onto one of the primary alcohols of a compound of formula (1),



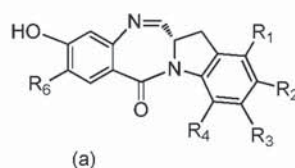
to form a compound of formula (2),



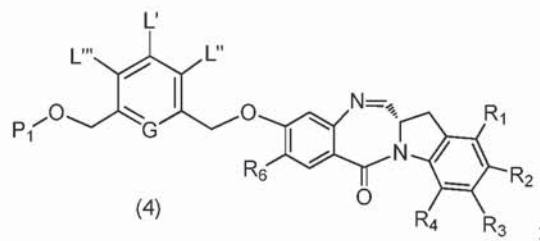
(2) reacting the compound of formula (2) with a halogenating reagent, a sulfonating reagent or an esterification reagent to form a compound of formula (3),



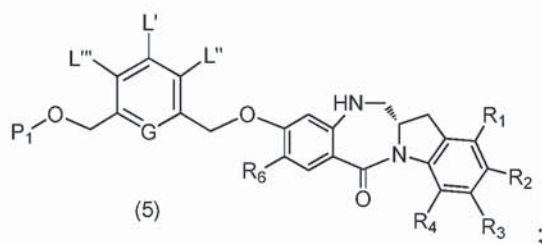
(3) reacting the compound of formula (3) with a monomer compound of the formula (a),



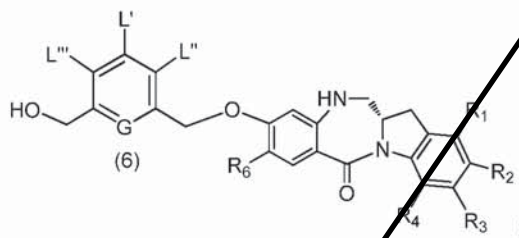
to form a compound of formula (4),



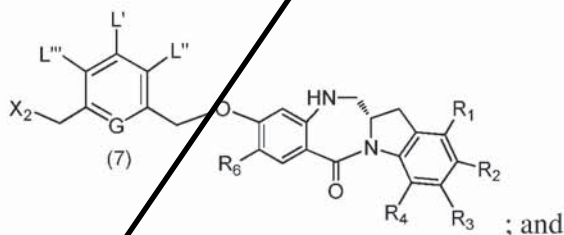
(4) reacting the compound of formula (4) with an imine reducing agent to form a compound of formula (5),



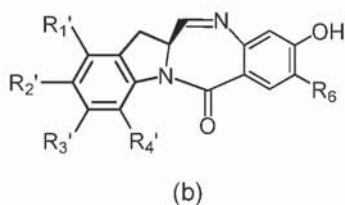
(5) reacting the compound of formula (5) with an alcohol deprotecting reagent to form a compound of formula (6),



5 (6) reacting the compound of formula (6) with a second halogenating reagent, a second sulfonating reagent or a second esterification reagent to form a compound of formula (7),



10 (7) reacting the compound of formula (7) with a monomer compound of the formula (b),



to form the compound of formula (I'); wherein:

15 L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent

(CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

M is -H or a cation;

5 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 - (CH₂CH₂O)_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
10 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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -
15 (CH₂CH₂O)_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;

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

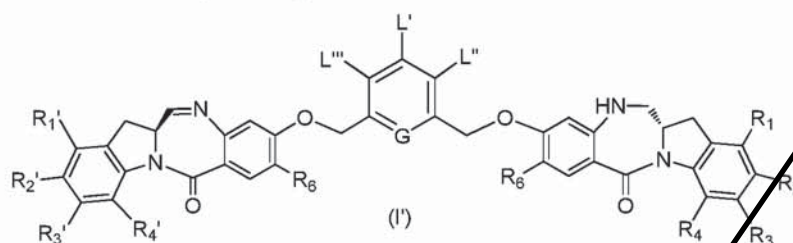
R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit (CH₂CH₂O)_n-R^c, halogen, guanidinium [-NH(C=NH)NH₂], -OR,
25 -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

P₁ is an alcohol protecting group; and,

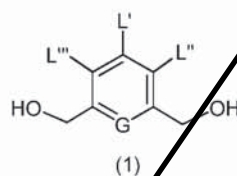
X₁ and X₂ are each independently a leaving group selected from the group
30 consisting of: -Br, -I, -Cl, a sulfonate ester and an activated ester (preferably, X₁ and X₂ are each independently -Br, -I, or a sulfonate ester) .

67. A method of forming a compound of formula (I'),

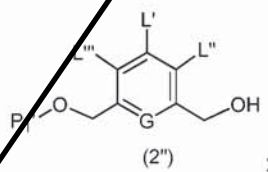


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

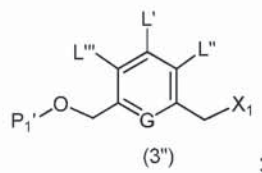
5 (1) introducing an alcohol protecting group onto one of the primary alcohols of a compound of formula (1),



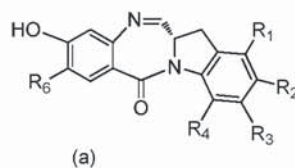
to form a compound of formula (2'')



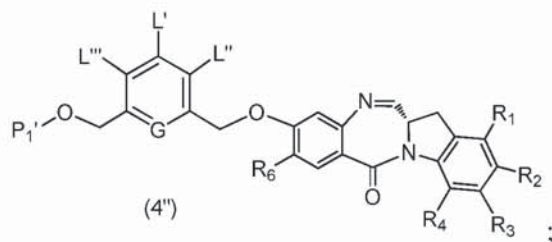
10 (2) reacting the compound of formula (2'') with a halogenating reagent, a sulfonating reagent or an esterification reagent to form a compound of formula (3''),



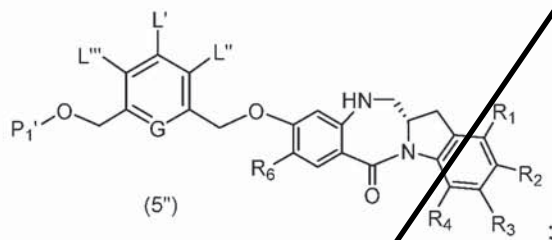
15 (3) reacting the compound of formula (3'') with a monomer compound of the formula (a),



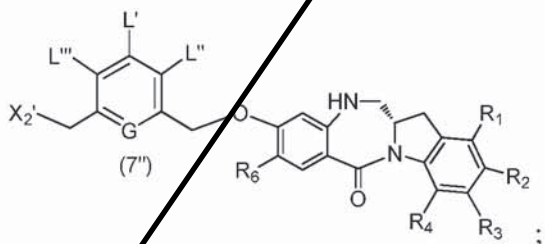
to form a compound of formula (4''),



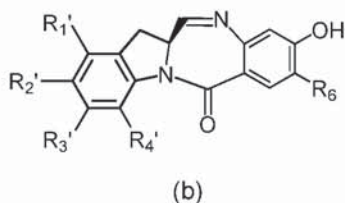
(4) reacting the compound of formula (4'') with an imine reducing agent to form a compound of formula (5''),



5 (5) reacting the compound of formula (5'') with an alcohol deprotecting reagent and a halogenating reagent to form a compound of formula (7''),



(6) reacting a compound of formula (7'') with a monomer compound of the formula (b),



10 to form the compound of formula (I'), wherein:

15 L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -CONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent

(CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

M is -H or a cation;

5 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 - (CH₂CH₂O)_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
10 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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -
15 (CH₂CH₂O)_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;

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

R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' 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 (CH₂CH₂O)_n-R^c, halogen, guanidinium [-NH(C=NH)NH₂], -OR,
25 -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

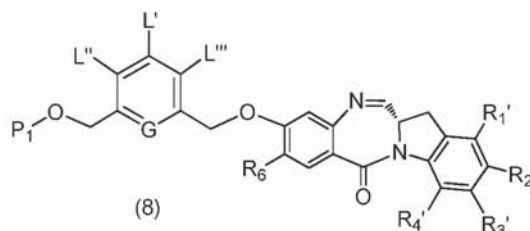
R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

P₁' is an acid labile alcohol protecting group;

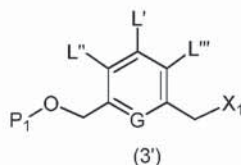
30 X₁ is a leaving group selected from the group consisting of: -Br, -I, -Cl, a sulfonate ester and an activated ester (preferably, -Br, -I, a sulfonate ester); and

X₂' is -Br or -I.

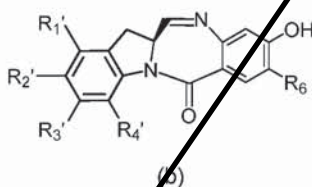
68. A method of preparing a compound of formula (8),



or a salt thereof, said method comprising reacting a compound of formula (3')



5 with a monomer compound of the formula (b),



wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -
(CH₂CH₂O)_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;

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

P₁ is an alcohol protecting group;

X₁ is a leaving group selected from the group consisting of: -Br, -I, and a sulfonate ester;

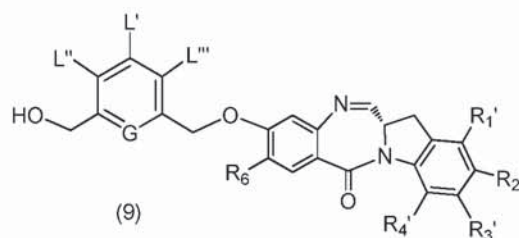
R₁', R₂', R₃', and R₄' are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(CH₂CH₂O)_n-R_c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R''; and,

R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen.

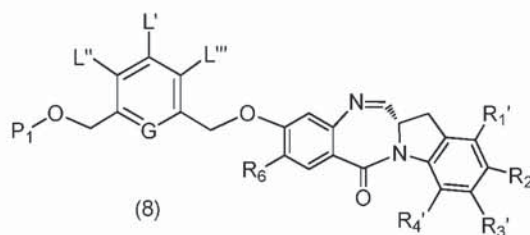
69. The method of claim 68, wherein the compound of formula (8) is reacted with the monomer compound of formula (b) in the presence of a base.

70. The method of claim 69, wherein the base is sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, or potassium hydride.

71. A method of preparing a compound of formula (9),



or a salt thereof, said method comprising reacting a compound of formula (8),



with an alcohol deprotecting reagent; wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)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;

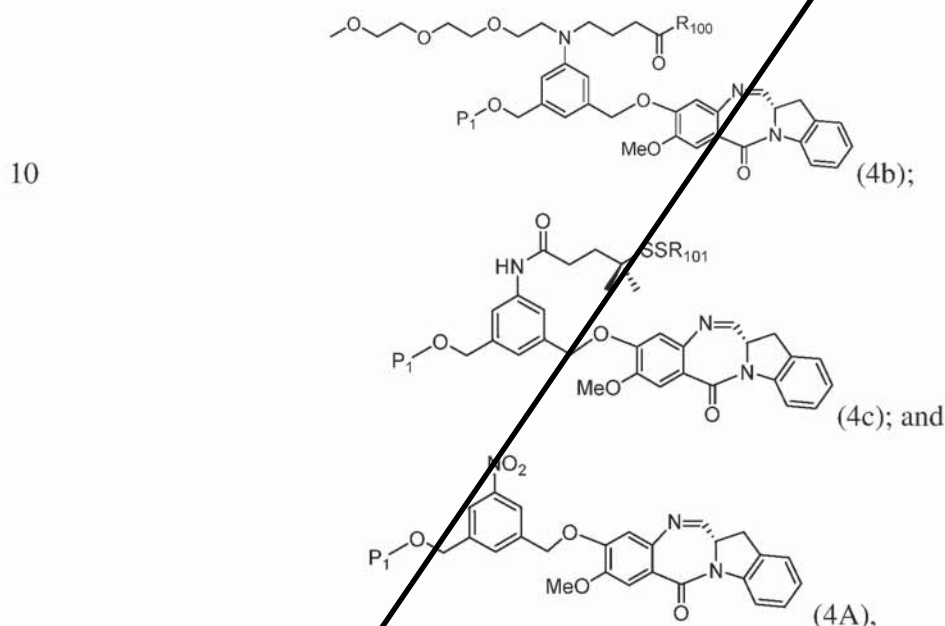
n' is an integer from 1 to 24;

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

P₁ is an alcohol protecting group;

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 $-(CH_2CH_2O)_n-R_c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, $-NR'R''$,
 5 -NO₂, -NCO, $-NR'COR''$, -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R''; and,
 R_6 is -H, -R, -OR, -SR, $-NR'R''$, -NO₂, or halogen.

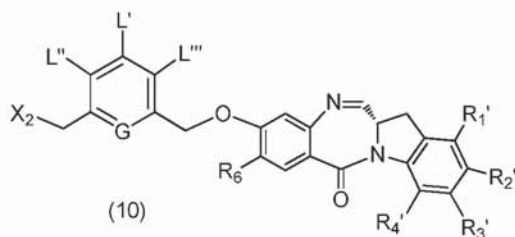
72. The method of claim 71, wherein the compound of formula (8) is represented by a formula selected from the following:



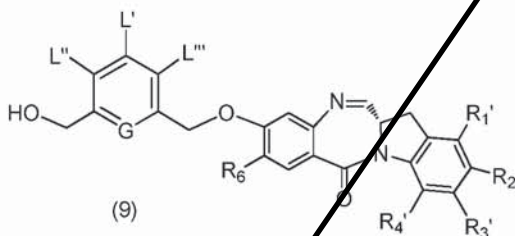
wherein R_{100} is a (C₁-C₃)alkoxy; and R_{101} is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

- 15 73. The method of claim 71 or 72, wherein the alcohol deprotecting reagent is tetra-n-butylammonium fluoride, tris(dimethylamino)sulfonium difluorotrimethylsilicate, hydrogen fluoride or a solvate thereof, hydrogen fluoride pyridine, silicon tetrafluoride, hexafluorosilicic acid, cesium fluoride, hydrochloric acid, acetic acid, pyridinium p-toluenesulfonate, formic acid,
 20 periodic acid, trifluoroacetic acid, or p-toluenesulfonic acid (p-TsOH).
74. The method of claim 73, wherein the alcohol deprotecting reagent is hydrochloric acid or tetra-n-butylammonium fluoride.

75. A method of preparing a compound of formula (10),



or a salt thereof, said method comprising reacting a halogenating reagent, a sulfonating reagent or an esterification reagent with the compound of formula (9),



wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(CH₂CH₂O)_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;

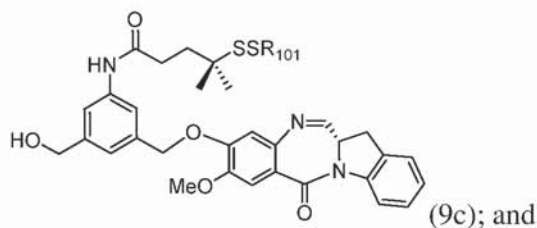
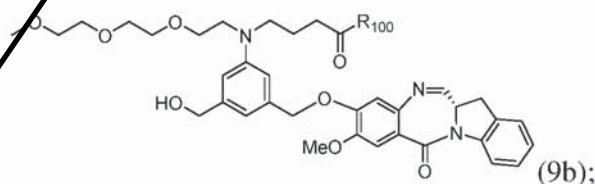
G is selected from -CH- or -N-;

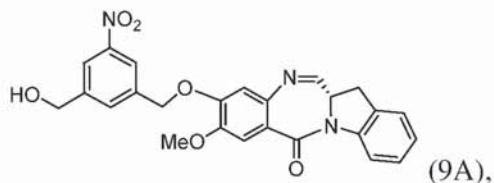
R₁', R₂', R₃', and R₄' are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(CH₂CH₂O)_n-R_c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen; and,

X₂ is a leaving group selected from the group consisting of -Br, -I, -Cl, a sulfonate ester, and an activated ester (preferably, X₂ is -Br, -I, or a sulfonate ester).

76. The method of claim 75, wherein the compound of formula (9) is represented by a formula selected from the following:

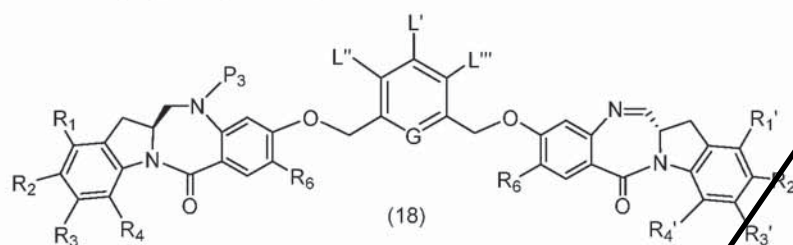




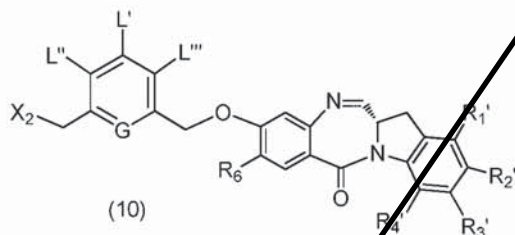
wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

77. The method of claim 75 or 76, wherein the sulfonate ester represented by X₂ is mesylate, tosylate, brosylate, or triflate.
78. The method of claim 77, wherein the sulfonate ester represented by X₂ is mesylate.
79. The method of any one of claims 75-78, wherein the method comprising reacting the compound of formula (6) with the sulfonating reagent in the presence of a non-nucleophilic base.
80. The method of claim 79, wherein the non-nucleophilic base is triethylamine, imidazole, triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or tetramethylpiperidine.
81. The method of claim 79, wherein the non-nucleophilic base is triethylamine or diisopropylethylamine.
82. The method of any one of claims 75-81, wherein the sulfonating reagent is methanesulfonic anhydride or methanesulfonyl chloride.
83. The method of claim 75 or 76, wherein the method comprising reacting the compound of formula (6) with a halogenating reagent and the halogenating reagent is bromine, hydrobromic acid, carbon tetrabromide, phosphorus tribromide, potassium bromide, hydroiodic acid, iodine, carbon tetraiodide, phosphorus triiodide, sodium iodide, or potassium iodide.

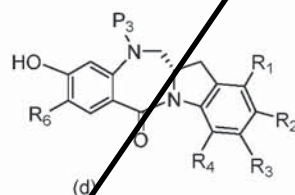
84. A method of preparing a compound of formula (18),



or a salt thereof, said method comprising reacting a compound of formula (10)



5 with a monomer compound of the formula (d),



wherein:

10 L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -CONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the

15 reactive group bonded thereto;

M is -H or a cation;

20 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;

5 R' and R'' are each independently selected from -H, -OH, -OR, -NHR, - $N(R)_2$, -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;

10 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;

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

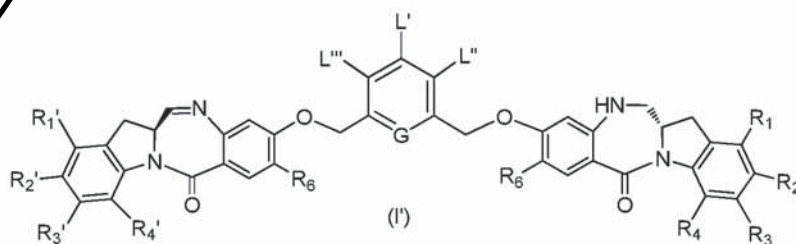
15 $R_1, R_2, R_3, R_4, R_1', R_2', R_3',$ and R_4' are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R^c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

20 R_6 is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

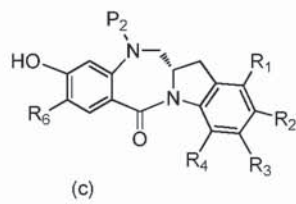
X_2 is a leaving group selected from the group consisting of: -Br, -I, -Cl, a sulfonate ester, and an activated ester (preferably, X_2 is -Br, -I, or a sulfonate ester) ; and,

P_3 is H or P_2 ; and P_2 is an amine protecting group.

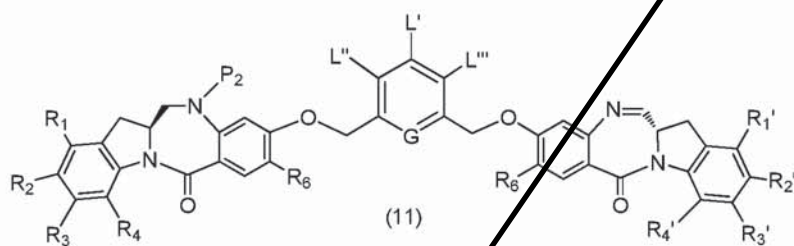
85. 25 The method of claim 84, wherein P_3 is H and the compound of (10) is reacted with the monomer compound of (d) to form a compound of (I'):



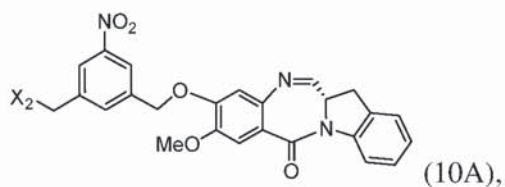
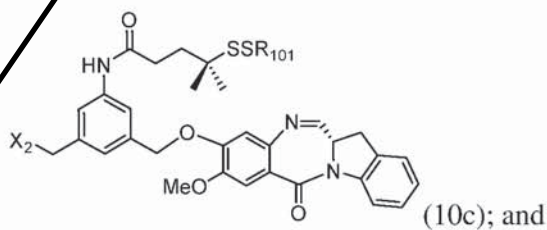
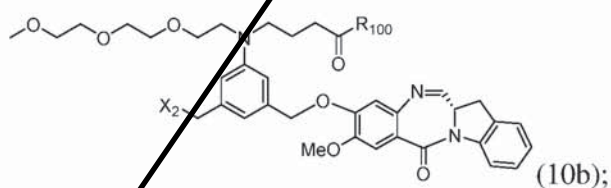
86. The method of claim 84, wherein P_3 is P_2 ; the monomer compound is represented by formula (c):



and the compound of formula (18) is represented by formula (11),



87. The method of claim 84-86, wherein the compound of formula (10) is represented by a formula selected from the following:



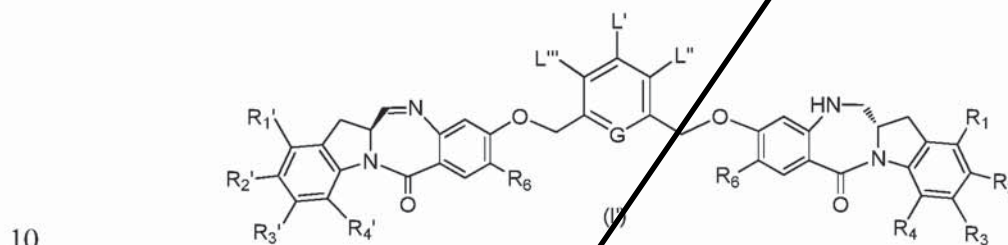
wherein R_{100} is a (C_1-C_3) alkoxy; and R_{101} is a (C_1-C_3) alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

88. The method of claim 84-87, wherein the compound of formula (10) is reacted with the monomer compound of formula (d) in the presence of a base.

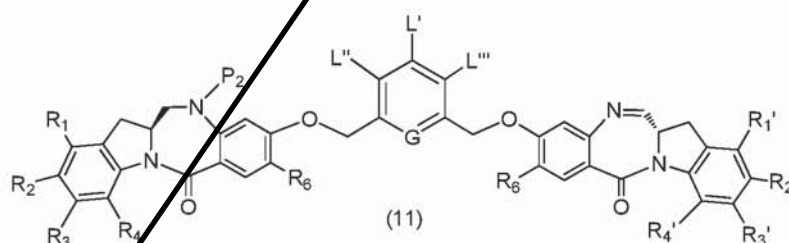
89. The method of claim 88, wherein the base is sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, or potassium hydride.

5 90. The method of any one of claims 84-89, wherein the amine protecting group is 2-trimethylsilylethyl, (2-phenyl-2-trimethylsilyl)ethyl, triisopropylsiloxy, 2-(trimethylsilyl)ethoxymethyl, allyloxycarbonyl, 9-fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, or 2, 2,2,2-trichloroethoxycarbonyl

91. A method of preparing a compound of formula (I'),



or a pharmaceutically acceptable salt thereof, said method comprising reacting a compound of formula (11),



with an amine deprotecting reagent; wherein:

15 L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

20

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 -
 5 (CH₂CH₂O)_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, -
 10 N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit - (CH₂CH₂O)_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
 15 1 to 4 carbon atoms, or the linking group with the reactive group bonded thereto;
 n' is an integer from 1 to 24;

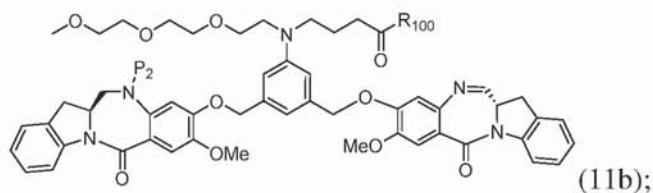
G is selected from -CH- or -N-;

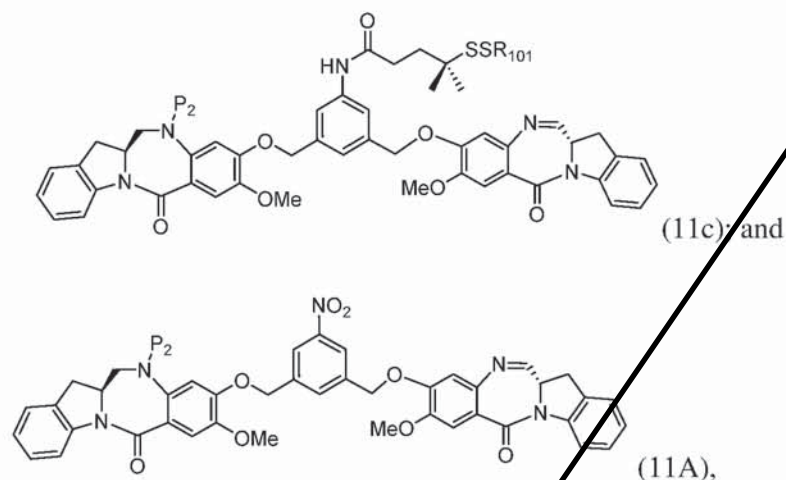
R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' are each independently selected from
 20 the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(CH₂CH₂O)_n-R^c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen; and,

25 P₂ is an amine protecting group.

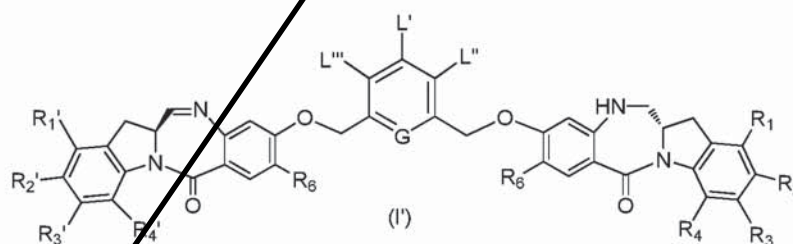
92. The method of claim 91, wherein the compound of formula (11) is represented by a formula selected from the following:



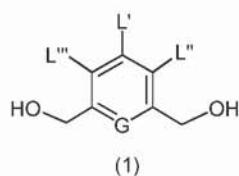


wherein R_{100} is a (C_1-C_3) alkoxy; and R_{101} is a (C_1-C_3) alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

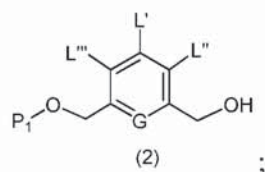
- 5 93. The method of claim 92, wherein the amine deprotecting reagent is tetra-*n*-butylammonium fluoride, acetic acid, hydrogen fluoride pyridine, cesium fluoride, piperidine, morpholine, or trifluoroacetic acid.
94. A method of preparing a compound of formula (I'),



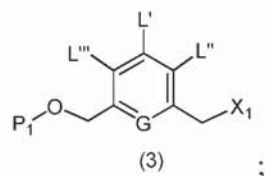
- 10 or a pharmaceutically acceptable salt thereof, said method comprising the steps of:
- (1) introducing an alcohol protecting group onto one of the primary alcohols of the compound of formula (1),



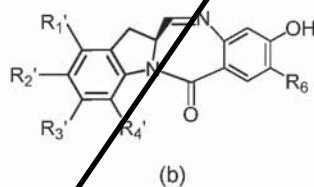
- 15 to form a compound of formula (2),



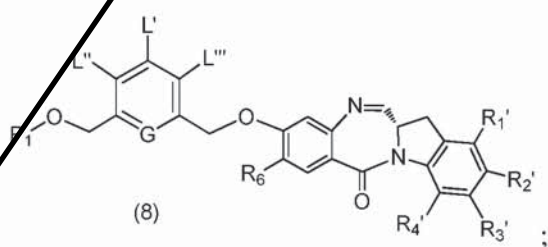
(2) reacting a halogenating reagent, a sulfonating reagent or an esterification reagent with the compound of formula (2) to form a compound of formula (3),



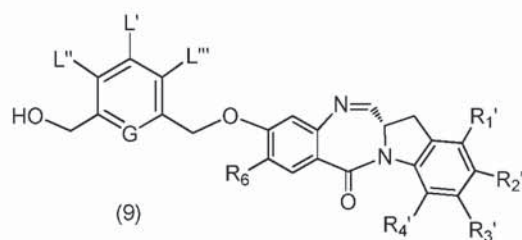
5 (3) reacting the compound of formula (3) with a monomer compound of the formula (b),



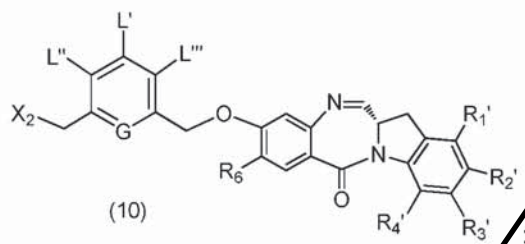
to form a compound of formula (8),



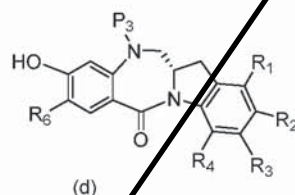
10 (4) reacting the compound of formula (8) with an alcohol deprotecting reagent to form a compound of formula (9),



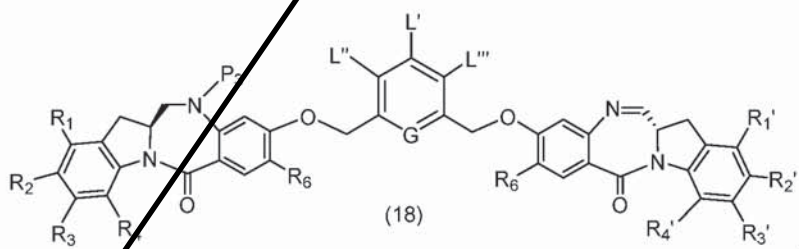
(5) reacting a second halogenating reagent, a second sulfonating reagent or a second esterification reagent with the compound of formula (9) to form a compound of formula (10),



5 (6) reacting the compound of formula (10) with a monomer compound of the formula (d)



to form a compound of formula (18),



10 (7) when P_3 is an amine protecting group; reacting the compound of formula (18) with an amine deprotecting reagent to form the compound of formula (I'), wherein:

15 L' , L'' , and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent

(CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

M is -H or a cation;

5 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 - (CH₂CH₂O)_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
10 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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -
15 (CH₂CH₂O)_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;

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

R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' 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 (CH₂CH₂O)_n-R^c, halogen, guanidinium [-NH(C=NH)NH₂], -OR,
25 -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

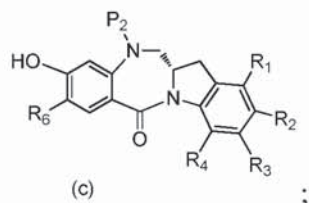
R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

P₃ is H or an amine protecting group;

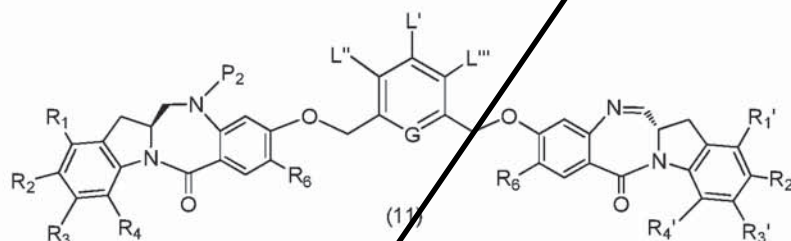
P₁ is an alcohol protecting group; and

30 X₁ and X₂ are each independently a leaving group selected from the group consisting of: -Br, -I, -Cl, a sulfonate ester, and an activated ester (preferably, -Br, -I, a sulfonate ester).

95. The method of claim 94, wherein P₃ is H and the compound of (10) is reacted with the monomer compound of (d) to form a compound of (I').
96. The method of claim 94, wherein P₃ is P₂; the monomer compound is represented by formula (c):



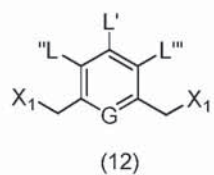
and the compound of formula (18) is represented by formula (11),



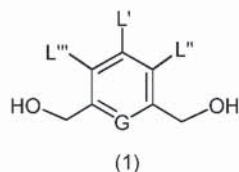
wherein:

P₂ is an amine protecting group;

97. A method of preparing a compound of formula (12),

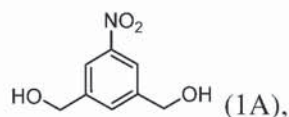


or a salt thereof, said method comprising reacting a compound of formula (1),



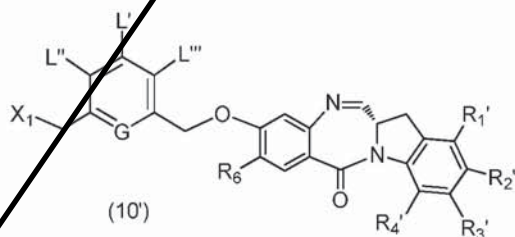
with a halogenating reagent, a sulfonating reagent, or an esterification reagent, wherein:

L', L'', and L''' are the same or different, and are independently -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(OCH₂CH₂)_n-R^c,

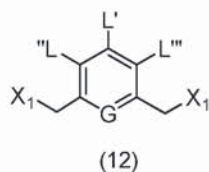


wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

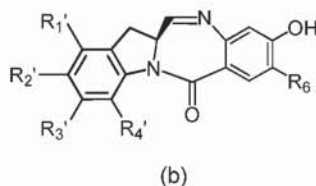
99. The method of claim 97 or 98, wherein X₁ is -Br or -I.
- 5 100. The method of any one of claims 97-99, wherein the halogenating reagent reacts with the primary alcohols of the compound of formula (1) in the presence of an alcohol activating agent.
101. The method of claim 100, wherein the alcohol activating agent is thionyl chloride.
- 10 102. The method of any one of claims 97-101, wherein the halogenating reagent is lithium bromide, sodium bromide, potassium bromide, potassium iodide, or sodium iodide.
103. A method of preparing a compound of formula (10'),



- 15 or a salt thereof, said method comprising reacting a compound of formula (12),



with a monomer compound of the formula (b),



wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)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;

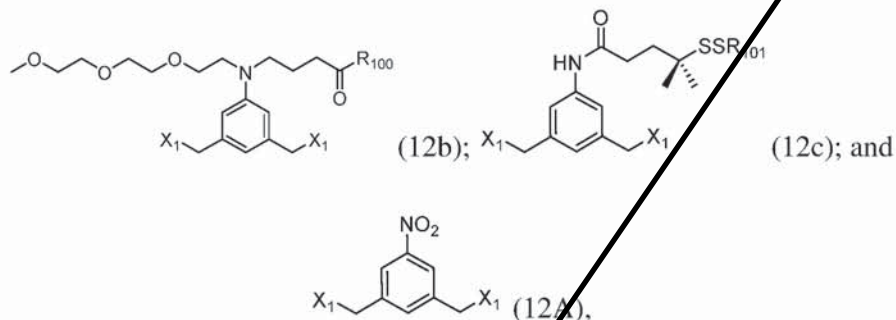
G is selected from -CH- or -N-;

X₁ is -Br, -I, -Cl, a sulfonate ester, or an activated ester (preferably, X₁ is -Br, -I, or a sulfonate ester)

R₁', R₂', R₃', and R₄' 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 $-(CH_2CH_2O)_n-R_c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'',

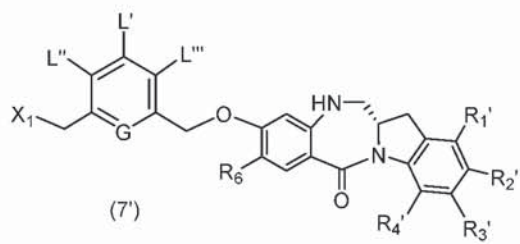
-NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R''; and, R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen.

104. The method of claim 103, wherein the compound of formula (12) is represented by a formula selected from the following:

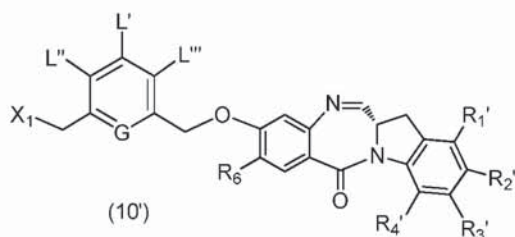


wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (e.g., 4-nitropyridyl).

105. The method of claim 103 or 104, wherein the compound of formula (12) is reacted with the monomer compound of formula (b) in the presence of a base.
106. The method of claim 105, wherein the base is sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, or potassium hydride.
107. The method of any one of claims 103-106, wherein excess molar equivalent of the compound of formula (12) relative to the monomer compound of formula (b) is used.
108. A method of preparing a compound of formula (7'),



or a salt thereof, said method comprising reacting a compound of formula (10'),



or a salt thereof, with an imine reducing agent,

wherein:

X₁ is -Br, -I, -Cl, a sulfonate ester, or an activated ester (preferably, X₁ is -Br, -I, a sulfonate ester);

L', L'', and L''' are the same or different, and are independently -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(OCH₂CH₂)_n-R^c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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 -(CH₂CH₂O)_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;

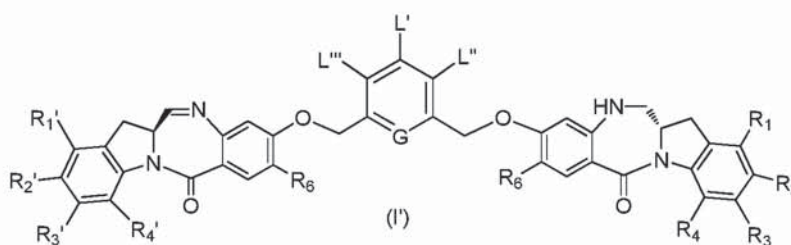
R' and R'' are each independently selected from -H, -OH, -OR, -NHR, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(CH₂CH₂O)_n-R^c, and an optionally substituted 3- to 18-membered heterocyclic 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;

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

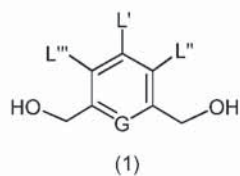
- 5 R_1, R_2, R_3 , and R_4 are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R_c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, 10 -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R''; and R_6 is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen.

109. The method of claim 108, wherein the imine reducing reagent is a hydride reducing reagent.
110. The method of claim 108, wherein the imine reducing reagent is sodium 15 borohydride, sodium triacetoxo borohydride, sodium cyanoborohydride, lithium aluminum hydride, hydrogen gas, ammonium formate, borane, 9-borabicyclo[3.3.1]nonane (9-BBN), diisobutylaluminium hydride (DIBAL), lithium borohydride (LiBH₄), potassium borohydride (KBH₄), or sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al) .
- 20 111. The method of claim 110, wherein the imine reducing reagent is sodium triacetoxo borohydride (NaBH(OAc)₃).
112. The method of any one of claims 108-111, wherein X₁ is mesylate.
113. A method of preparing a compound of formula (I'),

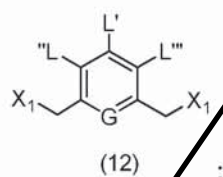


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

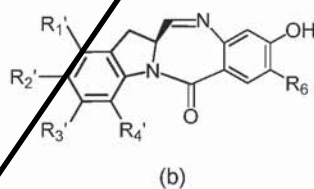
(1) reacting a halogenating reagent, a sulfonating reagent or an esterification reagent with a compound of formula (1),



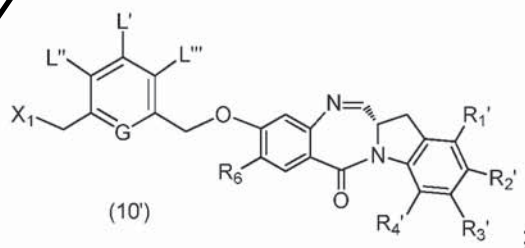
to form a compound of formula (12),



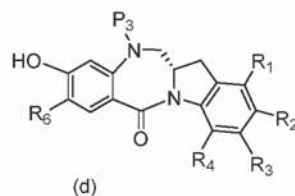
(2) reacting the compound of formula (12) with a monomer compound of the formula (b),



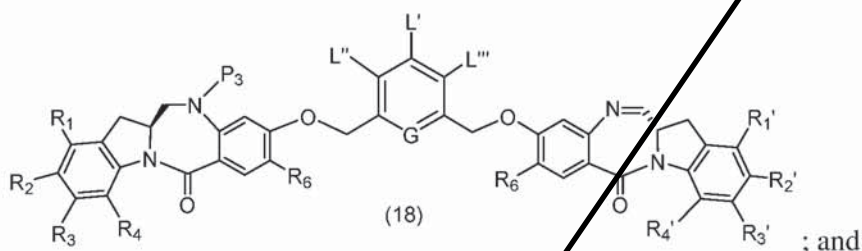
to form a compound of a formula (10'),



(3) reacting the compound of formula (10') with a monomer compound of the formula (d),



to form a compound of formula (18),



(4) when P_3 is an amine protecting group, reacting the compound of formula (18) with an amine deprotecting reagent to form the compound of formula (I'); wherein:

X_1 is -Br, -I, -Cl, a sulfonate ester, or an activated ester (preferably, X_1 is -Br, -I, or a sulfonate ester);

P_3 is H or an amine protecting group;

L' , L'' , and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L' , L'' , and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit - (CH₂CH₂O)_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;

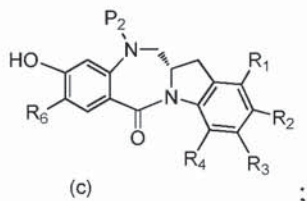
G is selected from -CH- or -N-;

R₁, R₂, R₃, and R₄ 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 -(CH₂CH₂O)_n-R_c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R''; and

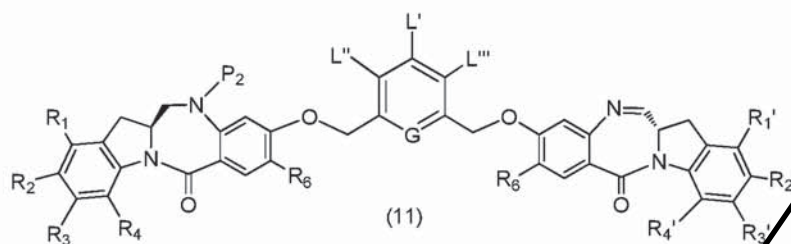
R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen.

114. The method of claim 113, wherein P₃ is H and the compound of (10') is reacted with the monomer compound of (d) to form a compound of (I').

115. The method of claim 113, wherein P₃ is P₂; the monomer compound is represented by formula (c):

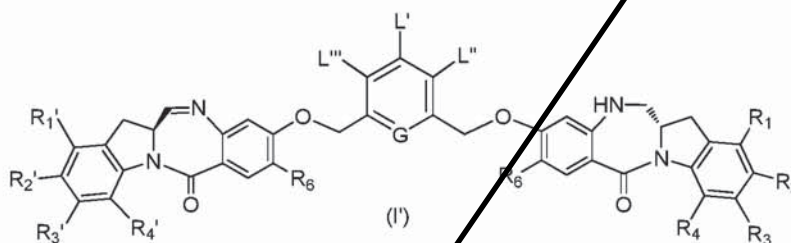


and the compound of formula (18) is represented by formula (11),



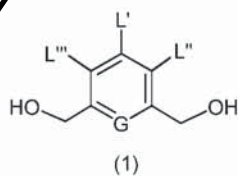
wherein P₂ is an amine protecting group.

116. A method of preparing a compound of formula (I'),

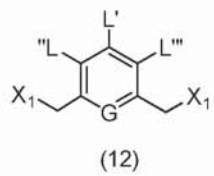


5 or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

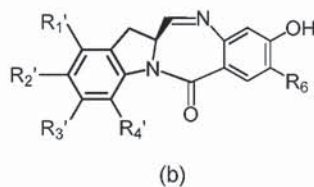
(1) reacting a halogenating reagent, a sulfonating reagent or an esterification reagent with a compound of formula (1),



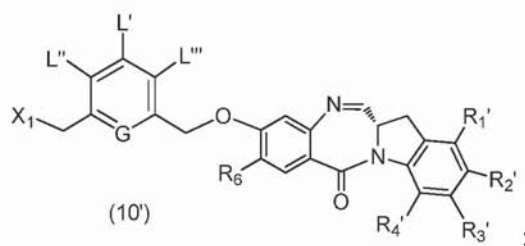
10 to form a compound of formula (12),



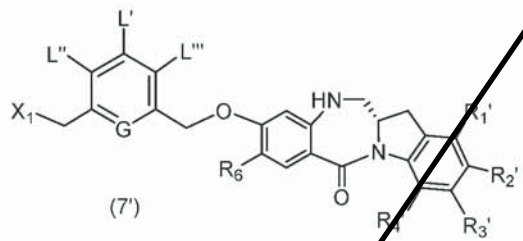
(2) reacting the compound of formula (12) with a monomer compound of the formula (b),



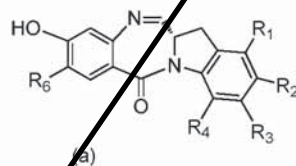
15 to form a compound of a formula (10'),



(3) reacting the compound (10') with an imine reducing reagent to form a compound (7'),



5 (4) reacting the compound of formula (7') with a monomer compound of the formula (a),



to form a compound of formula (I'), or a pharmaceutically acceptable salt thereof, wherein:

10 X₁ is -Br, -I, -Cl, a sulfonate ester, or an activated ester (preferably, X₁ is -Br, -I, or a sulfonate ester);

L', L'', and L''' are the same or different, and are independently -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(OCH₂CH₂)_n-R^c,
 15 halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L', L'', and L''' is the linking group with the
 20 reactive group bonded thereto;

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 -
 $(\text{CH}_2\text{CH}_2\text{O})_n\text{-R}^c$, 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, -
 $\text{N}(\text{R})_2$, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl
 or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -
 $(\text{CH}_2\text{CH}_2\text{O})_n\text{-R}^c$, 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;

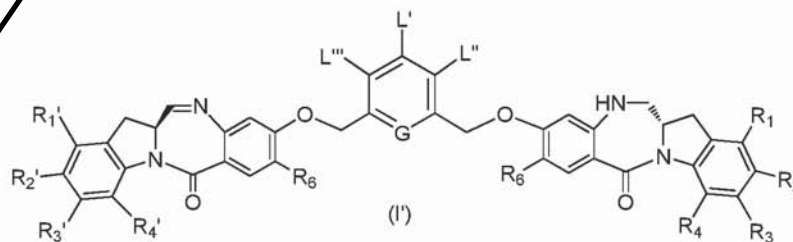
G is selected from -CH- or -N-;

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
 $(\text{CH}_2\text{CH}_2\text{O})_n\text{-R}^c$, halogen, guanidinium [$-\text{NH}(\text{C}=\text{NH})\text{NH}_2$], -OR, -NR'R'',
 $-\text{NO}_2$, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H,
 $-\text{SO}_2\text{NR}'\text{R}''$, cyano, an azido, -COR', -OCOR', and -OCONR'R''; and

R_6 is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen.

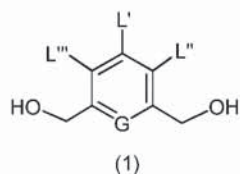
117. The method of claim 116, wherein X_1 is mesylate.

118. A method of preparing a compound of formula (I'),

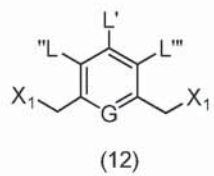


or a pharmaceutically acceptable salt thereof, said method comprising the steps
 of:

(1) reacting a halogenating reagent, a sulfonating reagent or an esterification reagent with a compound of formula (1),

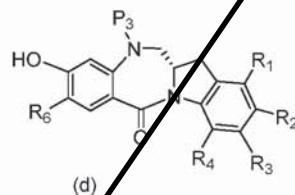


to form a compound of formula (12),

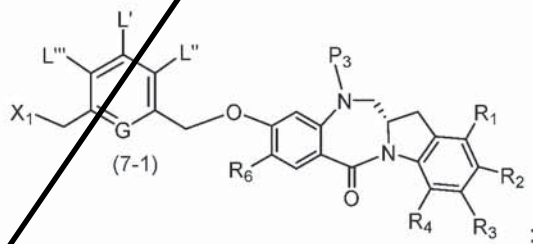


5

(2) reacting the compound of formula (12) with a monomer compound of the formula (d),

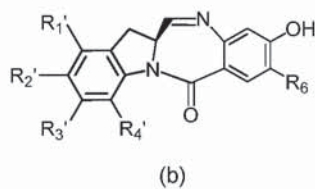


to form a compound of a formula (7-1),

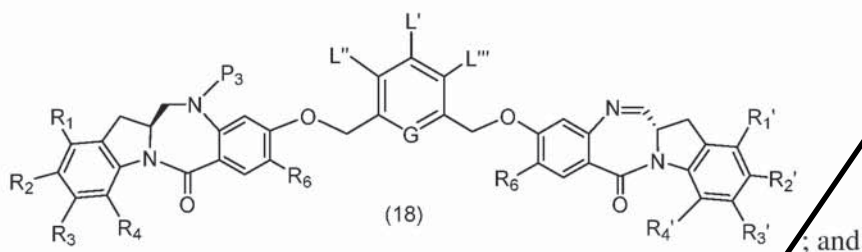


10

(3) reacting the compound of formula (7-1) with a monomer compound of the formula (b),



to form a compound of formula (18),



(4) when P_3 is an amine protecting group, reacting the compound of formula (18d) with an amine deprotecting reagent to form the compound of formula (Id'); wherein:

5 X_1 is -Br, -I, -Cl, a sulfonate ester, or an activated ester (preferably, X_1 is -Br, -I, or a sulfonate ester);

P_3 is H or an amine protecting group;

10 L' , L'' , and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that only one of L' , L'' , and L''' is the linking group with the

15 M is -H or a cation;

20 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

25 R' and R'' are each independently selected from -H, -OH, -OR, -NHR, -N(R)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;

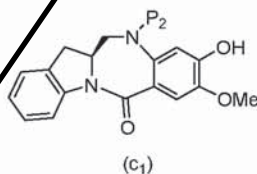
5 G is selected from -CH- or -N-;

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 $-(CH_2CH_2O)_n-$, R_c , halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R''; and

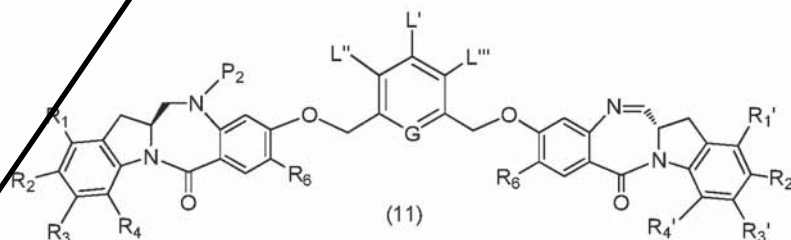
10 R_6 is -H, -R, -OR, -SR, -NR'R'', -NO₂ or halogen.

119. The method of claim 118, wherein P_3 is H and the compound of (10') is reacted with the monomer compound of (d) to form a compound of (I').

15 120. The method of claim 118, wherein P_3 is P_2 ; the monomer compound is represented by formula (c):



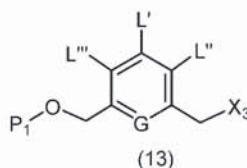
and the compound of formula (18) is represented by formula (11),



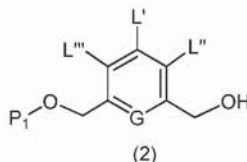
20 wherein P_2 is an amine protecting group.

121. The method of any one of claims 118-120, wherein X_1 is mesylate.

122. A method of preparing a compound of formula (13),



or a salt thereof, said method comprising reacting a chlorinating reagent with a compound of formula (2),



5

wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

10

15

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;

20

R' and R'' are each independently selected from -H, -OH, -OR, -NHR, -N(R)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

25

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;

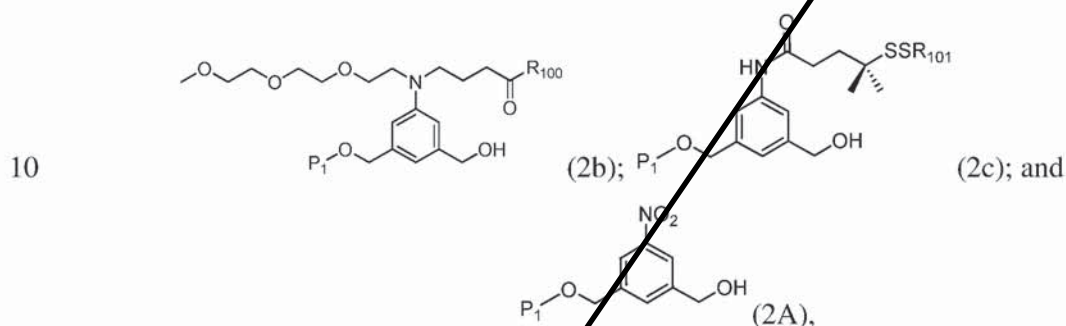
n' is an integer from 1 to 24;

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

P_1 is an alcohol protecting group; and,

X_3 is -Cl.

123. The method of claim 122, wherein the compound of formula (2) is selected from the group consisting of:



wherein R_{100} is a (C_1-C_3) alkoxy, and R_{101} is a (C_1-C_3) alkyl, pyridyl or nitropyridyl (e.g., 4-nitropyridyl).

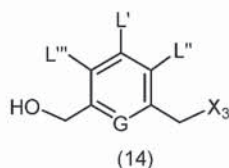
124. The method of claim 122 or 123, wherein the alcohol protecting group is a silyl protecting group.

125. The method of claim 124, wherein the silyl protecting group is the silyl protecting group is dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, trimethylsilyl, triisopropylsilyl, tribenzylsilyl, triphenylsilyl, 2-norbornyldimethylsilyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, 2-trimethylethylsilyl (TEOC), or [2-(trimethylsilyl)ethoxy]methyl.

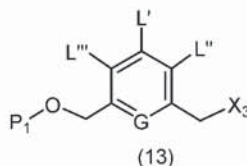
126. The method of claim 125, wherein the silyl protecting group is triethylsilyl, triisopropylsilyl, or *tert*-butyldimethylsilyl.

127. The method of claim 126, wherein the silyl protecting group is *tert*-butyldimethylsilyl.

128. The method of any one of claims 122–127, wherein the chlorinating reagent is selected from the group consisting of carbon tetrachloride, methanesulfonyl chloride, sulfuryl chloride, thionyl chloride, cyanuric chloride, *N*-chlorosuccinimide, phosphorus(V) oxychloride, phosphorus pentachloride, and phosphorus trichloride.
129. The method of claim 128, wherein the chlorinating reagent is methanesulfonyl chloride.
130. The method of any one of claims 122–129, wherein the chlorinating reagent is reacted with a compound of formula (2) in the presence of a non-nucleophilic base.
131. The method of claim 130, wherein the non-nucleophilic base is triethylamine, imidazole, diisopropylethylamine, pyridine, 2,6-lutidine, dimethylformamide, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or tetramethylpiperidine .
132. The method of claim 131, wherein the non-nucleophilic base is pyridine.
133. The method of any one of claims 122–132, wherein the the chlorinating reagent is reacted with a compound of formula (2) in a polar aprotic solvent.
134. The method of claim 133, wherein the polar aprotic solvent is *N,N*-dimethylformamide or dimethylacetamide.
135. A method of preparing a compound of formula (14),



or a salt thereof, said method comprising reacting a compound of formula (13)



with an alcohol deprotecting reagent. wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)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;

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

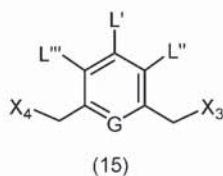
P₁ is an alcohol protecting group; and,

X₃ is -Cl.

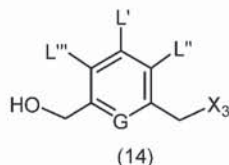
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142. The method of claim 141, wherein the alcohol deprotecting agent is hydrogen fluoride pyridine.

143. A method of preparing a compound of formula (15):



or a salt thereof, said method comprising reacting a sulfonating reagent or an esterification reagent with a compound of formula (14),



wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)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;

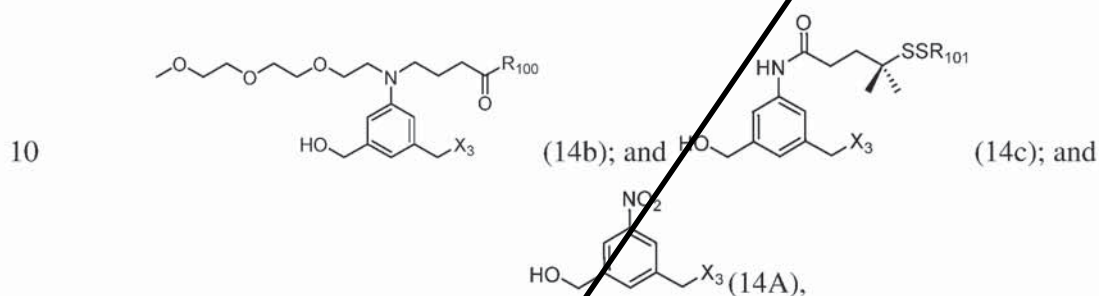
n' is an integer from 1 to 24;

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

X_3 is -Cl; and

X_4 is a sulfonate ester or an activated ester (preferably, a sulfonate ester).

144. The method of claim 143, wherein the compound of formula (14) is selected from the group consisting of:



wherein R_{100} is a (C₁-C₃)alkoxy; and R_{101} is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (e.g., 4-nitropyridyl).

145. The method of claim 143 or 144, wherein the sulfonating reagent is
15 methanesulfonyl anhydride, methanesulfonyl chloride, p-toluenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, or trifluoromethanesulfonyl anhydride.

146. The method of claim 145, wherein the sulfonate ester represented by X_1 is
mesylate, tosylate, brosylate, or triflate.

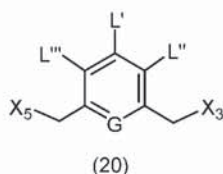
147. The method of claim 146, wherein the sulfonate ester represented by X_1 is
20 mesylate.

148. The method of any one of claims 143–147, wherein the sulfonate ester is reacted
with a compound of formula (14) in the presence of a non-nucleophilic base

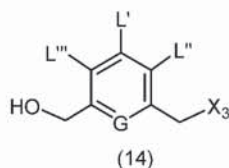
149. The method of claim 148, wherein the non-nucleophilic base is triethylamine,
imidazole, diisopropylethylamine, pyridine, 2,6-lutidine, dimethylformamide,
25 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or tetramethylpiperidine.

150. The method of claim 149, wherein the amine base is diisopropylethylamine.

151. A method of preparing a compound of formula (20):



or a salt thereof, said method comprising reacting a brominating or iodinating reagent with a compound of formula (14),



wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -

$(\text{CH}_2\text{CH}_2\text{O})_n\text{-R}^c$, 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;

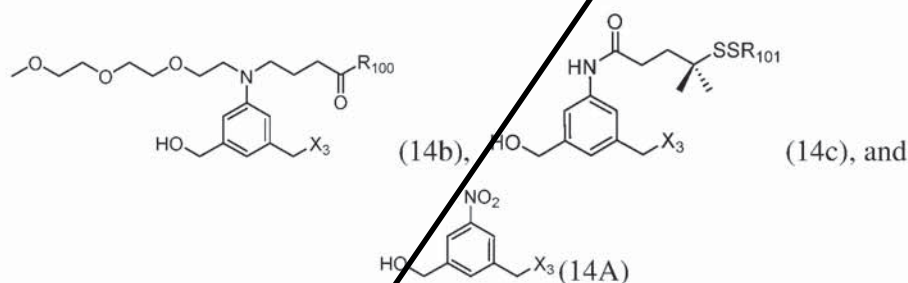
5 n' is an integer from 1 to 24;

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

X_3 is -Cl; and

X_5 is -Br or -I.

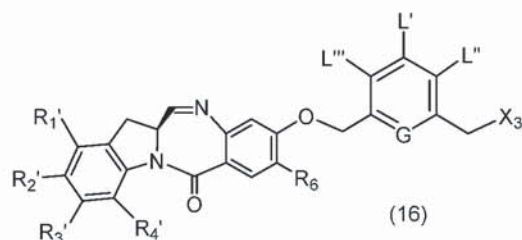
10 152. The method of claim 151, wherein the compound of formula (14) is selected from the group consisting of:



wherein R_{100} is a $(\text{C}_1\text{-C}_3)$ alkoxy; and R_{101} is a $(\text{C}_1\text{-C}_3)$ alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

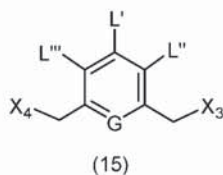
15 153. The method of claim 151 or 152, wherein the brominating or iodinating reagent is bromine, hydrobromic acid, carbon tetrabromide, phosphorus tribromide, potassium bromide, hydroiodic acid, iodine, carbon tetraiodide, phosphorus triiodide, sodium iodide, or potassium iodide.

154. A method of preparing a compound of formula (16):

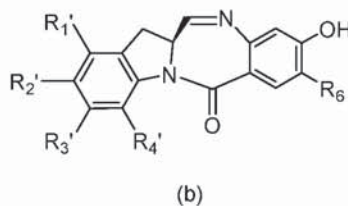


20

or a salt thereof, said method comprising reacting a compound of formula (15)



with a monomer compound of formula (b),



wherein:

5 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 $-(CH_2CH_2O)_n-R_c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

10 L' , L'' , and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L' , L'' , and L''' is the linking group with the reactive group bonded thereto;

20 M is -H or a cation;

25 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, -NR₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit - (CH₂CH₂O)_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;

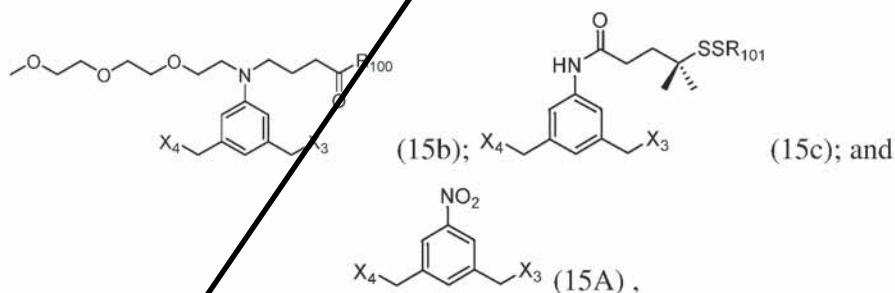
n' is an integer from 1 to 24;

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

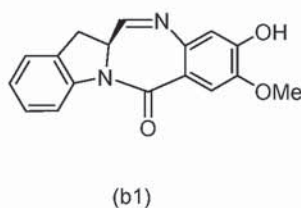
X₃ is -Cl; and

X₄ is a sulfonate ester or an activated ester (preferably, a sulfonate ester).

155. The method of claim 154, wherein the compound of formula (15) is selected from the group consisting of:



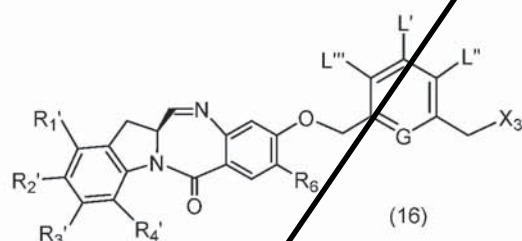
and the monomer compound of formula (b) is represented by the following formula:



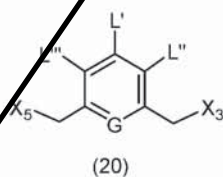
wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

156. The method of claim 154 or 155, wherein the compound of formula (15) is reacted with a monomer compound of formula (b) in the presence of a base.

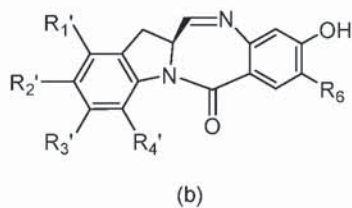
157. The method of claim 156, wherein the base is sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, or potassium hydride.
158. The method of any one of claims 154–157, wherein the compound of formula (15) is reacted with a monomer compound of formula (b) in the presence of a polar aprotic solvent.
159. The method of claim 158, wherein the polar aprotic solvent is dimethylacetamide.
160. A method of preparing a compound of formula (16):



or a salt thereof, said method comprising reacting a compound of formula (20)



with a monomer compound of formula (b),



wherein:

- R₁', R₂', R₃', and R₄' 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 -(CH₂CH₂O)_n-R_c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -NR₂, -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;

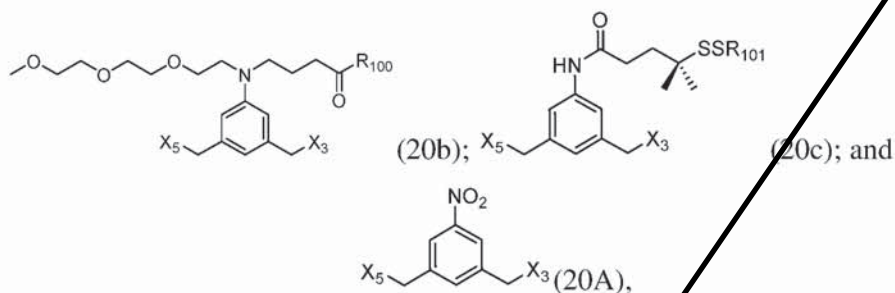
n' is an integer from 1 to 24;

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

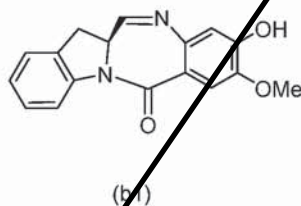
X₃ is -Cl; and

X₅ is -Br or -I.

161. The method of claim 160, wherein the compound of formula (20) is selected from the group consisting of:



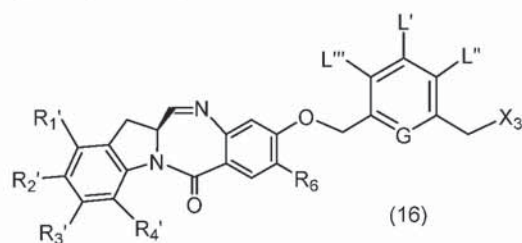
- 5 and the monomer compound of formula (b) is represented by the following formula:



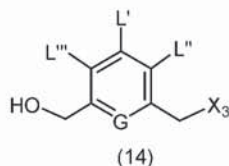
wherein R_{100} is a (C_1-C_3) alkoxy; and R_{101} is a (C_1-C_3) alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

- 10 162. The method of claim 160 or 161, wherein the compound of formula (20) is reacted with a monomer compound of formula (b) in the presence of a base.
163. The method of claim 162, wherein the base is sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, or potassium hydride.
164. The method of claim 163, wherein the base is potassium carbonate.
- 15 165. The method of any one of claims 160–164, wherein the compound of formula (20) is reacted with a monomer compound of formula (b) in the presence of a polar aprotic solvent.
166. The method of claim 165, wherein the polar aprotic solvent is dimethylacetamide.

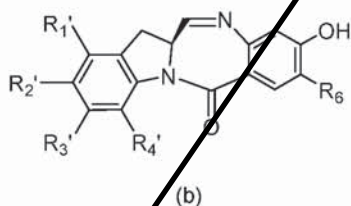
167. A method of preparing a compound of formula (16):



or a salt thereof, said method comprising reacting a compound of formula (14)



5 with a monomer compound of formula (b),



wherein:

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 $-(CH_2CH_2O)_n-R^c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

L' , L'' , and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L' , L'' , and L''' is the linking group with the reactive group bonded thereto;

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;

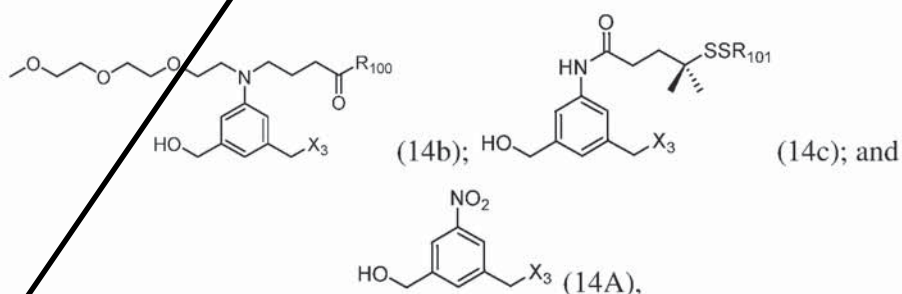
R' and R'' are each independently selected from -H, -OH, -OR, -NHR, -NR₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R^c$, and an optionally substituted 3- to 18-membered heterocyclic 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;

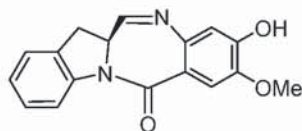
G is selected from -CH- or -N-; and

X₃ is -Cl.

168. The method of claim 167, wherein the compound of formula (14) is selected from the group consisting of:



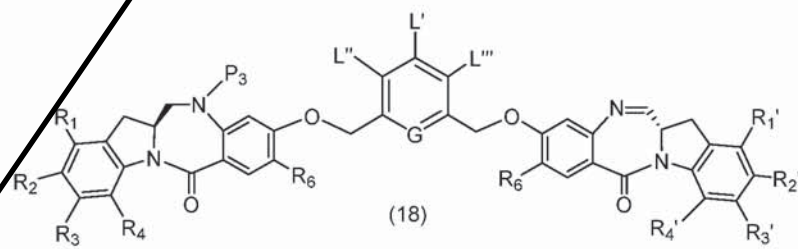
wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl), and the monomer compound of formula (b) is represented by the following formula:



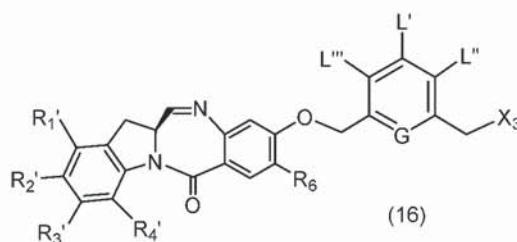
(b1)

wherein R_{100} is a (C_1-C_3) alkoxy; and R_{101} is a (C_1-C_3) alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

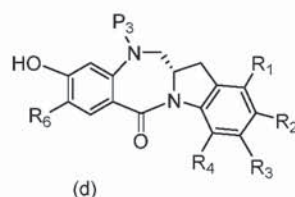
169. The method of claim 167 or 168, wherein the compound of formula (14) is
 5 reacted with a monomer of formula (b) in the presence of an alcohol activating agent.
170. The method of claim 169, wherein the alcohol activating agent is triphenylphosphine.
171. The method of any one of claims 167 - 170, wherein the compound of formula
 10 (14) is reacted with a monomer of formula (b) in the presence of an azodicarboxylate.
172. The method of claim 171, wherein the azodicarboxylate is selected from the group consisting of: diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), 1,1'-(azodicarbonyl)dipiperidine (ADDP), and
 15 di-*tert*-butyl azodicarboxylate (DTAD).
173. A method of preparing a compound of formula (18):



or a pharmaceutically acceptable salt thereof, said method comprising reacting a compound of formula of (16):



with a reduced monomer of formula (d):



wherein:

5 L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto

10 capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

M is -H or a cation;

15 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

20 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;

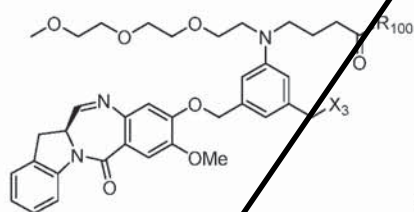
25 R' and R'' are each independently selected from -H, -OH, -OR, -NHR, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -

5

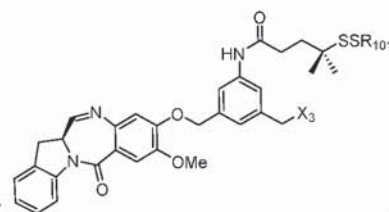
10

15

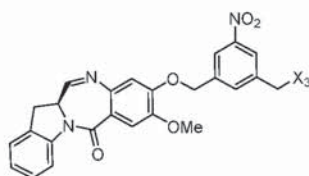
174. The method of claim 173, wherein the compound of formula (16) is selected from the group consisting of:



(16b);



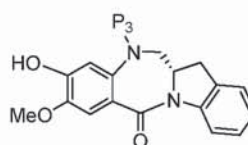
(16c); and



(16A),

20

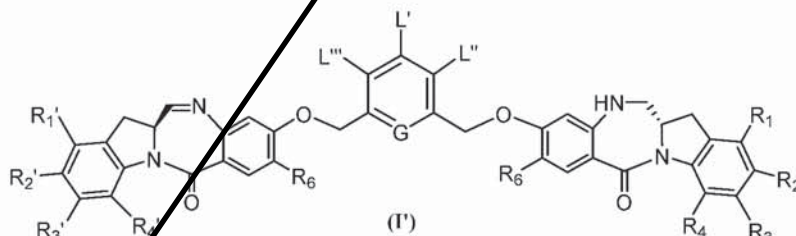
and the reduced monomer of formula (d) is represented by the following formula:



(d₁)

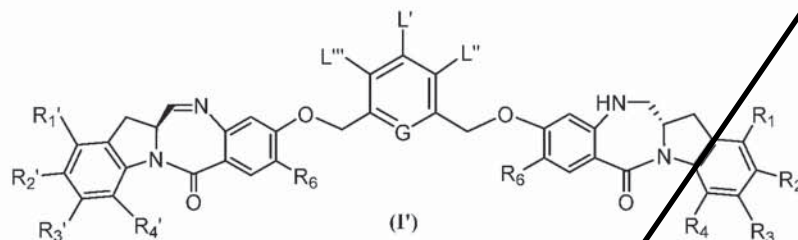
wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

175. The method of claim 173 or 174, wherein the compound of formula (16) is reacted with a monomer compound of formula (d) in the presence of a base.
- 5 176. The method of claim 175, wherein the base is sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, or potassium hydride.
177. The method of any one of claims 173–176, wherein the compound of formula (16) is reacted with a monomer compound of formula (d) in the presence of a polar aprotic solvent.
- 10 178. The method of claim 177, wherein the polar aprotic solvent is dimethylacetamide or dimethylacetamide.
179. The method of any one of claims 173–178, wherein the compound of formula (16) is reacted with reduced monomer of formula (d), wherein P₃ is H, to form a compound of formula (I'):



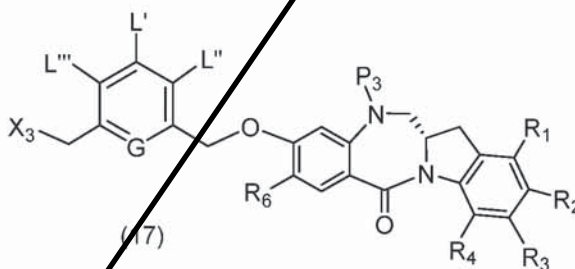
180. The method of any one of claims 173–178, wherein P₃ is an amine protecting group.
181. The method of claim 180, wherein the amine protecting group is selected from the group consisting of 2-trimethylsilylethyl, (2-phenyl-2-trimethylsilyl)ethyl, triisopropylsiloxy, 2-(trimethylsilyl)ethoxymethyl, allyloxycarbonyl, 9-fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, and 2, 2,2,2-trichloroethoxycarbonyl.
- 20

182. The method of claim 180 or 181, wherein the compound of formula (18) is further reacted with an amine deprotecting reagent to form a compound of formula (I'):

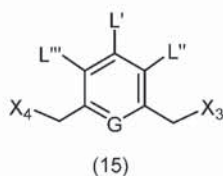


183. The method of claim 182, wherein the amine deprotecting reagent is selected from the group consisting of tetra-n-butylammonium fluoride, acetic acid, hydrogen fluoride pyridine, cesium fluoride, piperidine, morpholine, or trifluoroacetic acid.

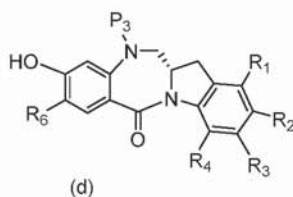
184. A method of preparing a compound of formula (17):



or a salt thereof, said method comprising reacting a compound of formula (15)



with a monomer compound of formula (d),



wherein:

R₁, R₂, R₃, and R₄ 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 $-(CH_2CH_2O)_n-R^c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, $-OR$, $-NR'R''$, $-NO_2$, $-NCO$, $-NR'COR''$, $-SR$, $-SOR'$, $-SO_2R'$, $-SO_3H$, $-OSO_3H$, $-SO_2NR'R''$, cyano, an azido, $-COR'$, $-OCOR'$, and $-OCONR'R''$;

5 L' , L'' , and L''' are the same or different, and are independently $-H$, 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 $[-NH(C=NH)NH_2]$, $-OR$, $-NR'R''$, $-NO_2$, $-NR'COR''$, $-SR$, $-SOR'$, $-SO_2R'$, $-SO_3M$, $-OSO_3M$, $-SO_2NR'R''$, cyano, an azido, $-COR'$, $-OCOR'$, $-OCONR'R''$, or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L' , L'' , and L''' is the linking group with the reactive group bonded thereto;

M is $-H$ or a cation;

15 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;

20 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;

25 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;

30 n' is an integer from 1 to 24;

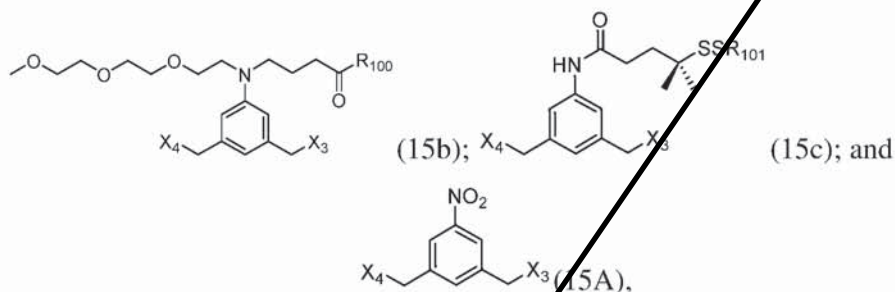
G is selected from $-CH-$ or $-N-$;

X_3 is $-Cl$;

X₄ is a sulfonate ester or an activated ester (preferably, a sulfonate ester);
and

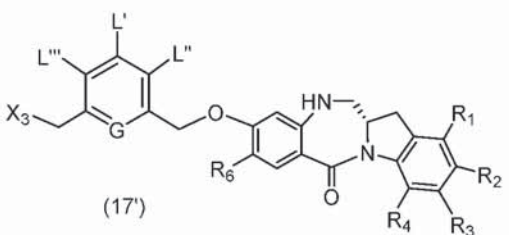
P₃ is H or an amine protecting group.

185. The method of claim 184, wherein the compound of formula (15) is selected
5 from the group consisting of:

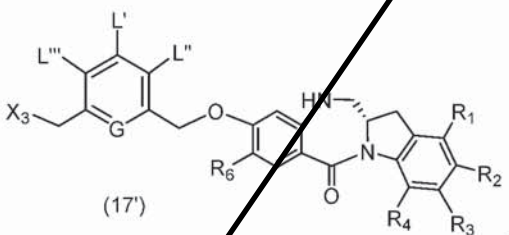


wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or
nitropyridyl (e.g., 4-nitropyridyl).

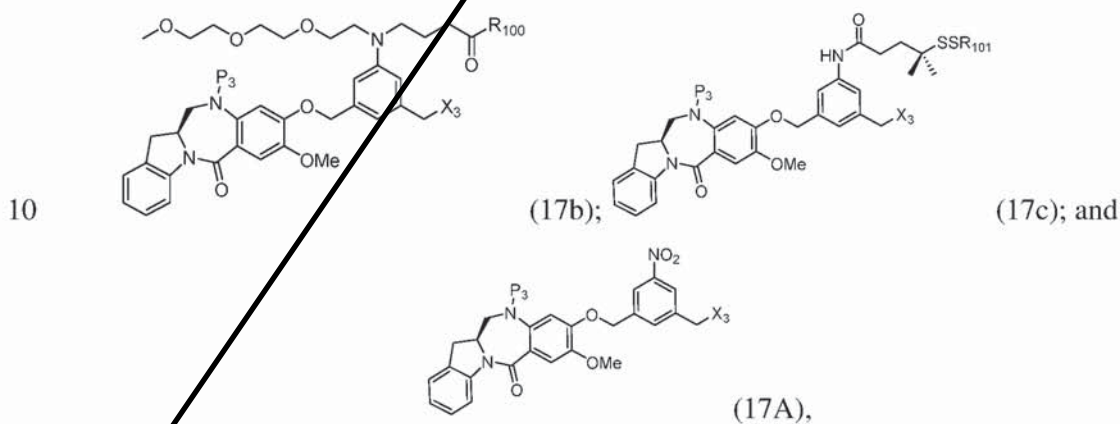
- 10 186. The method of claim 184 or 185, wherein the compound of formula (15) is
reacted with a monomer compound of formula (d) in the presence of a base.
187. The method of claim 186, wherein the base is sodium carbonate, potassium
carbonate, cesium carbonate, sodium hydride, or potassium hydride.
188. The method of claim 187, wherein the base is potassium carbonate.
- 15 189. The method of any one of claims 184–188, wherein the compound of formula
(15) is reacted with a monomer compound of formula (b) in the presence of a
polar aprotic solvent.
190. The method of claim 189, wherein the polar aprotic solvent is
dimethylacetamide.
- 20 191. The method of any one of claims 184–190, wherein the compound of formula
(15) is reacted with the monomer compound of formula (d), wherein P₃ is H, to
form a compound of formula (17'):



192. The method of any one of claims 184–190, wherein P₃ is an amine protecting group.
193. The method of claim 192, further comprising the step of reacting the compound of formula (17) with an amine deprotecting reagent to form a compound of formula (17'):



194. The method of claim 193, wherein the compound of formula (17) is selected from the group consisting of:

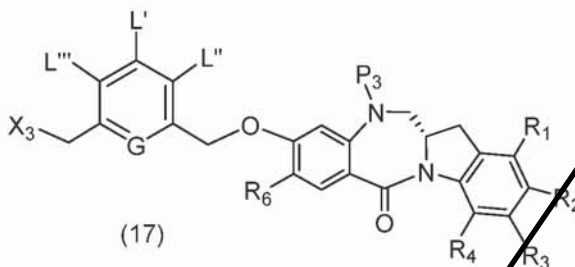


wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

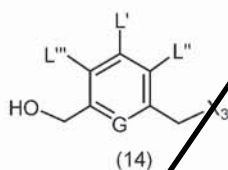
195. The method of claim 193 or 194, wherein the amine deprotecting reagent is selected from the group consisting of tetra-*n*-butylammonium fluoride, acetic

acid, hydrogen fluoride pyridine, cesium fluoride, piperidine, morpholine, or trifluoroacetic acid.

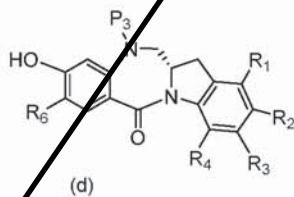
196. A method of preparing a compound of formula (17):



5 or a salt thereof, said method comprising reacting a compound of formula (14)



with a monomer compound of formula (d),



wherein:

10 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 $-(CH_2CH_2O)_n-R_c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

15 L' , L'' , and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent

20

(CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -NR₂, -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;

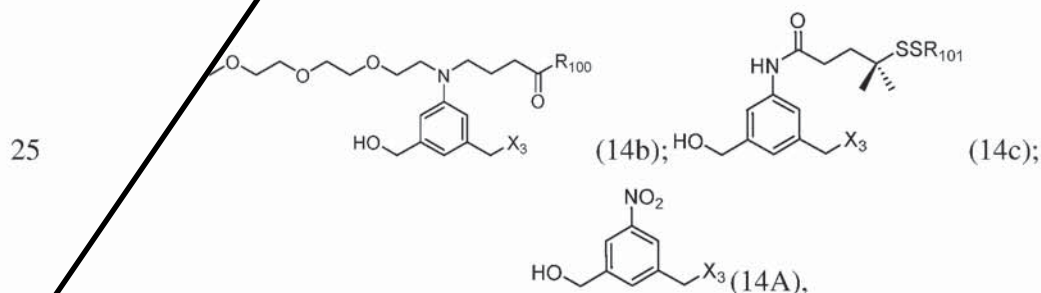
n' is an integer from 1 to 24;

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

X₃ is -Cl; and

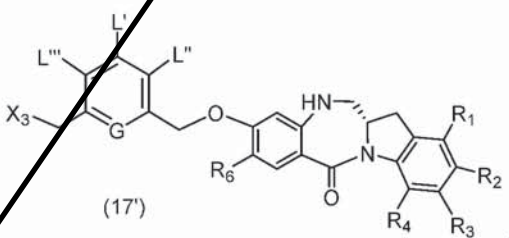
P₃ is H or an amine protecting group.

197. The method of claim 196, wherein the compound of formula (14) is selected from the group consisting of:

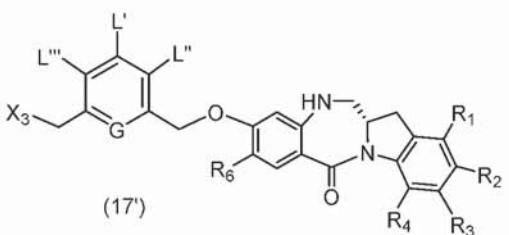


wherein R₁₀₀ is a (C₁-C₃)alkoxy; and R₁₀₁ is a (C₁-C₃)alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

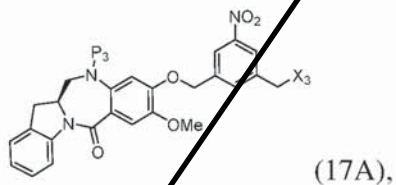
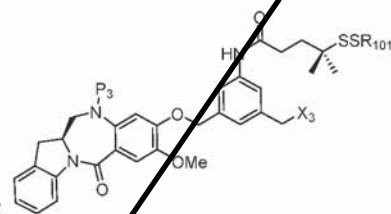
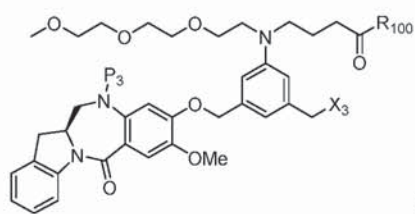
198. The method of claim 196 or 197, wherein the compound of formula (14) is reacted with a monomer of formula (b) in the presence of an alcohol activating agent.
199. The method of claim 198, wherein the alcohol activating agent is triphenylphosphine.
200. The method of any one of claims 196–199, wherein the compound of formula (14) is reacted with a monomer of formula (b) in the presence of an azodicarboxylate.
201. The method of claim 200, wherein the azodicarboxylate is selected from the group consisting of: diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), 1,1'-(azodicarbonyl)dipiperidine (ADDP), and di-tert-butyl azodicarboxylate (DTAD).
202. The method of any one of claims 196–201, wherein the compound of formula (15) is reacted with the monomer compound of formula (d), wherein P₃ is H, to form a compound of formula (17'):



203. The method of any one of claims 196–202, wherein P₃ is an amine protecting group.
204. The method of claim 203, further comprising the step of reacting the compound of formula (17) with an amine deprotecting reagent to form a compound of formula (17'):



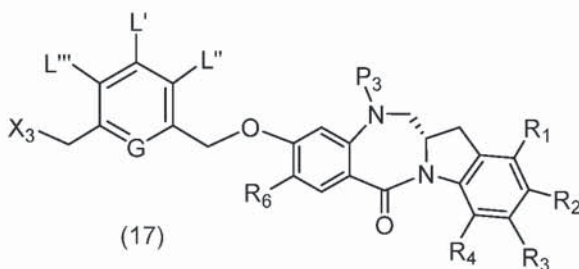
205. The method of claim 204, wherein the compound of formula (17) is selected from the group consisting of:



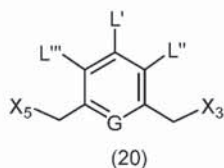
wherein R_{100} is a (C_1-C_3) alkoxy; and R_{101} is a (C_1-C_3) alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

206. The method of claim 204 or 205, wherein the amine deprotecting reagent is selected from the group consisting of tetra-*n*-butylammonium fluoride, acetic acid, hydrogen fluoride pyridine, cesium fluoride, piperidine, morpholine, or trifluoroacetic acid.

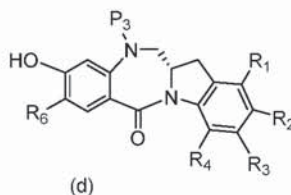
207. A method of preparing a compound of formula (17):



or a salt thereof, said method comprising reacting a compound of formula (20)



with a monomer compound of formula (d),



wherein:

5 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 $-(CH_2CH_2O)_n-R^c$, halogen, guanidinium $[NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

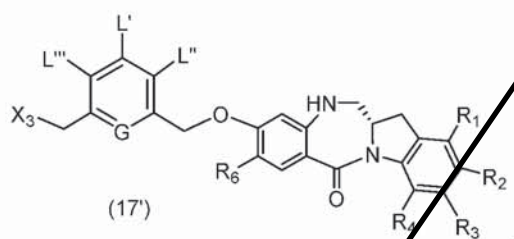
10 L' , L'' , and L''' are the same or different, and are independently -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(OCH_2CH_2)_n-R^c$, halogen, guanidinium $[NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L' , L'' , and L''' is the linking group with the reactive group bonded thereto;

20 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;

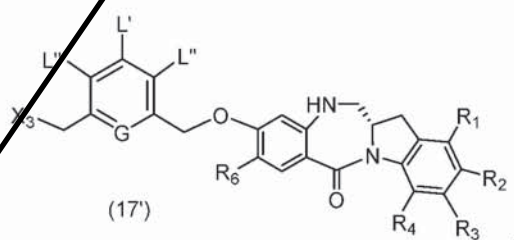
213. The method of claim 212, wherein the polar aprotic solvent is dimethylacetamide.

214. The method of any one of claims 207–213, wherein the compound of formula (20) is reacted with the monomer compound of formula (d), wherein P_3 is H, to form a compound of formula (17'):

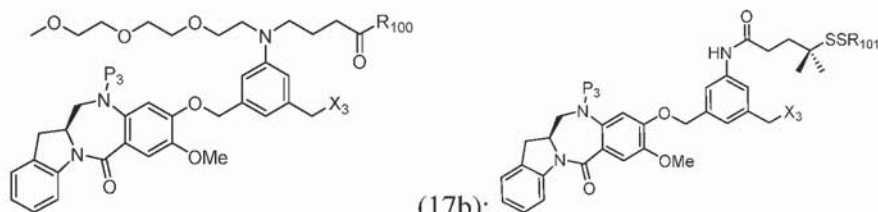


215. The method of any one of claims 207–213, wherein P_3 is an amine protecting group.

216. The method of claim 215, further comprising the step of reacting the compound of formula (17) with an amine deprotecting reagent to form a compound of formula (17'):

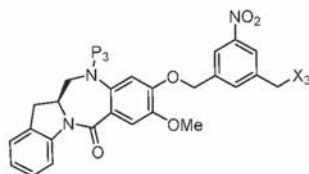


217. The method of claim 216, wherein the compound of formula (17) is selected from the group consisting of:



(17b);

(17c); and

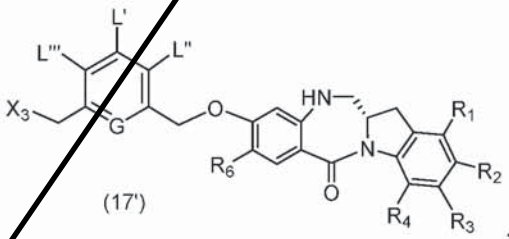


(17A),

wherein R_{100} is a (C_1-C_3) alkoxy; and R_{101} is a (C_1-C_3) alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).

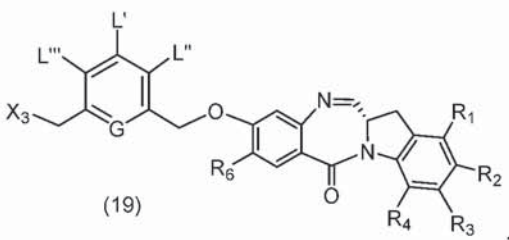
- 5 218. The method of claim 216 or 217, wherein the amine deprotecting reagent is selected from the group consisting of tetra-*n*-butylammonium fluoride, acetic acid, hydrogen fluoride pyridine, cesium fluoride, piperidine, morpholine, or trifluoroacetic acid.

219. A method of preparing a compound of formula (17'):



(17')

or a salt thereof, said method comprising reacting a compound of formula (19)



(19)

with an imine reducing agent, wherein:

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 $-(CH_2CH_2O)_n-R_c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'',

-NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

L', L'', and L''' are the same or different, and are independently -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(OCH₂CH₂)_n-R^c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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 -(CH₂CH₂O)_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, -NR₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(CH₂CH₂O)_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;

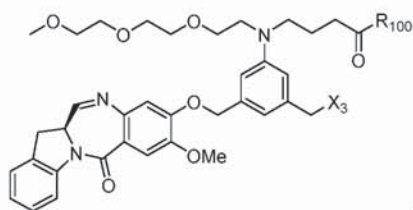
R^c is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms, or the linking group with the reactive group bonded thereto;

n' is an integer from 1 to 24;

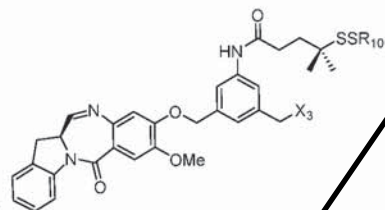
G is selected from -CH- or -N-; and

X₃ is -Cl.

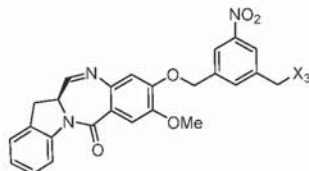
220. The method of claim 219, wherein the compound of formula (19) is selected from the group consisting of:



(16b);

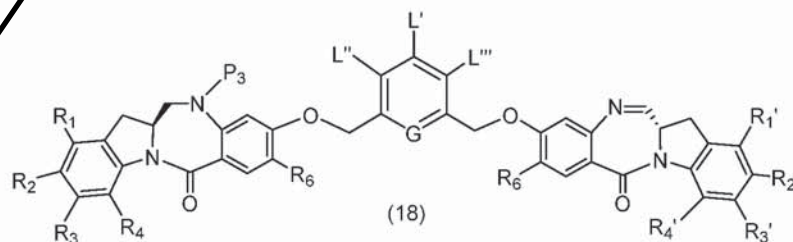


(16c); and



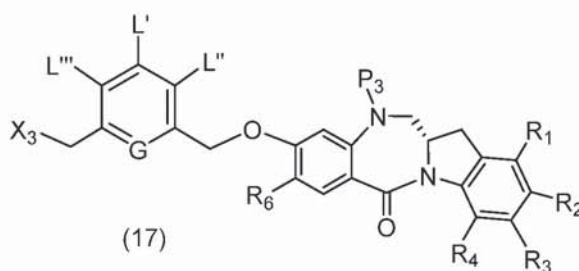
(16A),

- 5 wherein R_{100} is a (C_1-C_3) alkoxy; and R_{101} is a (C_1-C_3) alkyl, pyridyl or nitropyridyl (*e.g.*, 4-nitropyridyl).
221. The method of claim 219 or 220, wherein the imine reducing reagent is a hydride reducing reagent.
222. The method of claim 221, wherein the imine reducing reagent is sodium borohydride, sodium triacetoxymethyl borohydride, sodium cyanoborohydride, lithium aluminum hydride, hydrogen gas, ammonium formate, borane, 9-borabicyclo[3.3.1]nonane (9-BBN), diisobutylaluminum hydride (DIBAL), lithium borohydride ($LiBH_4$), potassium borohydride (KBH_4), or sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al).
- 10
223. The method of claim 222, wherein the imine reducing reagent is sodium triacetoxymethyl borohydride ($NaBH(OAc)_3$).
- 15
224. A method of preparing a compound of formula (18),

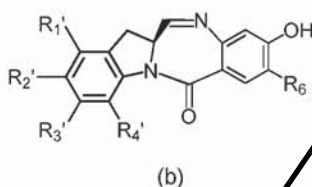


(18)

or a pharmaceutically acceptable salt thereof, said method comprising reacting a compound of formula of (17):



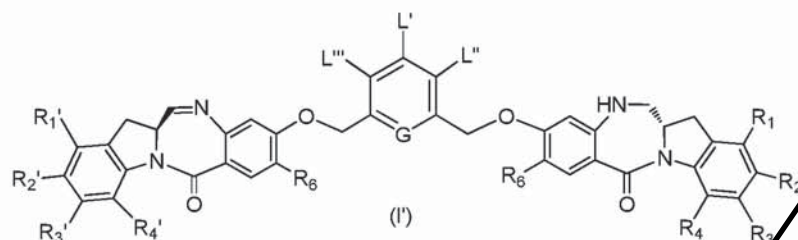
with a monomer of formula (b):



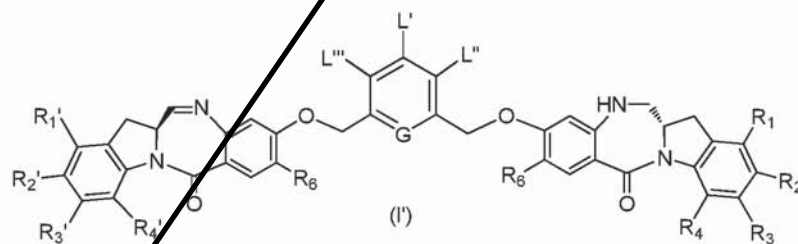
wherein:

- 5 X₃ is -Cl;
- P₃ is H or an amine protecting group;
- L', L'', and L''' are the same or different, and are independently -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(OCH₂CH₂)_n-R^c,
10 halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with
15 the reactive group bonded thereto;
- 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 -
20 (CH₂CH₂O)_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;

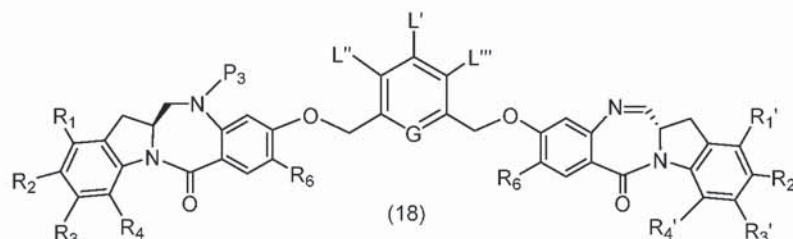
- R' and R'' are each independently selected from -H, -OH, -OR, -NHR, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(CH₂CH₂O)_n-R^c, and an optionally substituted 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms independently selected from O, S, N and P;
- 5 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;
- G is selected from -CH- or -N-;
- 10 R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' 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 -(CH₂CH₂O)_n-R_c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H,
- 15 -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R''; and
- R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;
225. The method of claim 224, wherein the compound of formula (17) is reacted with a monomer compound of formula (d) in the presence of a base.
226. The method of claim 225, wherein the base is sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, or potassium hydride.
- 20 227. The method of claim 226, wherein the base is potassium carbonate.
228. The method of any one of claims 224-227, wherein the compound of formula (17) is reacted with a monomer compound of formula (b) in the presence of a polar aprotic solvent.
- 25 229. The method of claim 228, wherein the polar aprotic solvent is dimethylformamide or dimethylacetamide.
230. The method of any one of claims 224-229, wherein the compound of formula (17) is reacted with reduced monomer of formula (d), wherein P₃ is H, to form a compound of formula (I'):



231. The method of any one of claims 224-229, wherein P_3 is an amine protecting group.
232. The method of claim 231, wherein the amine protecting group is selected from the group consisting of 2-trimethylsilylethyl, (2-phenyl-2-trimethylsilyl)ethyl, triisopropylsiloxy, 2-(trimethylsilyl)ethoxymethyl, allyloxycarbonyl, 9-fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, and 2, 2,2,2-trichloroethoxycarbonyl.
233. The method of claim 231 or 232, wherein the compound of formula (18) is further reacted with an amine deprotecting reagent to form a compound of formula (I'):

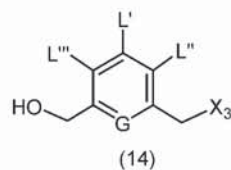


234. The method of claim 231, wherein the amine deprotecting reagent is selected from the group consisting of tetra-n-butylammonium fluoride, acetic acid, hydrogen fluoride pyridine, cesium fluoride, piperidine, morpholine, or trifluoroacetic acid.
235. A method of preparing a compound of formula (18),

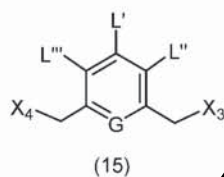


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

(1) reacting a sulfonating reagent or an esterification reagent with the compound of formula (14),

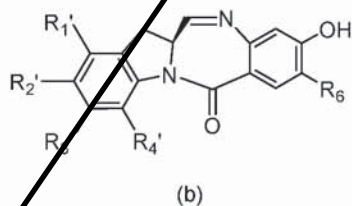


to form a compound of formula (15):

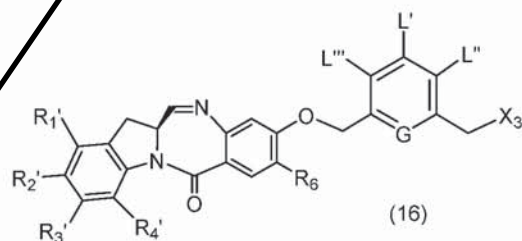


or a salt thereof;

(2) reacting the compound of formula (15) with a monomer compound of formula (b),

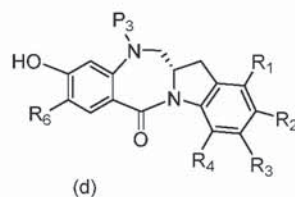


to form a compound of formula (16):



or a salt thereof; and

(3) reacting the compound of formula of (16) with a reduced monomer of formula (d):



to form a compound of formula (19), or a pharmaceutically acceptable salt thereof, wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)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;

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

R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' 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 $-(CH_2CH_2O)_n-R^c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR,

-NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

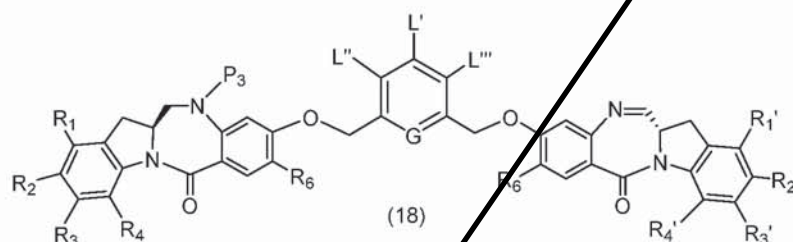
X₃ is -Cl;

5 X₄ is a sulfonate ester or an activated ester (preferably, a sulfonate ester);

and

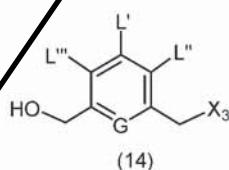
P₃ is H or an amine protecting group.

236. A method of preparing a compound of formula (18),

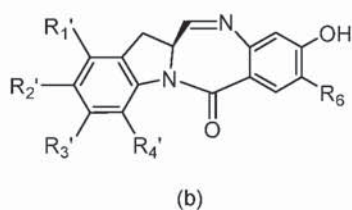


10 or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

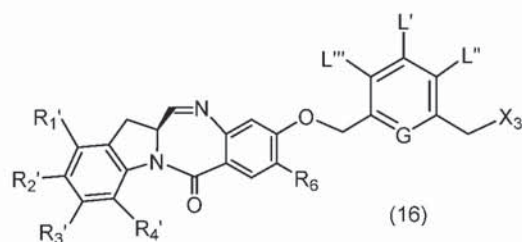
(1) reacting the compound of formula (14)



with a monomer compound of formula (b),

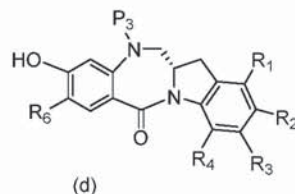


15 to form a compound of formula (16):



or a salt thereof; and

(2) reacting the compound of formula of (16) with a reduced monomer of formula (d):



to form a compound of formula (18), or a pharmaceutically acceptable salt thereof, wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)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;

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

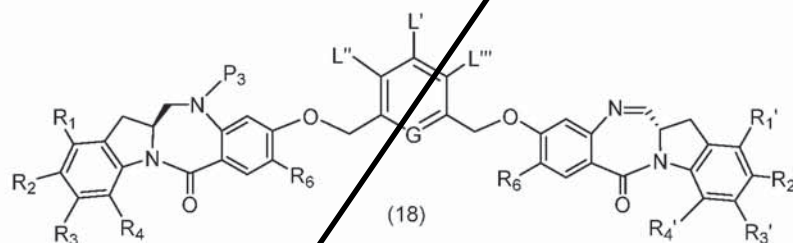
R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(CH₂CH₂O)_n-R_c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

X₃ is -Cl; and

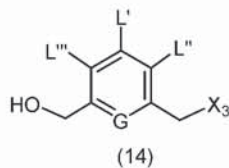
P₃ is H or an amine protecting group.

237. A method of preparing a compound of formula (18),

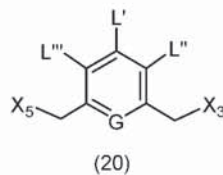


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

(1) reacting a halogenating reagent with the compound of formula (14)

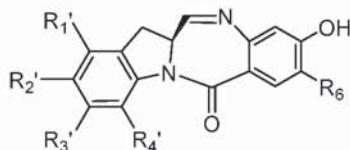


to form a compound of formula (20):



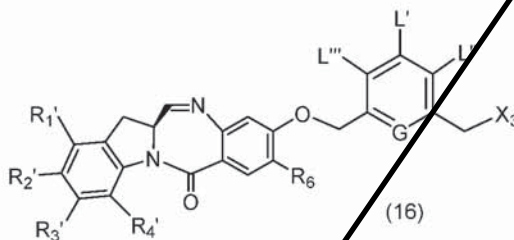
or a salt thereof;

(2) reacting a compound of formula (20) or a salt thereof with a monomer compound of formula (b),



(b)

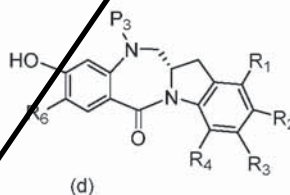
to form a compound of formula (16):



(16)

or a salt thereof; and

- 5 (3) reacting the compound of formula (16) with a reduced monomer of formula (d):



(d)

to form a compound of formula (18), or a pharmaceutically acceptable salt thereof, wherein:

- 10 L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR, -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

M is -H or a cation;

- 20 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;

5 R' and R'' are each independently selected from -H, -OH, -OR, -NHR, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit - (CH₂CH₂O)_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;

10 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;

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

15 R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' 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 -(CH₂CH₂O)_n-R_c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

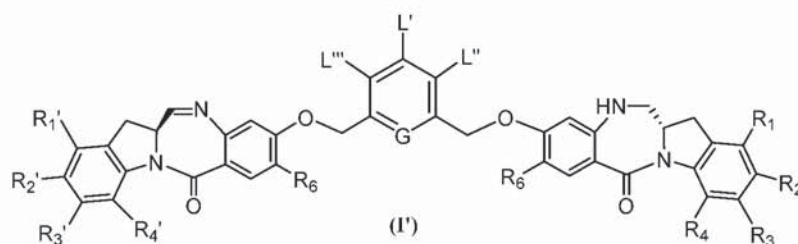
20 R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

X₃ is -Cl;

X₅ is -Br or -I; and

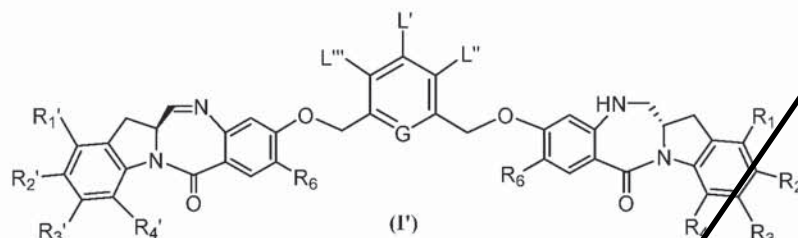
P₃ is H or an amine protecting group.

238. The method of claim 235, 236 or 237, wherein the compound of formula (16) is
25 reacted with reduced monomer of formula (d), wherein P₃ is H, to form a compound of formula (I'):

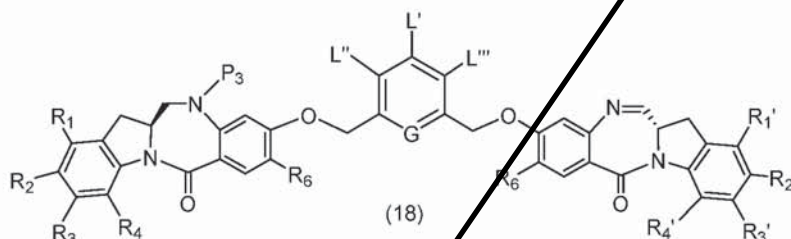


239. The method of claim 235, 236 or 237, wherein P₃ is an amine protecting group.

240. The method of claim 239, wherein the compound of formula (18) is further reacted with an amine deprotecting reagent to form a compound of formula (I'):

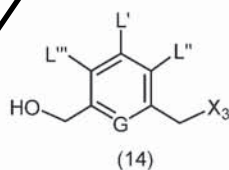


241. A method of preparing a compound of formula (18),

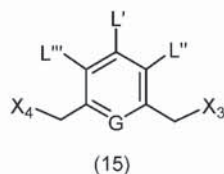


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

- (1) reacting a sulfonating reagent or an esterification reagent with the compound of formula (14)

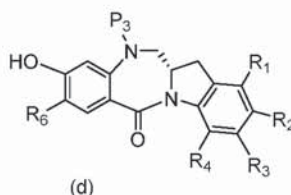


to form a compound of formula (15):

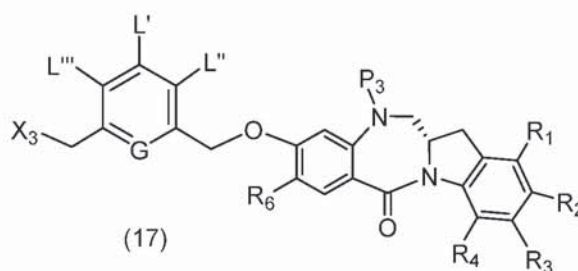


or a salt thereof;

- (2) reacting the compound of formula (15) with a reduced monomer compound of formula (d),

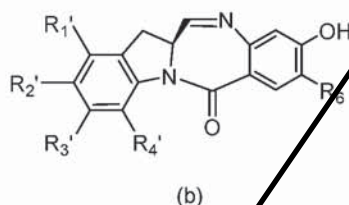


to form a compound of formula (17):



or a salt thereof; and

(3) reacting the compound of formula of (17) with a monomer of formula (b):



to form a compound of formula (18), or a pharmaceutically acceptable salt thereof, wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(CH₂CH₂O)_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;

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

R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' 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 -(CH₂CH₂O)_n-R_c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

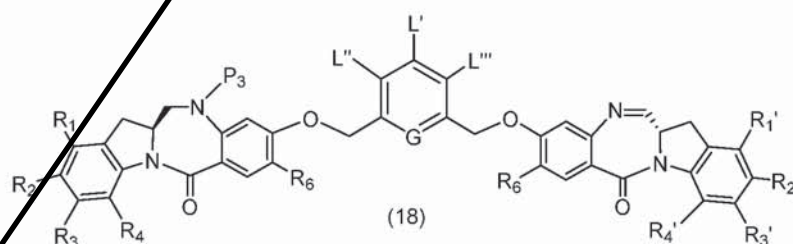
X₃ is -Cl;

X₄ is a sulfonate ester or an activated ester (preferably, a sulfonate ester);

P₁ is an alcohol protecting group; and

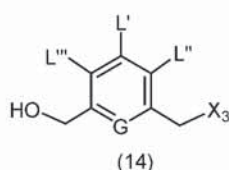
P₃ is H or an amine protecting group.

242. A method of preparing a compound of formula (18),

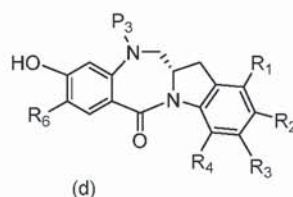


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

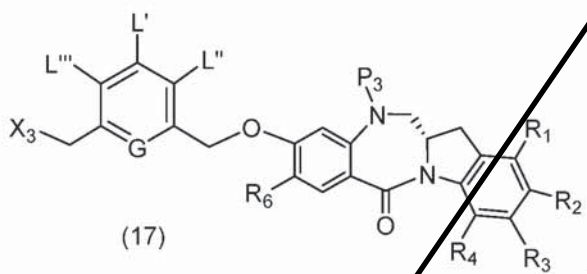
(1) reacting the compound of formula (14)



with a reduced monomer compound of formula (d),

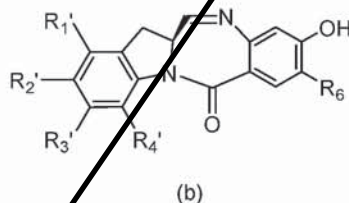


to form a compound of formula (17):



5 or a salt thereof; and

(2) reacting the compound of formula of (17) with a monomer of formula (b):



to form a compound of formula (18), or a pharmaceutically acceptable salt thereof, wherein:

10 L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

M is -H or a cation;

20 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 -

(CH₂CH₂O)_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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit - (CH₂CH₂O)_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;

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

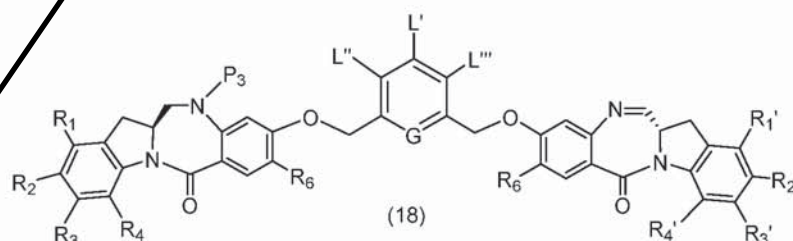
R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit -(CH₂CH₂O)_n-R^c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

X₃ is -Cl and

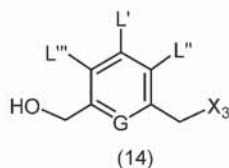
P₃ is H or an amine protecting group.

243. A method of preparing a compound of formula (18),

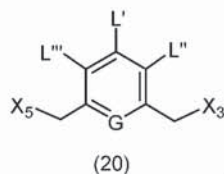


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

(1) reacting a halogenating reagent with the compound of formula (14)

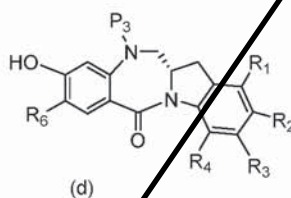


to form a compound of formula (20):

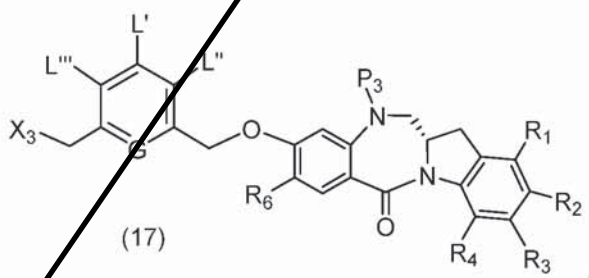


or a salt thereof;

- 5 (2) reacting the compound of formula (20) with a reduced monomer compound of formula (d),

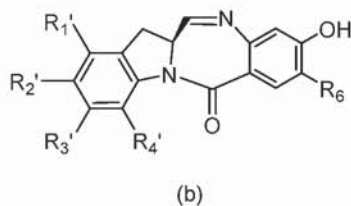


to form a compound of formula (17):



- 10 or a salt thereof; and

(3) reacting the compound of formula of (17) with a monomer of formula (b):



to form a compound of formula (18), or a pharmaceutically acceptable salt thereof, wherein:

- 15 L', L'', and L''' are the same or different, and are independently -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 [$-\text{NH}(\text{C}=\text{NH})\text{NH}_2$], $-\text{OR}$, $-\text{NR}'\text{R}''$, $-\text{NO}_2$, $-\text{NR}'\text{COR}''$, $-\text{SR}$, $-\text{SOR}'$, $-\text{SO}_2\text{R}'$, $-\text{SO}_3\text{M}$, $-\text{OSO}_3\text{M}$, $-\text{SO}_2\text{NR}'\text{R}''$, cyano, an azido, $-\text{COR}'$, $-\text{OCOR}'$, $-\text{OCONR}'\text{R}''$, or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L' , L'' , and L''' is the linking group with the reactive group bonded thereto;

M is $-\text{H}$ or a cation;

R , for each occurrence, is independently selected from the group consisting of $-\text{H}$, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(\text{CH}_2\text{CH}_2\text{O})_n-\text{R}^c$, 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 $-\text{H}$, $-\text{OH}$, $-\text{OR}$, $-\text{NHR}$, $-\text{N}(\text{R})_2$, $-\text{COR}$, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(\text{CH}_2\text{CH}_2\text{O})_n-\text{R}^c$, 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 $-\text{H}$ 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;

G is selected from $-\text{CH}-$ or $-\text{N}-$;

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 $-\text{H}$, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(\text{CH}_2\text{CH}_2\text{O})_n-\text{R}_c$, halogen, guanidinium [$-\text{NH}(\text{C}=\text{NH})\text{NH}_2$], $-\text{OR}$, $-\text{NR}'\text{R}''$, $-\text{NO}_2$, $-\text{NCO}$, $-\text{NR}'\text{COR}''$, $-\text{SR}$, $-\text{SOR}'$, $-\text{SO}_2\text{R}'$, $-\text{SO}_3\text{H}$, $-\text{OSO}_3\text{H}$, $-\text{SO}_2\text{NR}'\text{R}''$, cyano, an azido, $-\text{COR}'$, $-\text{OCOR}'$, and $-\text{OCONR}'\text{R}''$;

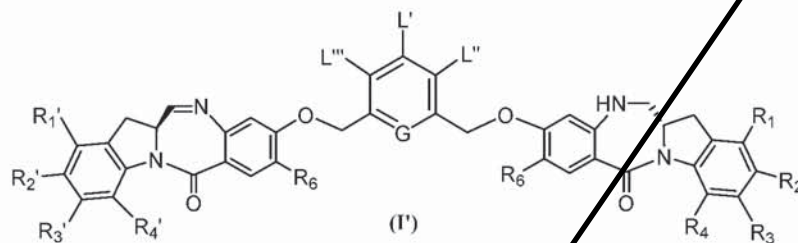
R_6 is $-\text{H}$, $-\text{R}$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}'\text{R}''$, $-\text{NO}_2$, or halogen;

X_3 is $-\text{Cl}$;

X₅ is -Br or -I; and

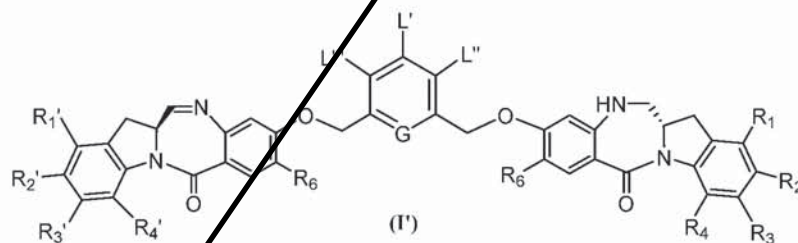
P₃ is H or an amine protecting group.

244. The method of claim 241, 242 or 243, wherein the compound of formula (16) is reacted with reduced monomer of formula (d), wherein P₃ is H, to form a compound of formula (I'):

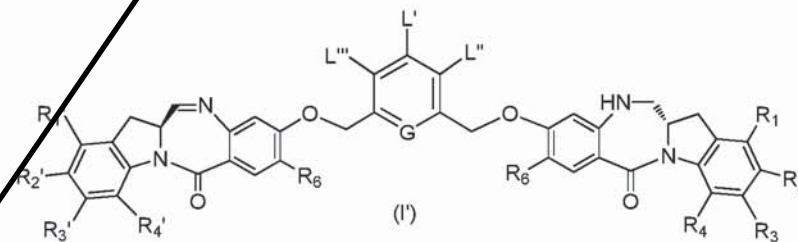


245. The method of any one of claims 241–243, wherein P₃ is an amine protecting group.

246. The method of claim 245, wherein the compound of formula (18) is further reacted with an amine deprotecting reagent to form a compound of formula (I'):

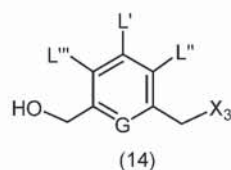


247. A method of preparing a compound of formula (I'),

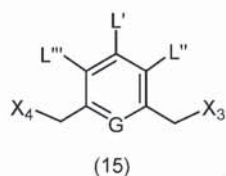


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

- (1) reacting a sulfonating reagent or an esterification reagent with the compound of formula (14)

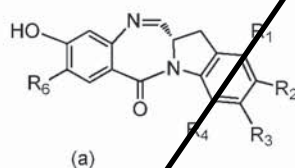


to form a compound of formula (15):

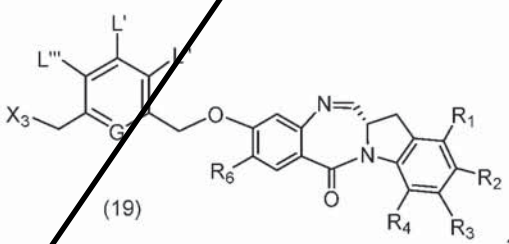


or a salt thereof;

- 5 (2) reacting the compound of formula (15) with a monomer compound of formula (a),

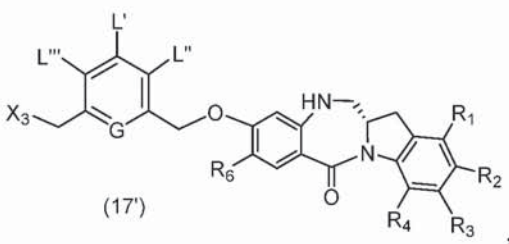


to form a compound of formula (19):



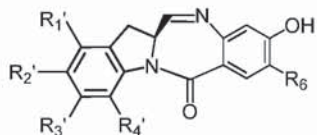
10 or a salt thereof;

- (3) reacting the compound of formula (19) with an imine reducing agent to form a compound of formula (17'):



or a salt thereof; and

- 15 (4) reacting the compound of formula (17') with a monomer of formula (b):



(b)

to form the compound of formula (I');

wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)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;

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

$R_1, R_2, R_3, R_4, R_1', R_2', R_3',$ 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 $-(CH_2CH_2O)_n-R_c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

R_6 is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

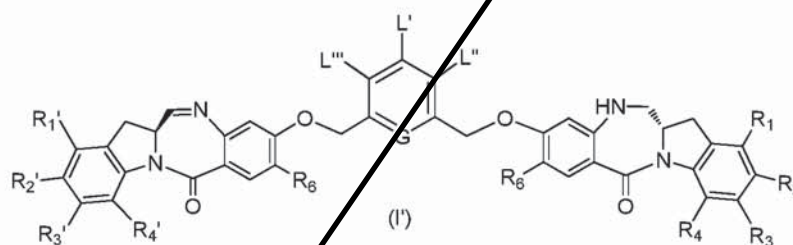
X_3 is -Cl;

X_4 is a sulfonate ester or an activated ester (preferably, a sulfonate ester);

and

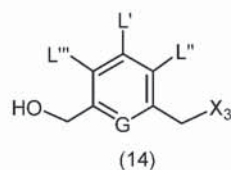
P_2 is an amine protecting group.

248. A method of preparing a compound of formula (I'),

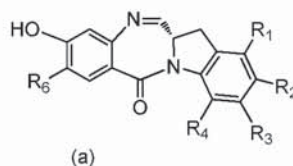


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

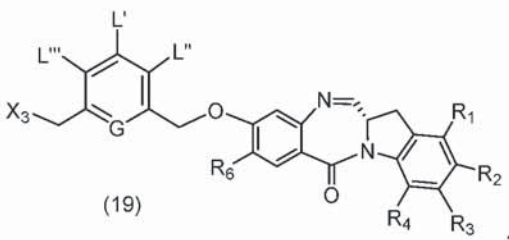
(1) reacting the compound of formula (14)



with a monomer compound of formula (a),

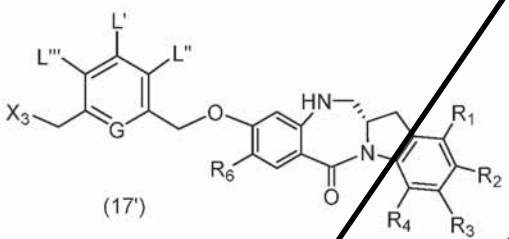


to form a compound of formula (19):



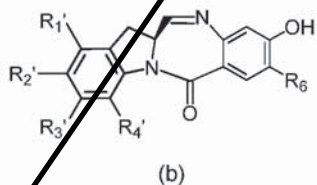
or a salt thereof;

(2) reacting the compound of formula (19) with an imine reducing agent to form compound of formula (17'):



or a salt thereof; and

(3) reacting the compound of formula (17') with a monomer of formula (b):



to form the compound of formula (I'); wherein:

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'', and L''' is the linking group with the reactive group bonded thereto;

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 -

(CH₂CH₂O)_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, -N(R)₂, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit - (CH₂CH₂O)_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;

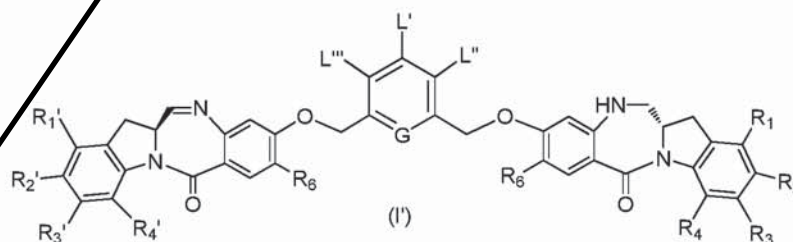
G is selected from -CH- or -N-;

R₁, R₂, R₃, R₄, R₁', R₂', R₃', and R₄' 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 -(CH₂CH₂O)_n-R^c, halogen, guanidinium [-NH(C=NH)NH₂], -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

R₆ is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

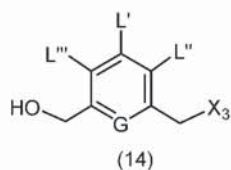
X₃ is -Cl

249. A method of preparing a compound of formula (I'),

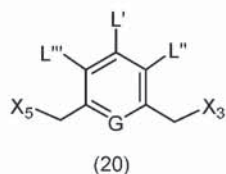


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

(1) reacting a brominating or iodinating reagent with a compound of formula (14):

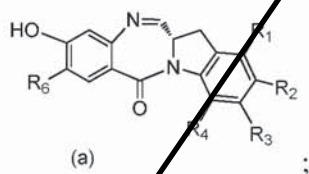


or a salt thereof, to form a compound of formula (20):

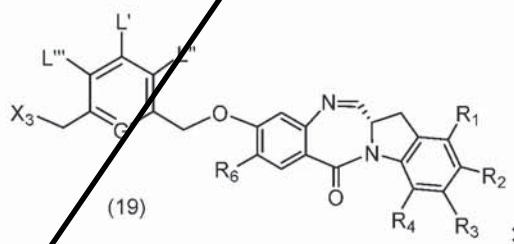


or a salt thereof;

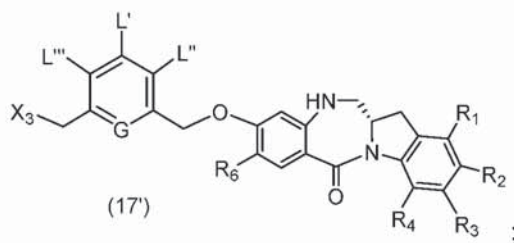
- 5 (2) reacting a compound of formula (20) or a salt thereof with a monomer compound of formula (a):



to form a compound of formula (19):

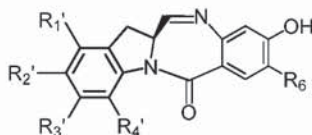


- 10 (3) reacting the compound of formula (19) with an imine reducing agent to form a compound of formula (17'):



or a salt thereof, and

- (4) reacting the compound of (17') with a monomer of formula (b):



(b)

to form the compound of formula (I'), wherein

L', L'', and L''' are the same or different, and are independently -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'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃M, -OSO₃M, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', -OCONR'R'', or a linking group with a reactive group bonded thereto capable of covalently linking a cytotoxic compound to a cell binding agent (CBA), provided that zero or one of L', L'' and L''' is the linking group with the reactive group bonded thereto;

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, -N(R)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;

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

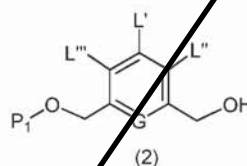
5 $R_1, R_2, R_3, R_4, R_1', R_2', R_3',$ and R_4' are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2O)_n-R_c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NCO, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -OCONR'R'';

R_6 is -H, -R, -OR, -SR, -NR'R'', -NO₂, or halogen;

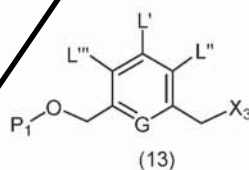
X_3 is -Cl; and

P_1 is an alcohol protecting group.

- 10 250. The method of any one of claims 235-249, wherein the compound of formula (14) or a salt thereof is prepared by a method comprising the steps of:
(1) reacting a chlorinating reagent with a compound of formula (2):



to form a compound of formula (13):

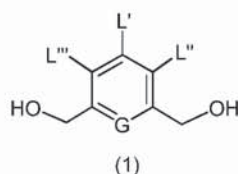


15

or a salt thereof; and

(2) reacting the compound of formula (13) with an alcohol deprotecting reagent to form the compound of formula (14) or a salt thereof.

- 20 251. The method of claim 250 wherein the compound of formula (2) is prepared by reacting a compound of formula (1) with an alcohol protecting reagent



252. The method of any one of claims 1-251, wherein G is -CH-.

254. The method of any one of claims 1–253, wherein one of L', L'', and L''' is represented by the following formula:

and the other two 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 $-(CH_2CH_2O)_n-R_c$, halogen, guanidinium $[-NH(C=NH)NH_2]$, -OR, -NR'R'', -NO₂, -NR'COR'', -SR, -SOR', -SO₂R', -SO₃H, -OSO₃H, -SO₂NR'R'', cyano, an azido, -COR', -OCOR', and -CONR'R'';

P is an amino acid residue or a peptide containing between 2 to 20 amino acid residues;

R_x is an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms; and,

255. The method of claim 254, wherein one of L', L'' and L''' is represented by formula (A), and the others are each independently -H, an linear or branched alkyl having from 1 to 6 carbon atoms, halogen, -OH, (C₁-C₆)alkoxy, or -NO₂.

~~257.~~ The method of claim 254, wherein L' is represented by formula (A); and L'' and L''' are both -H.

258. The method of any one of claims 254–257, wherein R_x is a linear, branched or cyclic alkyl having 1 to 6 carbon atoms optionally substituted with halogen, -OH,

(C₁-C₃)alkyl, (C₁-C₃)alkoxy, halo(C₁-C₃)alkyl, or a charged substituent or an ionizable group Q.

259. The method of any one of claims 254–258, wherein J is NHR^{cl}, -COOR^{cl} or -COE, wherein -COE represents a reactive ester, and R^{cl} is -H or linear or branched alkyl having 1 to 4 carbon atoms optionally substituted with halogen, -OH or (C₁-C₃)alkoxy.

260. The method of claim 259, wherein J is -COOR^{cl} and R^{cl} is a (C₁-C₃)alkyl.

261. The method of any one of claims 254–257, wherein L' is represented by the following formula:

10
$$-\text{NR}_5-\text{P}-\text{C}(=\text{O})-(\text{CR}_a\text{R}_b)_m-\text{J} \quad (\text{B1});$$

$$-\text{NR}_5-\text{P}-\text{C}(=\text{O})-\text{Cy}-(\text{CR}_a\text{R}_b)_{m'}-\text{J} \quad (\text{B2});$$

$$-\text{C}(=\text{O})-\text{P}-\text{NR}_5-(\text{CR}_a\text{R}_b)_m-\text{J} \quad (\text{C1}), \text{ or}$$

$$-\text{C}(=\text{O})-\text{P}-\text{NR}_5-\text{Cy}-(\text{CR}_a\text{R}_b)_{m'}-\text{J} \quad (\text{C2})$$

wherein:

15 J is -COOR^{cl};

R^{cl} is -H or linear or branched alkyl having 1 to 4 carbon atoms optionally substituted with halogen, -OH or (C₁-C₃)alkoxy;

R_a and R_b, for each occurrence, are each independently -H, (C₁-C₃)alkyl or a charged substituent or an ionizable group Q;

20 m is an integer from 1 to 6;

m' is 0 or an integer from 1 to 6; and,

Cy is a cyclic alkyl having 5 or 6 ring carbon atoms optionally substituted with halogen, -OH, (C₁-C₃)alkyl, (C₁-C₃)alkoxy, or halo(C₁-C₃)alkyl.

262. The method of claim 261, wherein R_a and R_b are both H; Cy is cyclohexane; and R₅ is H or Me.

263. The method of claim 261 or 262, wherein m' is 0 or 1.

264. The compound of any one of claims 254–257, wherein L' is represented by the following formula:

$$-\text{NR}_5-\text{P}-\text{C}(=\text{O})-(\text{CR}_a\text{R}_b)_m-\text{S}-\text{Z}^s \quad (\text{B3}); \text{ or}$$

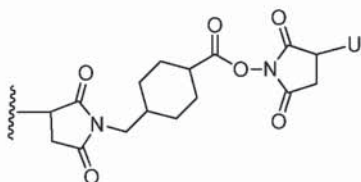


wherein:

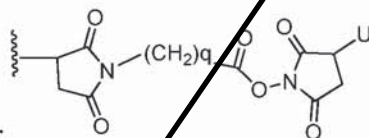
R_a and R_b , for each occurrence, are each independently -H, (C_1-C_3) alkyl or a charged substituent or an ionizable group Q;

5 m is an integer from 1 to 6;

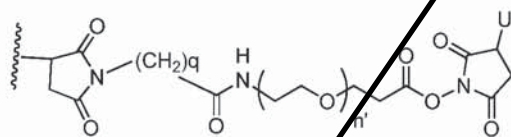
Z^s is -H, $-SR^d$, $-C(=O)R^{d1}$ or is selected from any one of the following formulas:



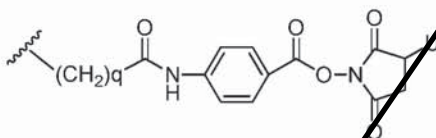
(a1);



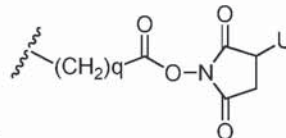
(a2);



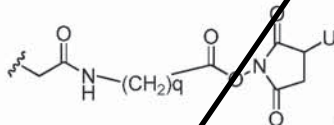
(a3);



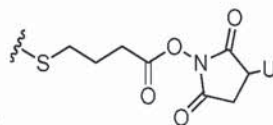
(a4);



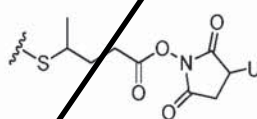
(a5);



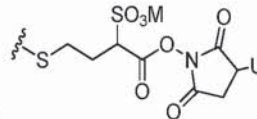
(a6);



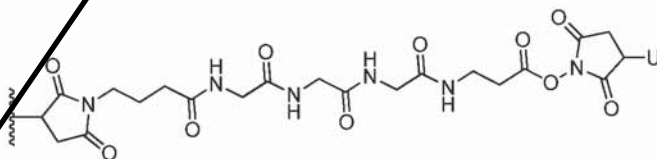
(a7);



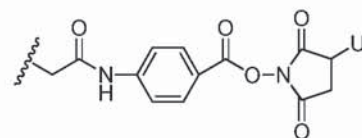
(a8);



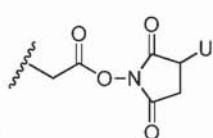
(a9);



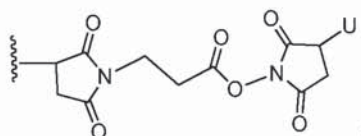
(a10);



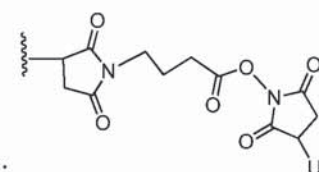
(a11);



(a12);

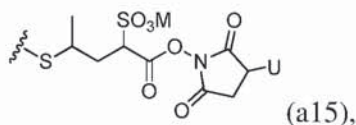


(a13);



(a14); or

15



wherein:

q is an integer from 1 to 5;

n' is an integer from 2 to 6;

5 U is -H or SO₃M;

M is H⁺, Na⁺ or K⁺;

R^d is a linear or branched alkyl having 1 to 6 carbon atoms or is selected from phenyl, nitrophenyl (*e.g.*, 2 or 4-nitrophenyl), dinitrophenyl (*e.g.*, 2,4-dinitrophenyl), carboxynitrophenyl (*e.g.*, 3-carboxy-4-nitrophenyl), pyridyl or
10 nitropyridyl (*e.g.*, 4-nitropyridyl); and

R^{dl} is a linear or branched alkyl having 1 to 6 carbon atoms.

265. The method of claim 264, wherein Z^s is -SR^d and R^d is a (C₁-C₃)alkyl, pyridyl or nitropyridyl.

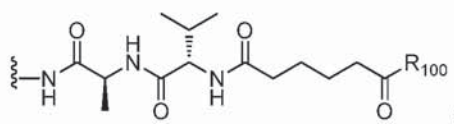
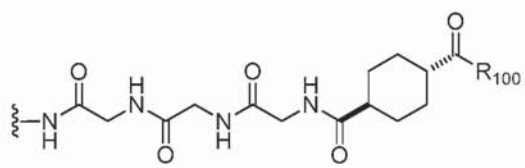
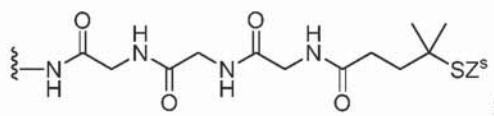
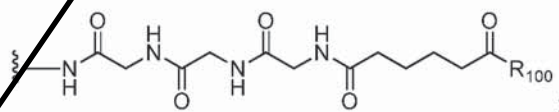
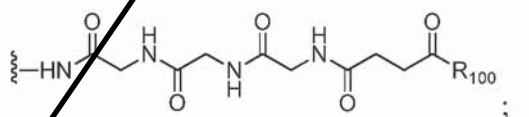
266. The method of any one of claims 261-265, wherein the charged substituent or an
15 ionizable group Q is i) -SO₃H, -Z'-SO₃H, -OPO₃H₂, -Z'-OPO₃H₂, -PO₃H₂, -Z'-PO₃H₂, -CO₂H, -Z'-CO₂H, -NR₁₁R₁₂, or -Z'-NR₁₁R₁₂, or a pharmaceutically acceptable salt thereof; or, ii) -N⁺R₁₄R₁₅R₁₆X^{A-} or -Z'-N⁺R₁₄R₁₅R₁₆X^{A-}; Z' is an optionally substituted alkylene, an optionally substituted cycloalkylene or an optionally substituted phenylene; R₁₁, R₁₂, R₁₄ to R₁₆ are each independently H
20 or an optionally substituted alkyl; and X^{A-} is a pharmaceutically acceptable anion.

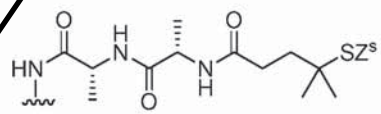
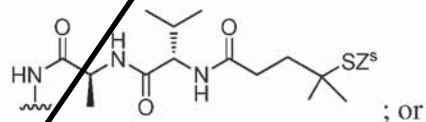
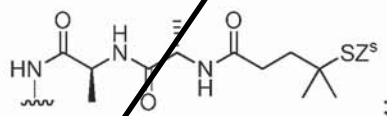
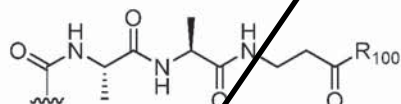
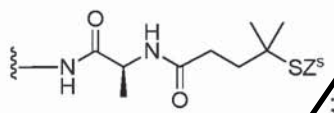
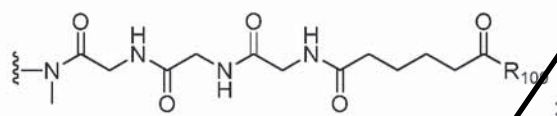
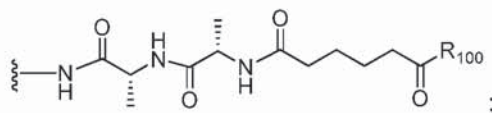
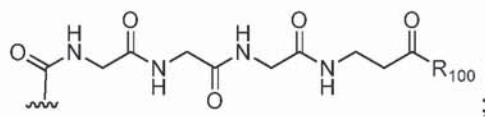
267. The method of claim 266, wherein Q is SO₃H or a pharmaceutically acceptable salt thereof.

268. The method of any one of claims 264-267, wherein R_a and R_b are both -H and R₅
25 is H or Me.

269. The method of any one of claims 264-267, wherein -(CR_aR_b)_m- is -(CH₂)_m-, C(Me₂)- and m' is an integer from 1 to 5.

270. The method of any one of claims 261–269, wherein P is a peptide containing 2 to 10 amino acid residues.
271. The method of claim 270, wherein P is a peptide containing 2 to 5 amino acid residues.
- 5 272. The method of claim 270, wherein P is Gly-Gly-Gly, Ala-Val, Val-Ala, Val-Cit, Val-Lys, Phe-Lys, Lys-Lys, Ala-Lys, Phe-Cit, Leu-Cit, Ile-Cit, Trp, Cit, Phe-Ala, Phe-N⁹-tosyl-Arg, Phe-N⁹-nitro-Arg, Phe-Phe-Lys, D-Phe-Phe-Lys, Gly-Phe-Lys, Leu-Ala-Leu, Ile-Ala-Leu, Val-Ala-Val, Ala-Leu-Ala-Leu, β-Ala-Leu-Ala-Leu and Gly-Phe-Leu-Gly, Val-Arg, Arg-Val, Arg-Arg, Val-D-Cit, Val-D-Lys, Val-D-Arg, D-Val-Cit, D-Val-Lys, D-Val-Arg, D-Val-D-Cit, D-Val-D-Lys, D-Val-D-Arg, D-Arg-D-Arg, Ala-Ala, Ala-D-Ala, D-Ala-Ala, D-Ala-D-Ala, Ala-Met, or Met-Ala, Gln-Val, Val-Gln, Gln-Ala, Ala-Gln, Asn-Ala, Ala-Asn.
- 10 273. The method of claim 270, wherein P is Gly-Gly-Gly, Ala-Val, Ala-Ala, Ala-D-Ala, D-Ala-Ala, or D-Ala-D-Ala.
- 15 274. The method of any one of claims 254–257, wherein L' is represented by any one of the following:





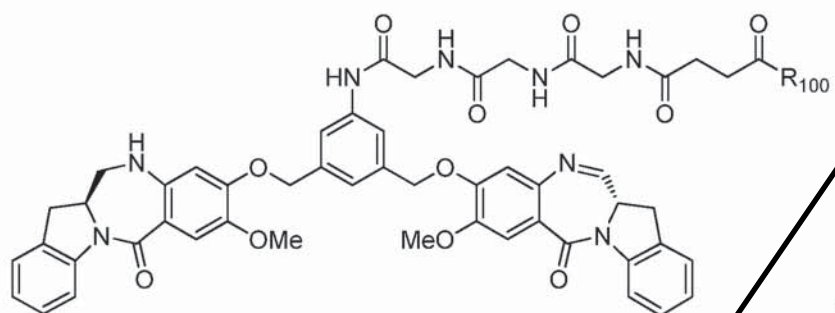
wherein:

R_{100} is a $(\text{C}_1\text{-C}_3)$ alkoxy;

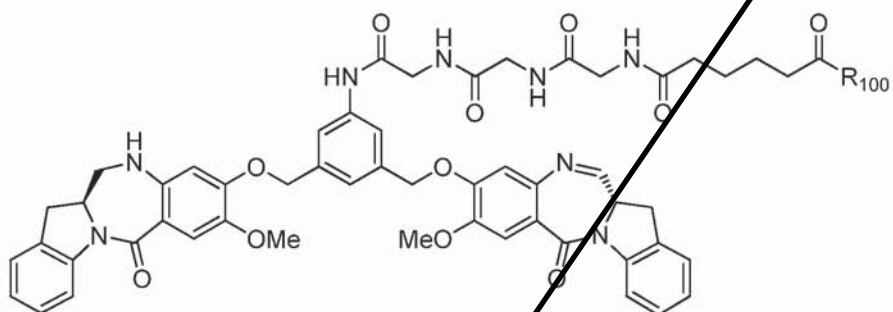
Z^s is $-\text{SR}_{101}$; and

R_{101} is a $(\text{C}_1\text{-C}_3)$ alkyl, pyridyl or nitropyridyl.

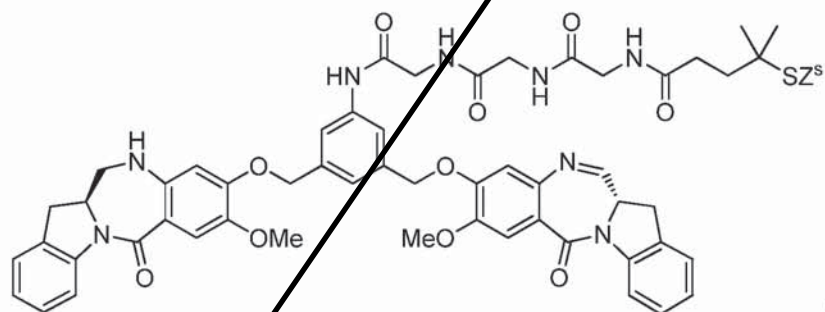
275. The method of any one of claims 62, 66, 67, 85, 91, 94, 95, 113, 114, 116, 118, 119, 179, 182, 230, 233, 238, 240, 244, 246, 247, 248, and 249, wherein the compound of formula (I') is represented by any one of the following:



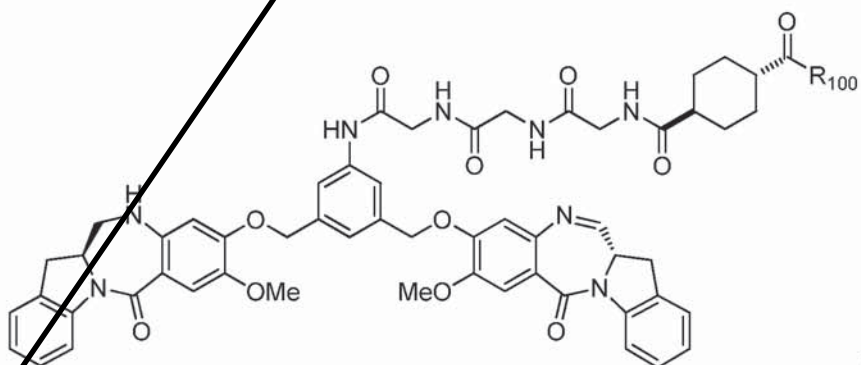
;



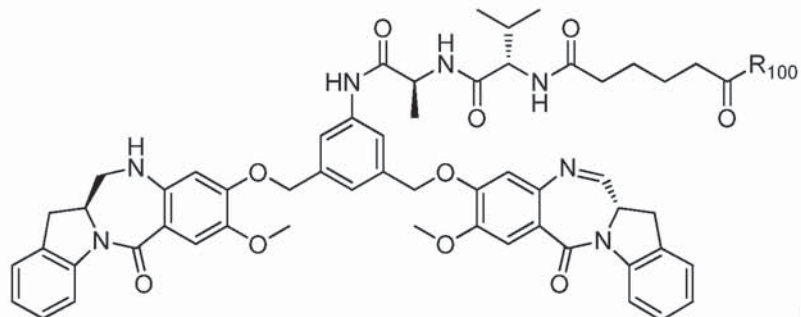
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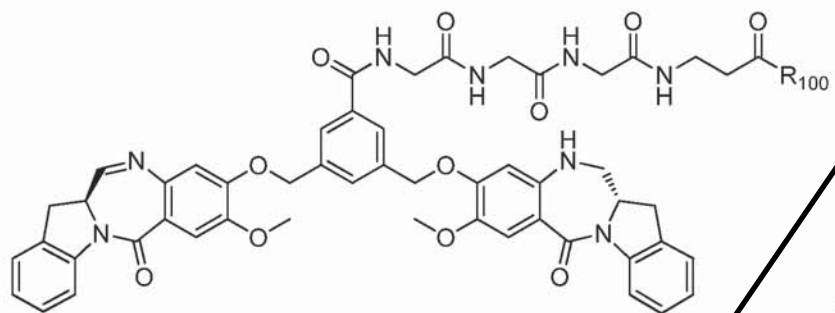
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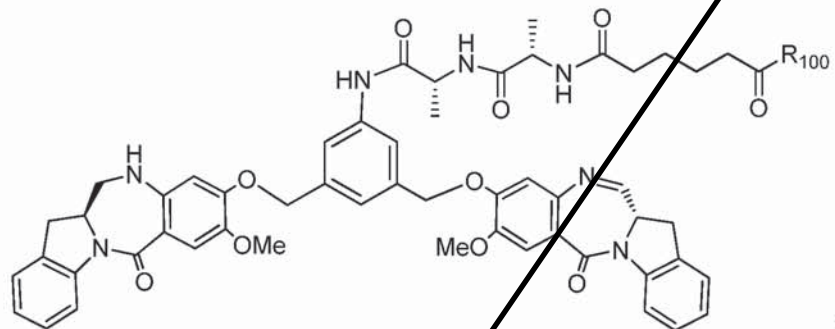
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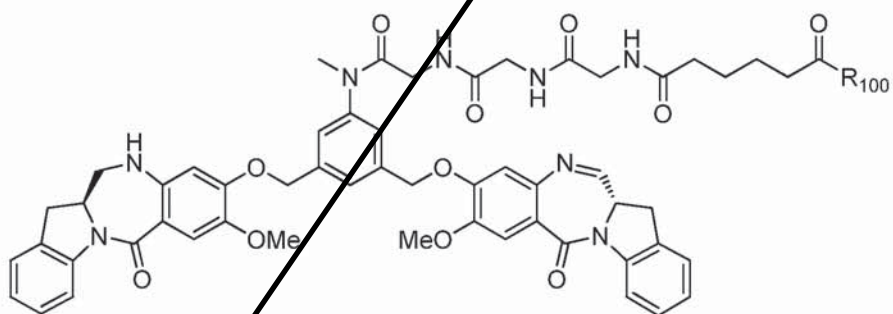
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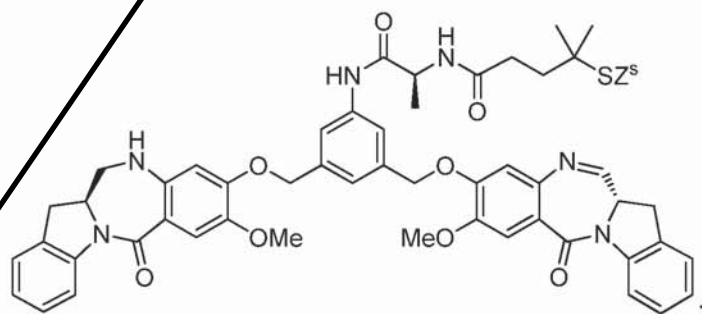
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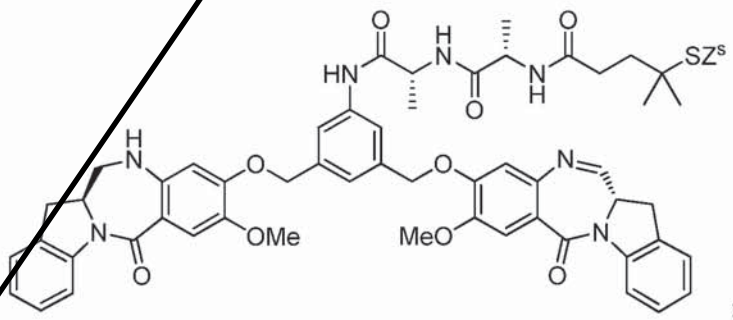
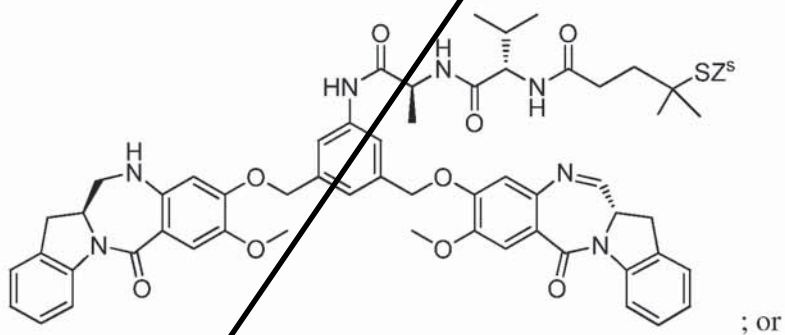
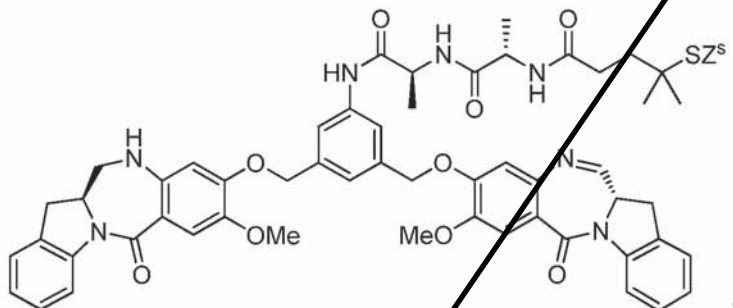
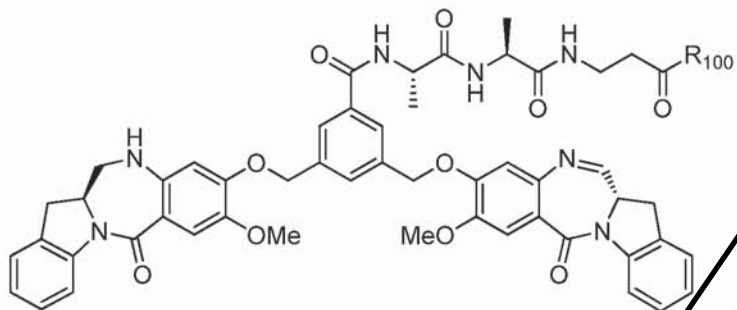


;



;

5



5 or a pharmaceutically acceptable salt thereof, wherein:

R_{100} is a (C₁-C₃)alkoxy;

Z^s is $-SR_{101}$; and

R_{101} is a (C₁-C₃)alkyl, pyridyl or nitropyridyl.

276. The method of any one of claims 1-275, wherein, when present, R_{100} is -OMe and R_{101} is Me or pyridyl.

277. The method of any one of claims 1–253, wherein one of L', L'', and L''' is represented by the following formula:



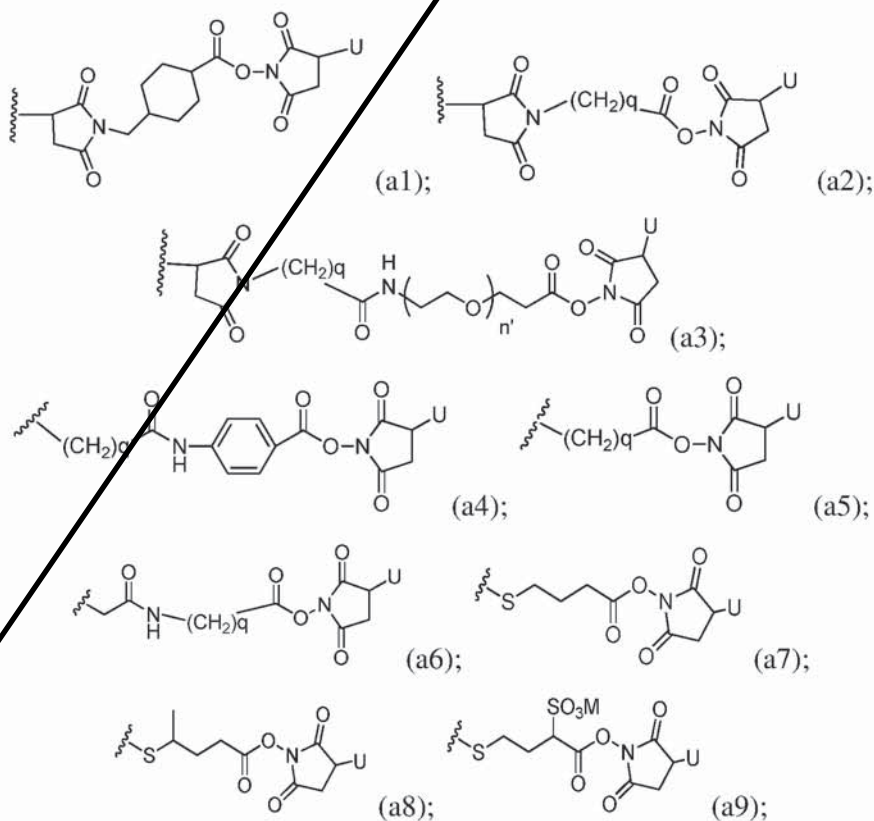
wherein:

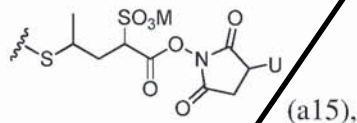
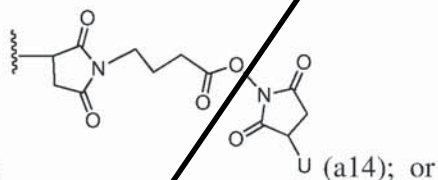
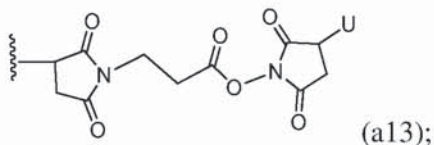
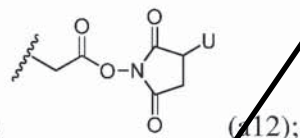
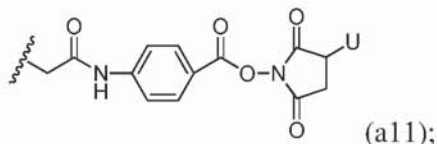
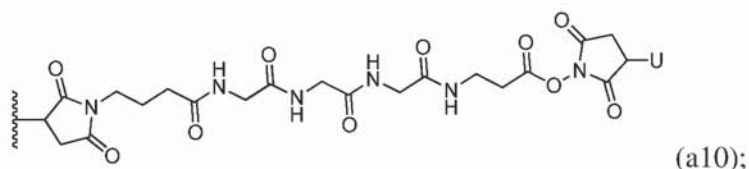
5 R^x is a linear or branched alkylene having 1 to 6 carbon atoms, optionally substituted with a charged substituent or an ionizable group Q;

10 Q is i) $-SO_3H$, $-Z'-SO_3H$, $-OPO_3H_2$, $-Z'-OPO_3H_2$, $-PO_3H_2$, $-Z'-PO_3H_2$, $-CO_2H$, $-Z'-CO_2H$, $-NR_{11}R_{12}$, or $-Z'-NR_{11}R_{12}$, or a pharmaceutically acceptable salt thereof; or, ii) $-N^+R_{14}R_{15}R_{16}X^{A-}$ or $-Z'-N^+R_{14}R_{15}R_{16}X^{A-}$; Z' is an optionally substituted alkylene, an optionally substituted cycloalkylene or an optionally substituted phenylene; R_{11} , R_{12} , R_{14} , R_{15} and R_{16} are each independently H or an optionally substituted alkyl; and X^{A-} is a pharmaceutically acceptable anion;

R^e is $-H$ or a linear or branched alkyl having 1 to 6 carbon atoms;

15 Z^s is $-H$, $-SR^d$, $-C(=O)R^{d1}$ or is selected from any one of the following formulas:





5 wherein:

q is an integer from 1 to 5;

R^d is a linear or branched alkyl having 1 to 6 carbon atoms or is selected from phenyl, nitrophenyl, dinitrophenyl, carboxynitrophenyl, pyridyl and nitropyridyl;

10 R^{dl} is a linear or branched alkyl having 1 to 6 carbon atoms

n' is an integer from 2 to 6;

U is -H or $-SO_3M$; and

M is -H or a cation.

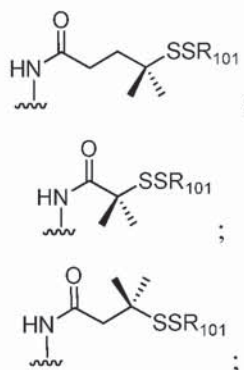
278. The method of claim 277, wherein one of L' , L'' and L''' is represented by
15 formula (B), and the others are each independently -H, an linear or branched alkyl having from 1 to 6 carbon atoms, halogen, -OH, (C_1-C_6) alkoxy, or $-NO_2$.

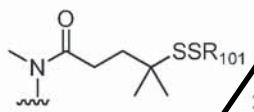
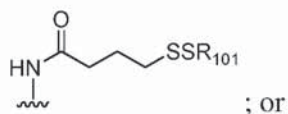
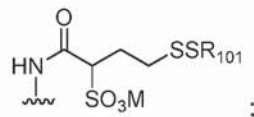
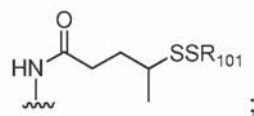
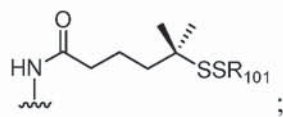
279. The method of claim 278, wherein one of L' , L'' and L''' is represented by
formula (B), and the others are -H.

280. The method of claim 278, wherein L' is represented by formula (B); and L'' and
20 L''' are both -H.

281. The method of any one of claims 277–280, wherein Z^s is $-SR^d$ and R^d is a (C_1-C_3) alkyl, pyridyl or nitropyridyl.

282. The method of any one of claims 277–281, wherein R^e is -H or -Me.
283. The method of any one of claims 277–282, 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.
- 5 284. The method of claim 283, wherein R^f and R^g are the same or different, and are selected from -H and -Me.
285. The method of claim 283, wherein R^f and R^g are both -Me; and p is 2.
286. The method of any one of claims 277–282, wherein R^x is a linear or branched alkylene having 1 to 4 carbon atoms substituted with a charged substituent or an ionizable group Q.
- 10 287. The method of claim 286, wherein the charged substituent or an ionizable group Q is: i) $-SO_3H$, $-Z'-SO_3H$, $-OPO_3H_2$, $-Z'-OPO_3H_2$, $-PO_3H_2$, $-Z'-PO_3H_2$, $-CO_2H$, $-Z'-CO_2H$, $-NR_{11}R_{12}$, or $-Z'-NR_{11}R_{12}$, or a pharmaceutically acceptable salt thereof; or, ii) $-N^+R_{14}R_{15}R_{16}X^{A-}$ or $-Z'-N^+R_{14}R_{15}R_{16}X^{A-}$; Z' is an optionally substituted alkylene, an optionally substituted cycloalkylene or an optionally substituted phenylene; R_{11} , R_{12} , R_{14} to R_{16} are each independently H or an optionally substituted alkyl; and X^{A-} is a pharmaceutically acceptable anion.
- 15 288. The method of claim 287, wherein Q is $-SO_3H$ or a pharmaceutically acceptable salt thereof.
- 20 289. The method of any one of claims 277–280, wherein L' is represented by the following formula:

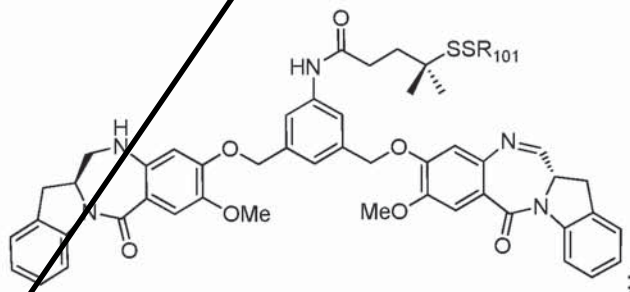




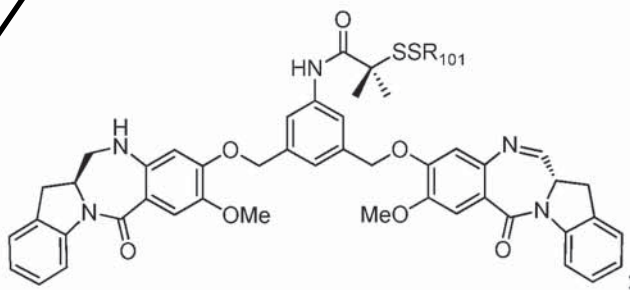
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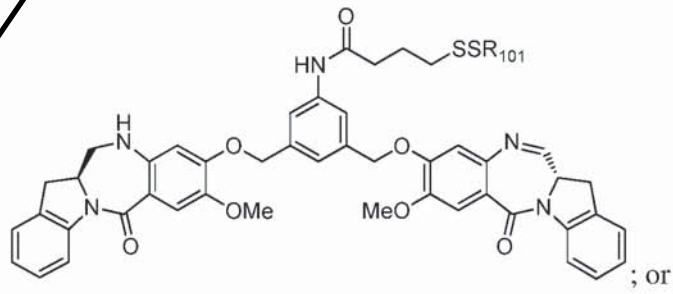
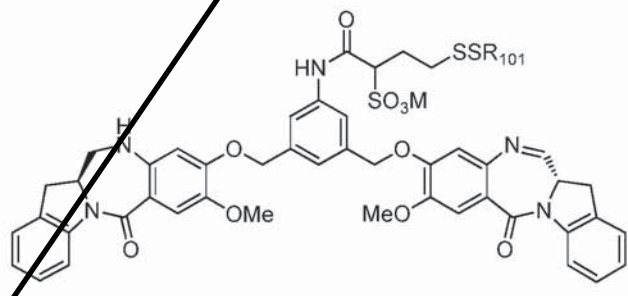
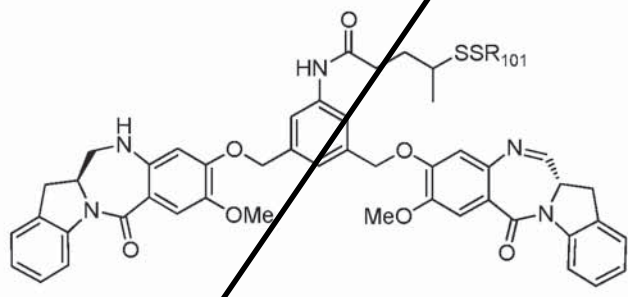
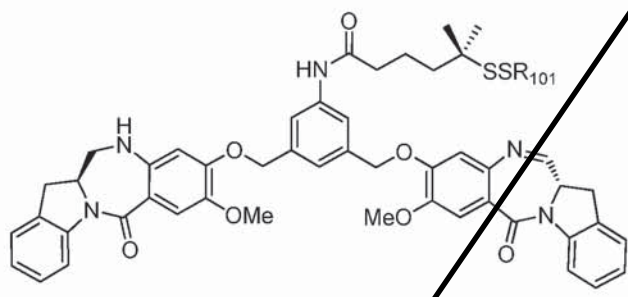
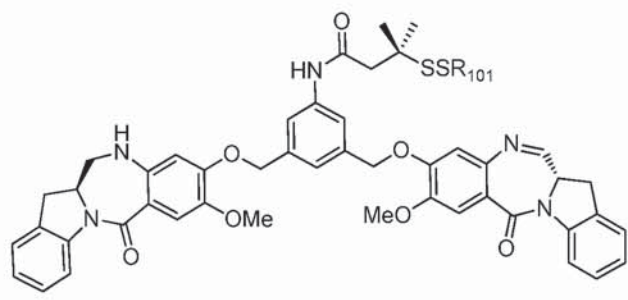
wherein R_{101} is a (C₁-C₃)alkyl, pyridyl or nitropyridyl; and M is H⁺, Na⁺ or K⁺.

290. The method of any one of claims 62, 66, 67, 85, 91, 94, 95, 113, 114, 116, 118, 119, 179, 182, 230, 233, 238, 240, 244, 246, 247, 248, and 249, wherein the compound of formula (I') is represented by any one of the following:

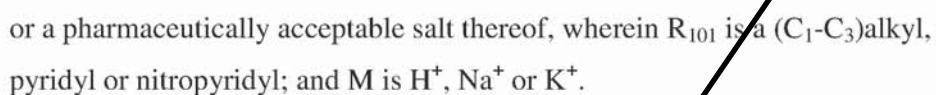


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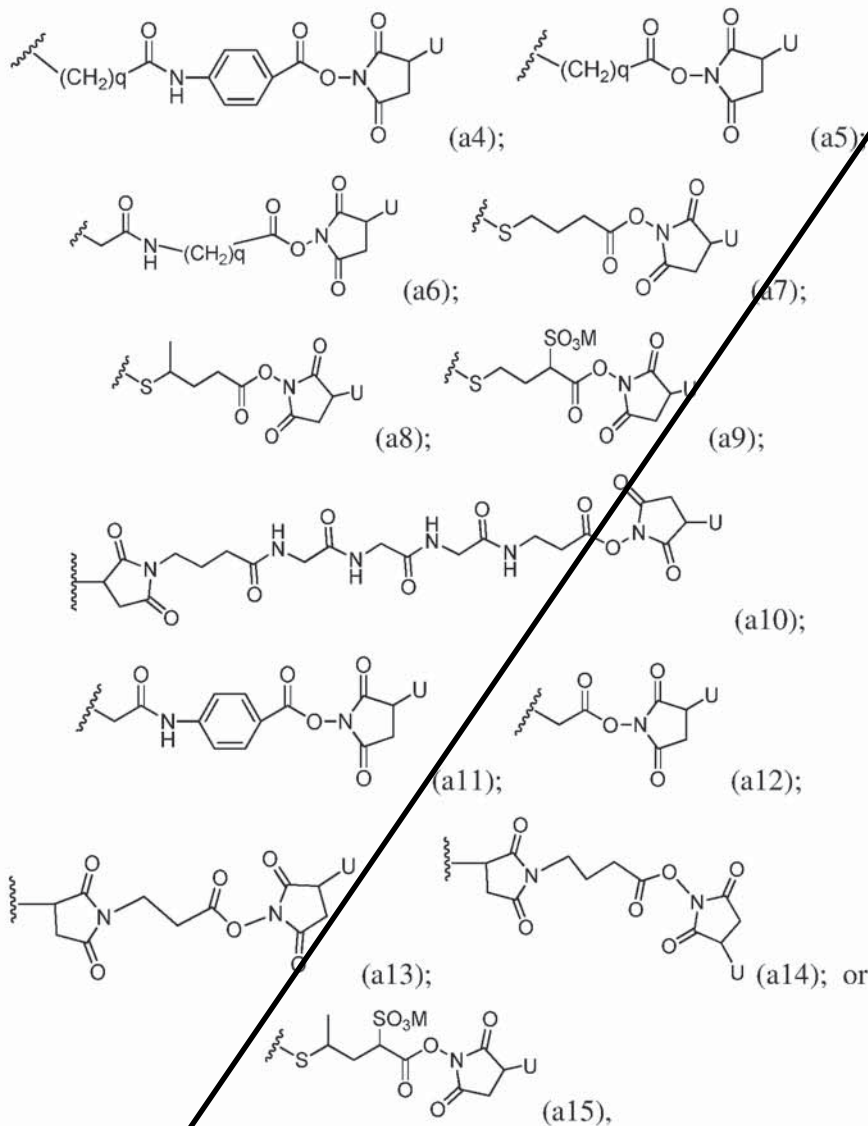
- 5 292. The method of any one of claims 1–253, wherein one of L', L'', and L''' is represented by the following formula:



10 R¹ is -H, a linear, branched or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms or -(CH₂-CH₂-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.*, -NHR¹⁰¹) or tertiary amino (-NR¹⁰¹R¹⁰²) group or a 5- or 6-membered nitrogen containing heterocycle, such as piperidine or morpholine, wherein R¹⁰¹
15 and R¹⁰² are each independently a linear, branched, or cyclic alkyl, alkenyl or alkynyl having 1 to 10 carbon atoms;

~~Z^s is -H, -SR^d, -C(=O)R^{d1} or is selected from any one of the following formulas:~~





wherein:

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

R^{dl} is a linear or branched alkyl having 1 to 6 carbon atoms;

q is an integer from 1 to 5;

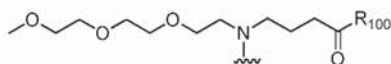
n is an integer from 2 to 6;

n' is an integer from 1 to 24;

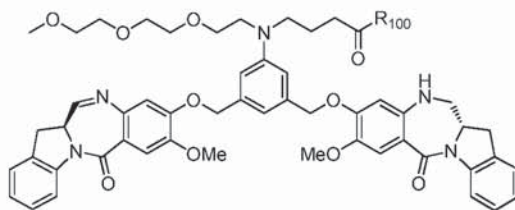
U is -H or -SO₃M;

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

293. The method of claim 292, wherein one of L', L'' and L''' is represented by formula (C), and the others are each independently -H, an linear or branched alkyl having from 1 to 6 carbon atoms, halogen, -OH, (C₁-C₆)alkoxy, or -NO₂.
294. The method of claim 292, wherein wherein one of L', L'' and L''' is represented by formula (C), and the others are -H.
295. The method of claim 292, wherein L' is represented by formula (C); and L'' and L''' are both -H.
296. The method of any one of claims 292-295, wherein Z^s is -SR^d and R^d is a (C₁-C₃)alkyl, pyridyl or nitropyridyl.
297. The method of claims 292-296, wherein R^e is -(CH₂-CH₂-O)_n-R^k, wherein R^k is -H, or a linear, branched, or cyclic alkyl having 1 to 6 carbon atoms.
298. The method of claim 297, wherein R^k is -H or -Me, and n is 3.
299. The method of any one of claims 292-298, wherein R^x is a linear or branched alkyl having 1 to 6 carbon atoms.
300. The method of claim 299, wherein R^x is -(CH₂)_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.
301. The method of claim 300, wherein R^f and R^g are the same or different, and are selected from -H and -Me; and p is 1.
302. The method of any one of claims 1-253, wherein L' is represented by the following formula:

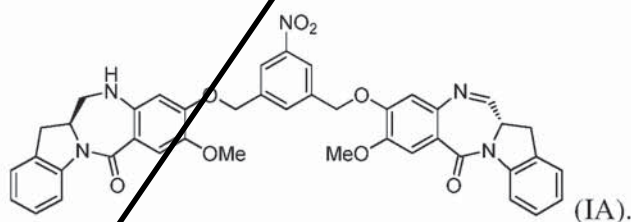


- L'' and L''' are both H; and R₁₀₀ is a (C₁-C₃)alkoxy.
303. The method of any one of claims 62, 66, 67, 85, 91, 94, 95, 113, 114, 116, 118, 119, 179, 182, 230, 233, 238, 240, 244, 246, 247, 248, and 249, wherein the compound of formula (I') is represented by any one of the following:

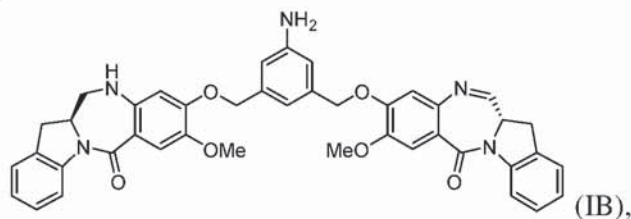


or a pharmaceutically acceptable salt thereof, wherein R_{101} is a (C_1-C_3) alkyl, pyridyl or nitropyridyl; and R_{100} is a (C_1-C_3) alkoxy.

304. The method of claim 302 or 303, wherein R_{101} is Me or pyridyl; and R_{100} is -OMe.
305. The method of any one of claims 1–253, wherein L' –NO₂; and L'' and L''' are both H..
306. The method of any one of claims 62, 66, 67, 85, 91, 94, 95, 113, 114, 116, 118, 119, 179, 182, 230, 233, 238, 240, 244, 246, 247, 248, and 249, wherein the compound of formula (I') is represented by formula (IA):



307. The method of claim 306, wherein the compound of formula (IA) is reacted with a reducing agent to form a compound of formula (IB):

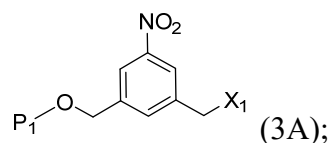


- or a pharmaceutically acceptable salt thereof.
308. The method of claim 307, wherein the reducing agent is selected from the group consisting of: hydrogen gas, sodium hydrosulfite, sodium sulfide, stannous chloride, titanium (II) chloride, zinc, iron and samarium iodide.

309. The method of claim 308, wherein the reducing agent is Fe/NH₄Cl or Zn/NH₄Cl.

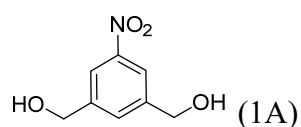
CLAIMS

1. A method of preparing a compound of formula (3A),

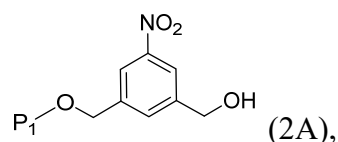


or a salt thereof, said method comprising the steps of:

- (i) introducing an alcohol protecting group onto one of the primary alcohols of a compound of formula (1) by reacting the compound of formula (1A) with an alcohol protecting reagent,



to form a compound of formula (2A),



or a salt thereof; and

- (ii) reacting a halogenating reagent, a sulfonating reagent or an esterification reagent with the compound of formula (2A),

wherein:

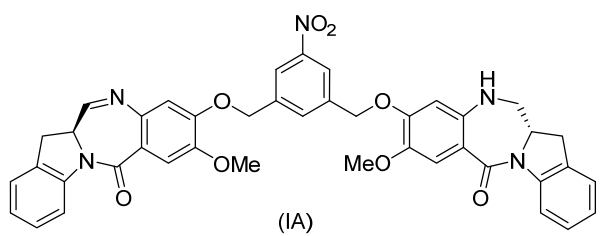
P_1 is an alcohol protecting group; and,

X_1 is a leaving group selected from the group consisting of: -Br, -I, -Cl, a sulfonate ester, and an activated ester (preferably, X_1 is -Br, -I, or a sulfonate ester).

2. The method of claim 1, wherein the sulfonate ester represented by X_1 is mesylate, tosylate, brosylate, or triflate, optionally, X_1 is mesylate.
3. The method of claim 1, wherein the method comprising reacting the compound of formula (2A) with a sulfonating reagent in the presence of a non-nucleophilic base, optionally wherein: (i) the non-nucleophilic base is triethylamine, imidazole, diisopropylethylamine, pyridine, 2,6-lutidine, dimethylformamide, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or tetramethylpiperidine; or (ii) the

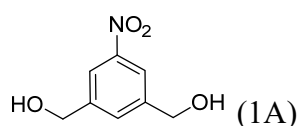
non-nucleophilic base is triethylamine or diisopropylethylamine.

4. The method of claim 1, wherein the sulfonating reagent is methanesulfonic anhydride or methanesulfonyl chloride (MsCl)
5. A method of preparing a compound of formula (IA),

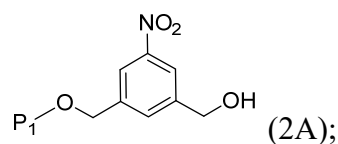


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

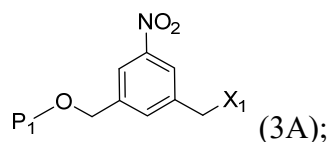
- (1) introducing an alcohol protecting group onto one of the primary alcohols of a compound of formula (1A),



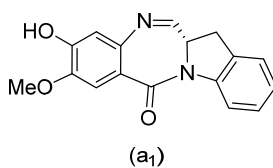
to form a compound of formula (2A),



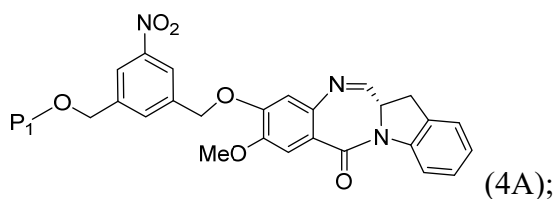
- (2) reacting the compound of formula (2A) with a halogenating reagent, a sulfonating reagent or an esterification reagent to form a compound of formula (3A),



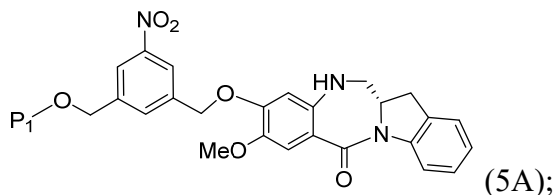
- (3) reacting the compound of formula (3A) with a monomer compound of the formula (a₁),



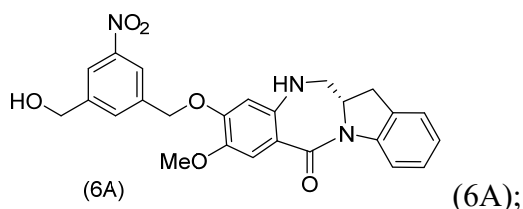
to form a compound of formula (4A),



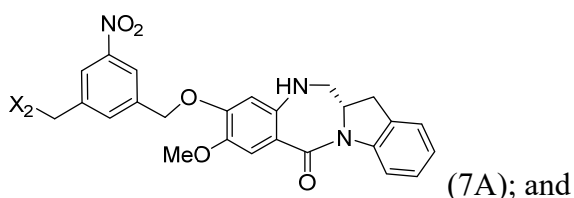
(4) reacting the compound of formula (4A) with an imine reducing agent to form a compound of formula (5A),



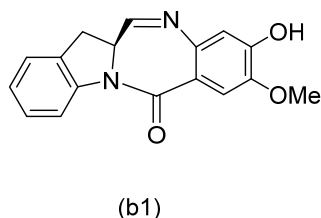
(5) reacting the compound of formula (5A) with an alcohol deprotecting reagent to form a compound of formula (6A),



(6) reacting the compound of formula (6A) with a second halogenating reagent, a second sulfonating reagent or a second esterification reagent to form a compound of formula (7A),



(7) reacting the compound of formula (7A) with a monomer compound of the formula (b1),

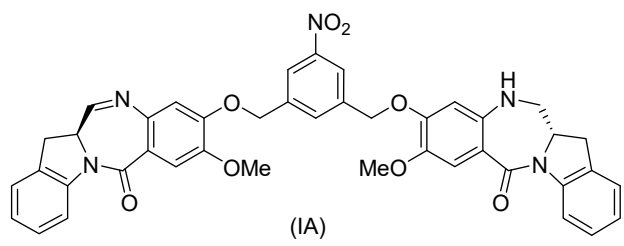


to form the compound of formula (IA); wherein:

P_1 is an alcohol protecting group; and,

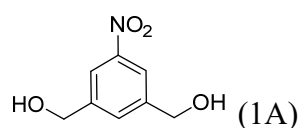
X_1 and X_2 are each independently a leaving group selected from the group consisting of: -Br, -I, -Cl, a sulfonate ester and an activated ester.

6. A method of preparing a compound of formula (IA),

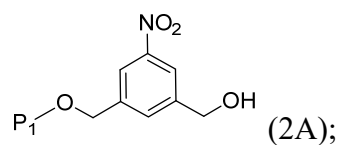


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

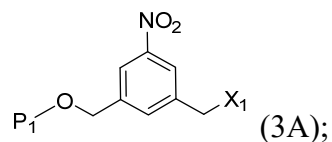
- (1) introducing an alcohol protecting group onto one of the primary alcohols of the compound of formula (1A),



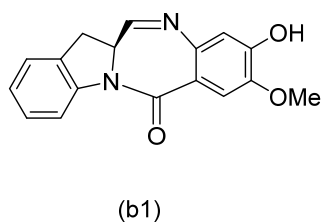
to form a compound of formula (2A),



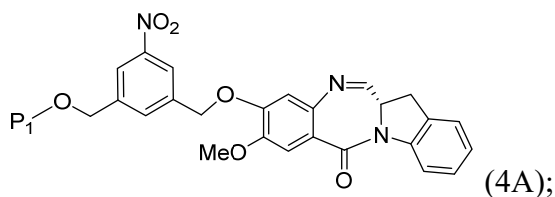
- (2) reacting a halogenating reagent, a sulfonating reagent or an esterification reagent with the compound of formula (2A) to form a compound of formula (3A),



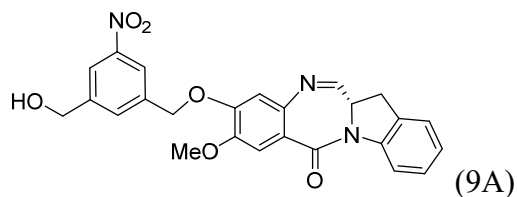
- (3) reacting the compound of formula (3A) with a monomer compound of the formula (b1),



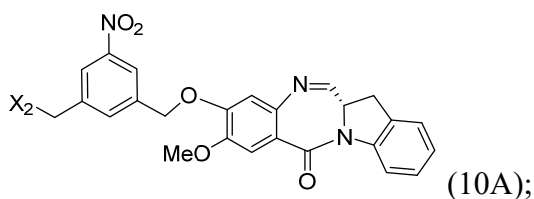
to form a compound of formula (4A),



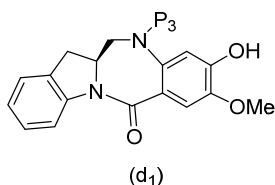
(4) reacting the compound of formula (4A) with an alcohol deprotecting reagent to form a compound of formula (9A),



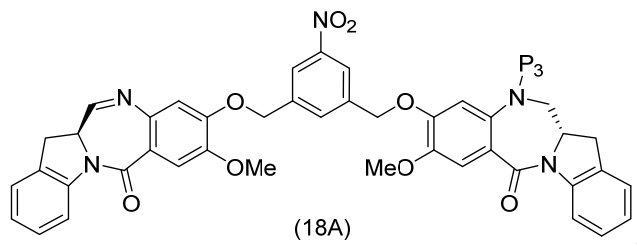
(5) reacting a second halogenating reagent, a second sulfonating reagent or a second esterification reagent with the compound of formula (9A) to form a compound of formula (10A),



(6) reacting the compound of formula (10A) with a monomer compound of the formula (d₁)



to form a compound of formula (18A),



(7) when P₃ is an amine protecting group; reacting the compound of formula (18A) with an amine deprotecting reagent to form the compound of formula (IA), wherein:

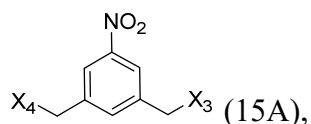
P₃ is H or an amine protecting group;

P₁ is an alcohol protecting group; and

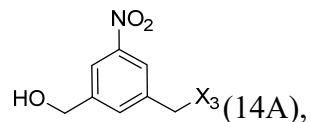
X₁ and X₂ are each independently a leaving group selected from the group consisting of: -Br, -I, -Cl, a sulfonate ester, and an activated ester.

7. The method of claim 5 or 6, wherein X₁ is mesylate and X₂ is mesylate.

8. A method of preparing a compound of formula (15A):



or a salt thereof, said method comprising reacting a sulfonating reagent or an esterification reagent with a compound of formula (14A),

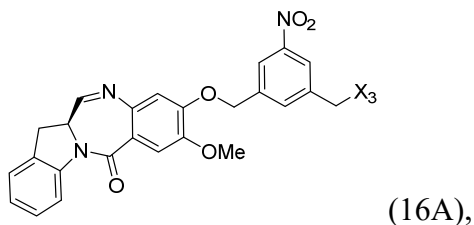


wherein:

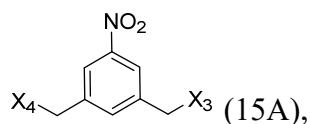
X₃ is -Cl; and

X₄ is a sulfonate ester or an activated ester.

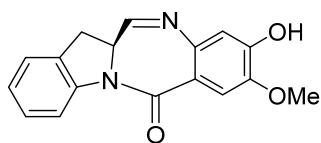
9. The method of claim 8, wherein the sulfonating reagent is methanesulfonyl anhydride, methanesulfonyl chloride, p-toluenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, or trifluoromethanesulfonyl anhydride.
10. The method of claim 8, wherein the sulfonate ester represented by X₄ is mesylate, tosylate, brosylate, or triflate, optionally X₄ is mesylate.
11. The method of claim 8, wherein the sulfonate ester is reacted with a compound of formula (14A) in the presence of a non-nucleophilic base, optionally wherein: (i) the non-nucleophilic base is triethylamine, imidazole, diisopropylethylamine, pyridine, 2,6-lutidine, dimethylformamide, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or tetramethylpiperidine; or (ii) the non-nucleophilic base is diisopropylethylamine.
12. A method of preparing a compound of formula (16A):



or a salt thereof, said method comprising reacting a compound of formula (15A)



with a monomer compound of formula (b1),



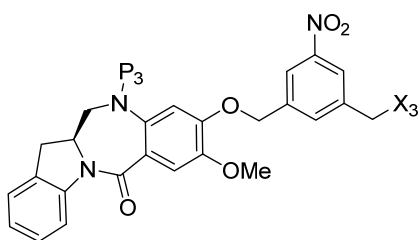
(b1)

wherein:

X₃ is -Cl; and

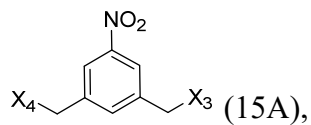
X₄ is a sulfonate ester or an activated ester.

13. A method of preparing a compound of formula (17A):



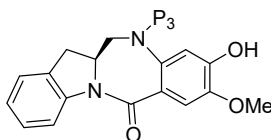
(17A),

or a salt thereof, said method comprising reacting a compound of formula (15A)



(15A),

with a monomer compound of formula (d1),



(d1)

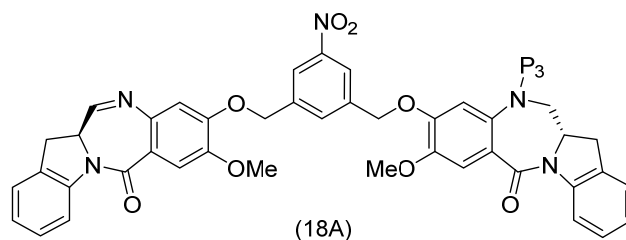
wherein:

X₃ is -Cl;

X₄ is a sulfonate ester or an activated ester; and

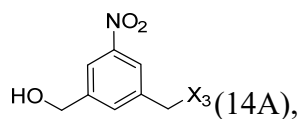
P₃ is H or an amine protecting group.

14. A method of preparing a compound of formula (18A),

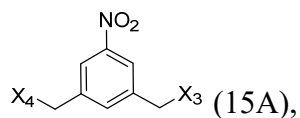


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

(1) reacting a sulfonating reagent or an esterification reagent with the compound of formula (14A),

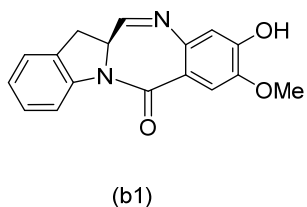


to form a compound of formula (15A):

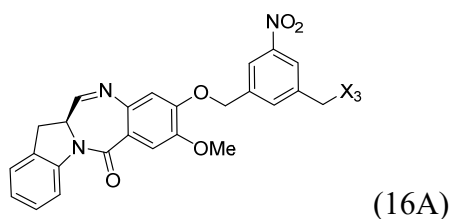


or a salt thereof;

(2) reacting the compound of formula (15A) with a monomer compound of formula (b1),

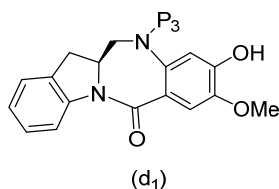


to form a compound of formula (16A):



or a salt thereof; and

(3) reacting the compound of formula of (16A) with a reduced monomer of formula (d1):



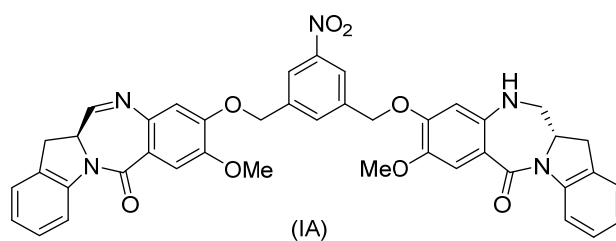
to form a compound of formula (18A), or a pharmaceutically acceptable salt thereof, wherein:

X₃ is -Cl;

X₄ is a sulfonate ester or an activated ester; and

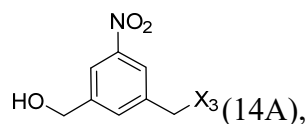
P₃ is H or an amine protecting group.

15. A method of preparing a compound of formula (IA),

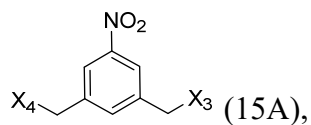


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

- (1) reacting a sulfonating reagent or an esterification reagent with the compound of formula (14A)

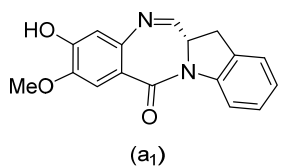


to form a compound of formula (15A):

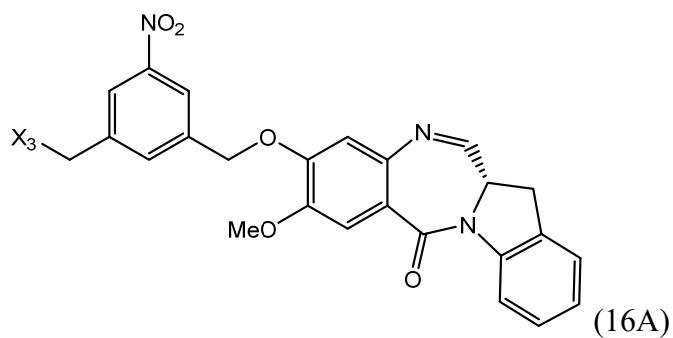


or a salt thereof;

- (2) reacting the compound of formula (15A) with a monomer compound of formula (a₁),

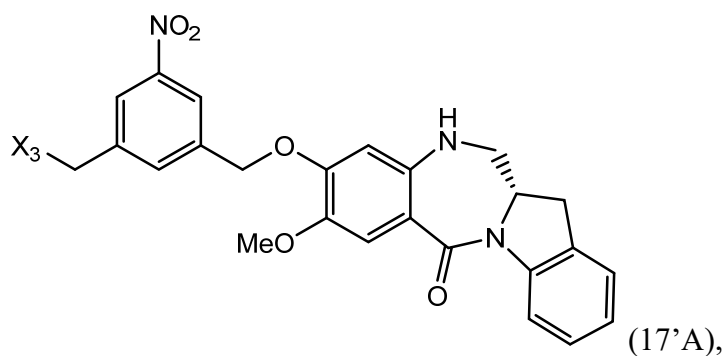


to form a compound of formula (16A):



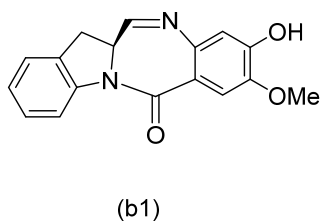
or a salt thereof;

(3) reacting the compound of formula (16A) with an imine reducing agent to form a compound of formula (17'A):



or a salt thereof; and

(4) reacting the compound of formula (17'A) with a monomer of formula (b1):



to form the compound of formula (IA);

wherein:

X₃ is -Cl; and

X₄ is a sulfonate ester or an activated ester.