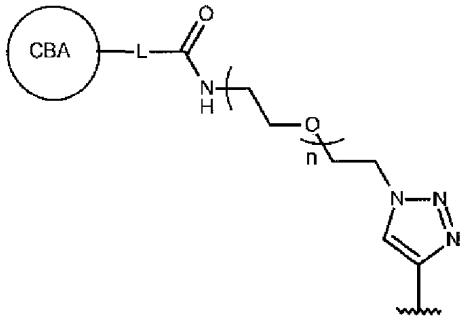
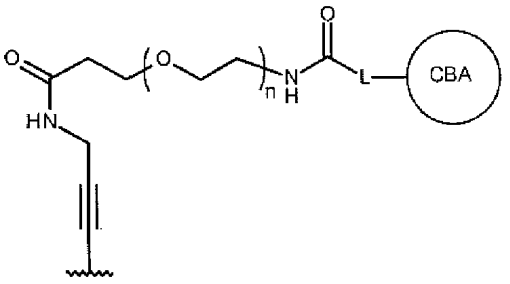
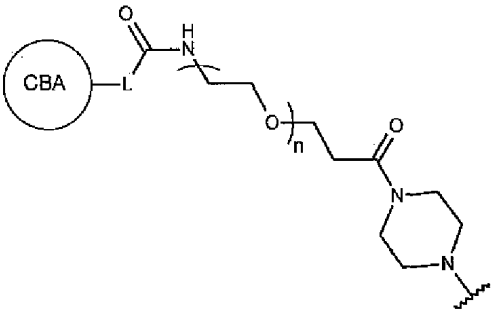
Y is selected from formulae A1, A2, A3, A4, A5 and A6:



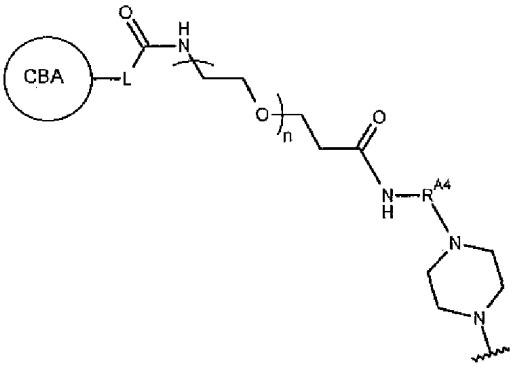
(A1)



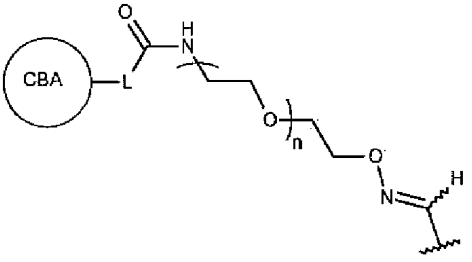
(A2)



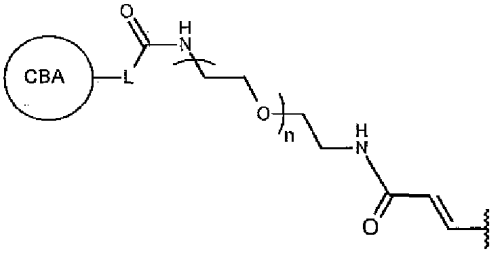
(A3)



(A4)



(A5)



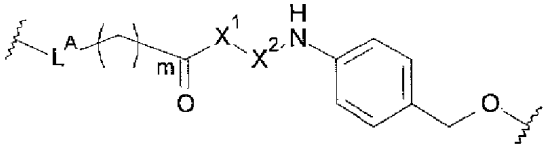
(A6)

L is a linker connected to a cell binding agent and of formula selected from the group:

$-L^A-(CH_2)_m-$ (L1),

$-L^A-(CH_2)_m-O-$ (L2)

, and



(L4);

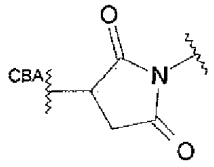
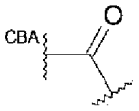
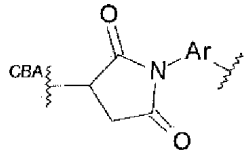
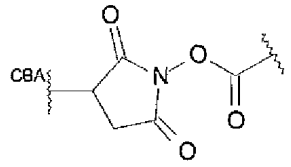
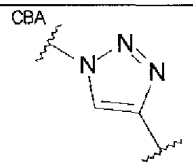
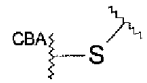
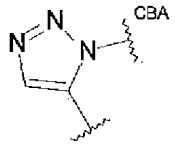
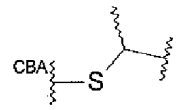
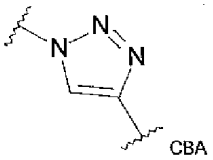
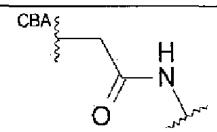
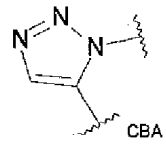
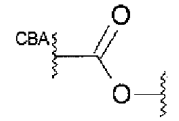
where m is from 0 to 6;

q is from 1 to 3; p is from 1 to 3;

the group $-X^1-X^2-$ is selected from:

-Phe-Lys-, -Val-Ala-, -Val-Lys-, -Ala-Lys-, -Val-Cit-; and

When L is (L4), L^A is selected from:

L^{A1-1})		(L^{A6})	
L^{A1-2})		(L^{A7})	
L^{A2})		(L^{A8-1})	
L^{A3-1})		(L^{A8-2})	
L^{A3-2})		(L^{A9-1})	
L^{A4})		(L^{A9-2})	
L^{A5})			

when L is (L1), L^A is selected from L^{A1-1} and L^{A3-2}

when L is (L2), L^A is selected from L^{A3-2}

where Ar represents a C_{5-6} arylene group;

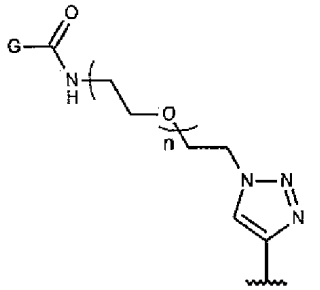
CBA is the cell binding agent;

n is an integer selected in the range of 0 to 48;

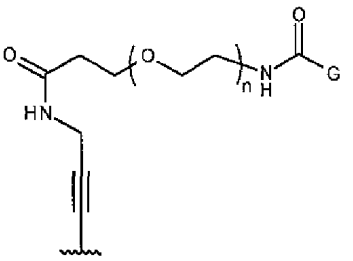
R^{A4} is a C_{1-6} alkylene group; either (a) R^{10} is H, and R^{11} is OH, OR^A, where R^A is C_{1-4} alkyl; or

(b) R^{10} and R^{11} form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are bound; or

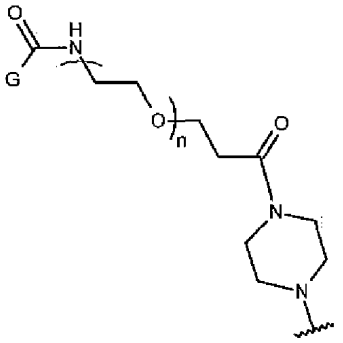
(c) R^{10} is H and R^{11} is OSO_zM, where z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation;



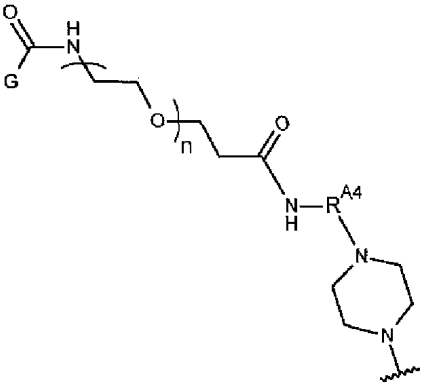
(B1)



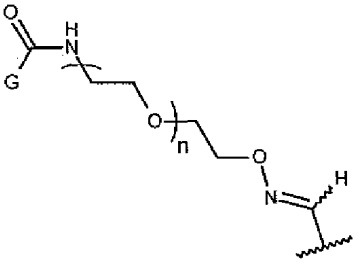
(B2)



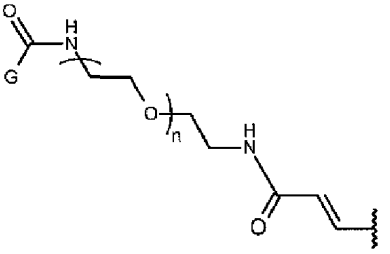
(B3)



(B4)



(B5)



(B6)

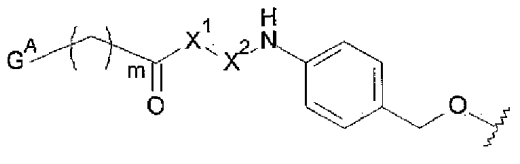
Where G is a reactive group for connecting to a cell binding agent

wherein n and R^{A4} are as defined in in the first aspect of the present disclosure and G is of formula selected from the group:

G^A-$(CH_2)_m$- (G1)

G^A-$(CH_2)_m$-O- (G2)

, and



(G4);

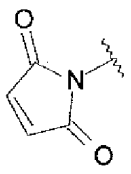
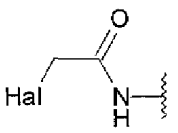
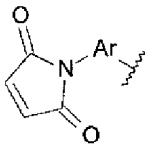
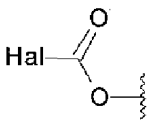
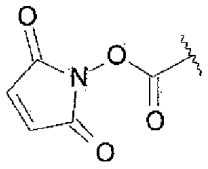
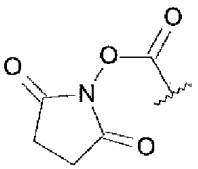
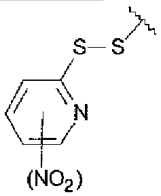
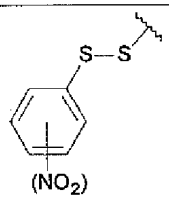
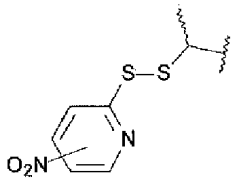
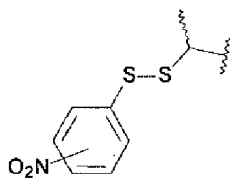
where m is from 0 to 6;

q is from 1 to 3;

p is from 1 to 3;

the group $-X^1-X^2-$ is selected from: -Phe-Lys-, -Val-Ala-, -Val-Lys-, -Ala-Lys-,-Val-Cit-; and

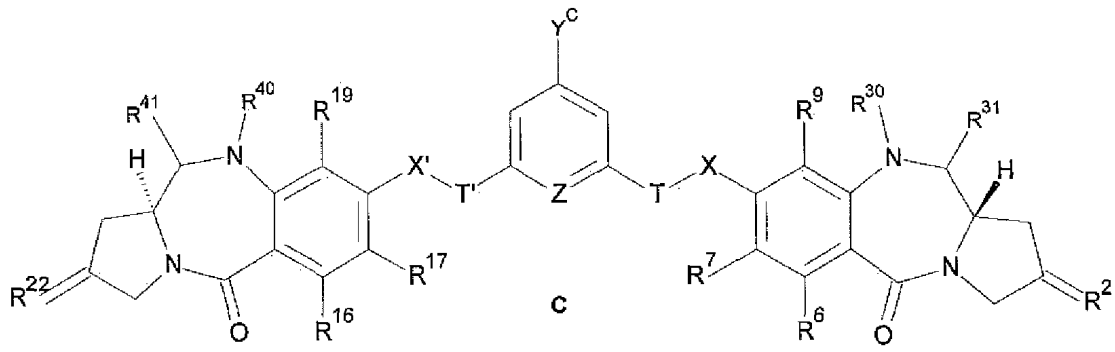
when G is (G4), G^A is selected from:

(G^{A1-1})		(G^{A4})	 Where Hal = I, Br, Cl
(G^{A1-2})		(G^{A5})	
(G^{A2})		(G^{A6})	
(G^{A3-1})	 where the NO_2 group is optional	(G^{A7})	
(G^{A3-2})	 where the NO_2 group is optional	(G^{A8})	
(G^{A3-3})	 where the NO_2 group is optional	(G^{A9})	
(G^{A3-4})	 where the NO_2 group is optional		

when G is (G1), G^A is selected from G^{A1-1} and G^{A3-3};

when G is (G2), G^A is selected from G^{A3-3};where Ar represents a C_{5-6} arylene group.

A third aspect of the present disclosure provides compounds of formula (C) which may be used in the preparation of the compounds and conjugate compounds of the invention:

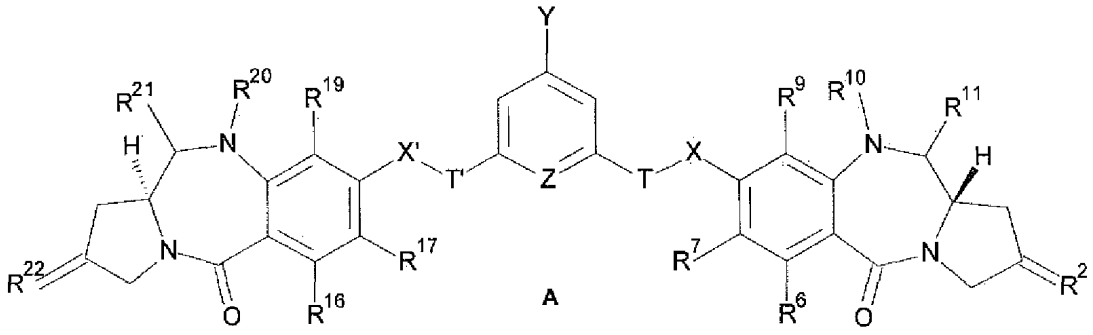


C

5

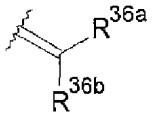
Claims

1. A conjugate of formula (A):



A

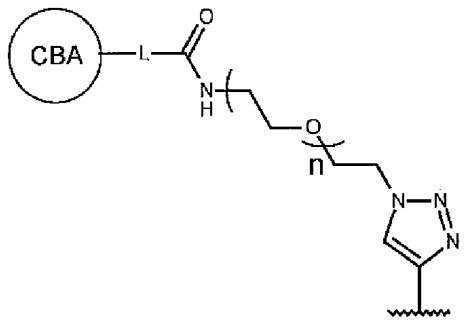
wherein:

R^2 is  , where R^{36a} and R^{36b} are independently selected from H, F, C_{1-4} saturated alkyl, C_{2-3} alkenyl, which alkyl and alkenyl groups are optionally substituted by a group selected from C_{1-4} alkyl amido and C_{1-4} alkyl ester; or, when one of R^{36a} and R^{36b} is H, the other is selected from nitrile and a C_{1-4} alkyl ester;

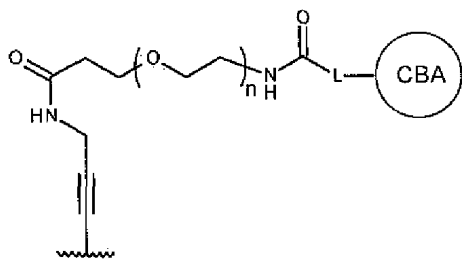
R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

R^7 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

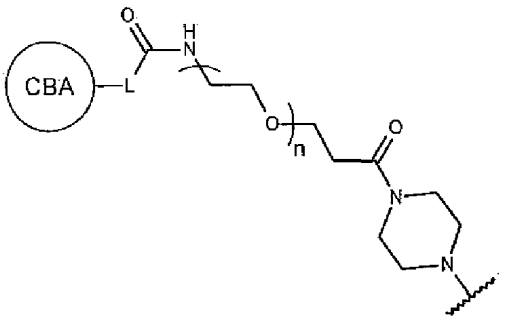
Y is selected from formulae A1, A2, A3, A4, A5 and A6:



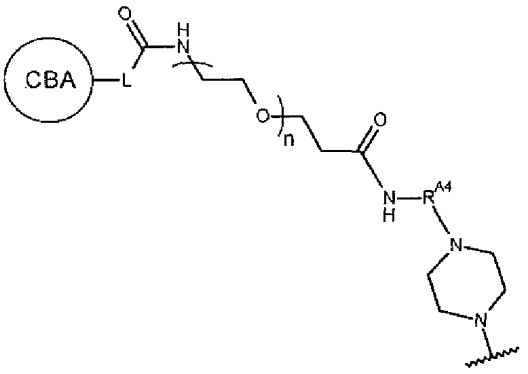
(A1)



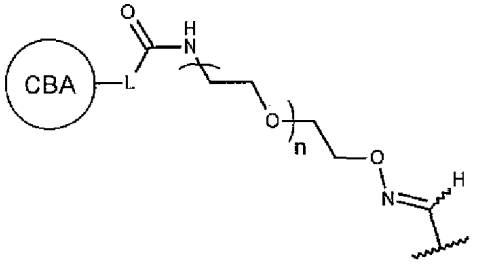
(A2)



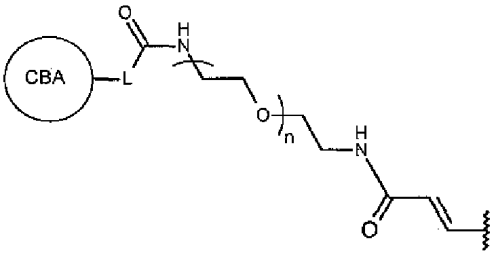
(A3)



(A4)



(A5)



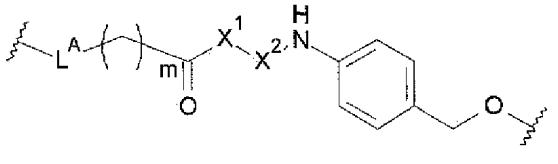
(A6)

L is a linker connected to a cell binding agent and of formula selected from the group:

$-L^A-(CH_2)_m-$ (L1),

$-L^A-(CH_2)_m-O-$ (L2),

and



(L4);

where *m* is from *0* to *6*;

q is from 1 to 3;

p is from 1 to 3;

the group $-X_1-X_2-$ is selected from:

-Phe-Lys-,

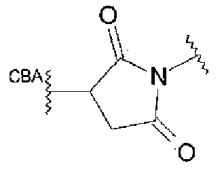
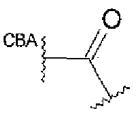
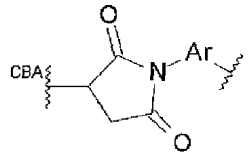
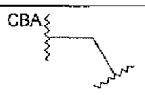
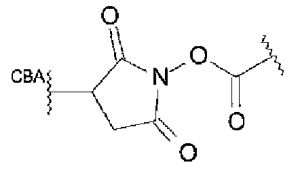
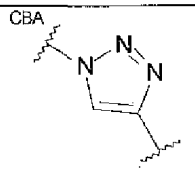
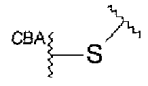
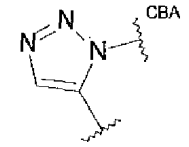
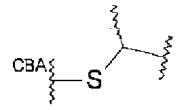
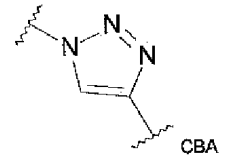
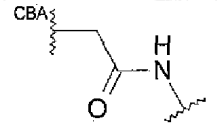
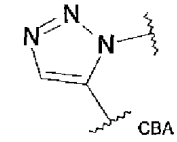
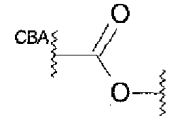
-Val-Ala-,

-Val-Lys-,

-Ala-Lys-,

-Val-Cit-; and

when L is (L4), L^A is selected from:

L^{A1-1})		(L^{A6})	
L^{A1-2})		(L^{A7})	
L^{A2})		(L^{A8-1})	
L^{A3-1})		(L^{A8-2})	
L^{A3-2})		(L^{A9-1})	
L^{A4})		(L^{A9-2})	
L^{A5})			

when L is (L1), L^A is selected from L^{A1-1} and L^{A3-2};

when L is (L2), L^A is selected from L^{A3-2};

where Ar represents a C_{5-6} arylene group;

CBA is the cell binding agent;

n is an integer selected in the range of 0 to 48;

R^{A4} is a C_{1-6} alkylene group;

either

(a) R^{10} is H, and R^{11} is OH, OR^A, where R^A is C_{1-4} alkyl; or

(b) R^{10} and R^{11} form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are bound; or

(c) R^{10} is H and R^{11} is OSO_zM, where z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation;

R and R' are each independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups, and optionally in relation to the group NRR', R and R' together with the nitrogen atom to which they are attached form an optionally substituted 4-, 5-, 6- or 7-membered heterocyclic ring;

wherein R^{16}, R^{17}, R^{19}, R^{20}, R^{21} and R^{22} are as defined for R^6, R^7, R^9, R^{10}, R^{11} and R^2 respectively;

wherein Z is CH or N;

wherein T and T' are independently selected from a single bond or a C_{1-9} alkylene, which chain may be interrupted by one or more heteroatoms e.g. O, S, N(H), NMe, provided

that the number of atoms in the shortest chain of atoms between X and X' is 3 to 12 atoms; and

X and X' are independently selected from O, S and N(H).

2. The conjugate according to claim 1, wherein R^9 is H.

3. The conjugate according to either claim 1 or claim 2, wherein R^6 is H.

4. The conjugate according to any one of claims 1 to 3, wherein R^7 is OR^{7A}, where R^{7A} is optionally substituted C_{1-4} alkyl.

5. The conjugate of claim 4, wherein R^{7A} is Me.

6. The conjugate according to any one of claims 1 to 5, wherein X is O.

7. The conjugate according to any one of claims 1 to 6, wherein T is selected from a single bond, C_1, and a C_2 alkylene group.

8. The conjugate according to claim 7, wherein T is a C_1 alkylene group.

9. The conjugate according to any one of claims 1 to 8, wherein R^{36a} and R^{36b} are both H.

10. The conjugate according to any one of claims 1 to 8, wherein R^{36a} and R^{36b} are both methyl.

11. The conjugate according to any one of claims 1 to 8, wherein one of R^{36a} and R^{36b} is H, and the other is selected from C_{1-4} saturated alkyl, C_{2-3} alkenyl, which alkyl and alkenyl groups are optionally substituted.

12. The conjugate according to claim 11, wherein the group of R^{36a} and R^{36b} which is not H is selected from methyl and ethyl.

13. The conjugate according to any one of claims 1 to 12, wherein R^{10} is H, and R^{11} is OH.

14. The conjugate according to any one of claims 1 to 12, wherein R^{10} and R^{11} form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are bound.

15. The conjugate according to any one of claims 1 to 14, wherein R^{16}, R^{17}, R^{19}, R^{20}, R^{21}, R^{22}, X' and T' are the same as R^6, R^7, R^9, R^{10}, R^{11}, R^2, X and T respectively

16. The conjugate of any one of claims 1 to 15, wherein L is of formula L1.

17. The conjugate according to claim 16, wherein m is 2, 3 or 5.

18. The conjugate of any one of claims 1 to 15, wherein L is of formula L2.

19. The conjugate according to claim 18, wherein m is 1.

20. The conjugate according to any one of claims 1 to 19, wherein q is 1.

21. The conjugate according to any one of claims 1 to 20, wherein p is 2.

22. The conjugate according to any one of claims 1 to 15, wherein L is of formula L4.

23. The conjugate according to claim 22, wherein m is 5.

24. The conjugate according to any one of claims 1 to 23, wherein n is an integer between 0 and 16.

25. The conjugate according to any one of claims 1 to 24, wherein n is an integer between 0 and 8.

26. The conjugate according to any one of claims 1 to 25, wherein n is 3 or 4.

27. The conjugate according to any one of claims 1 to 26, wherein the cell binding agent is an antibody or an active fragment thereof.

28. The conjugate according to claim 27, wherein the antibody or antibody fragment is an antibody or antibody fragment for a tumour-associated antigen.

29. The conjugate of claim 28 wherein the antibody or antibody fragment is an antibody which binds to one or more tumor-associated antigens or cell-surface receptors selected from (1)-(38):

(1) BMPR1B (bone morphogenetic protein receptor-type IB);

(2) E16 (LAT1, SLC7A5);

(3) STEAP1 (six transmembrane epithelial antigen of prostate);

(4) 0772P (CA125, MUC16);

(5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin);

(6) Napi3b (NAPI-3B, Napi2b, NPTIIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b);

(7) Sema 5b (FLJ10372, KIAA1445, Mm.42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B);

(8) PSCA hlg (2700050C12Rik, C530008O16Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene);

(9) ETBR (Endothelin type B receptor);

(10) MSG783 (RNF124, hypothetical protein FLJ20315);

(11) STEAP2 (HGNC_8639, IPCA-1, PCANAP1, STAMP1, STEAP2, STMP, prostate cancer associated gene 1, prostate cancer associated protein 1, six transmembrane epithelial antigen of prostate 2, six transmembrane prostate protein);

(12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4);

(13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor);

(14) CD21 (CR2 (Complement receptor 2) or C3DR (C3d/Epstein Barr virus receptor) or Hs 73792);

(15) CD79b (CD79B, CD79β, IGb (immunoglobulin-associated beta), B29);

(16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 domain containing phosphatase anchor protein 1a), SPAP1B, SPAP1C);

(17) HER2;

(18) NCA;

(19) MDP;

(20) IL20Rα;

(21) Brevican;

(22) EphB2R;

(23) ASLG659;

(24) PSCA;

(25) GEDA;

(26) BAFF-R (B cell -activating factor receptor, BLyS receptor 3, BR3);

(27) CD22 (B-cell receptor CD22-B isoform);

(28) CD79a (CD79A, CD79α, immunoglobulin-associated alpha);

(29) CXCR5 (Burkitt's lymphoma receptor 1);

(30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen));

(31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5);

(32) CD72 (B-cell differentiation antigen CD72, Lyb-2);

(33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family);

(34) FcRH1 (Fc receptor-like protein 1);

(35) IRTA2 (Immunoglobulin superfamily receptor translocation associated 2);

(36) TENB2 (putative transmembrane proteoglycan);

(37) CD33 (CD33 molecule, SIGLEC-3, SIGLEC3, p67; CD33 antigen (gp67); gp67; myeloid cell surface antigen CD33; sialic acid binding Ig-like lectin 3; sialic acid-binding Ig-like lectin); and

(38) LGR5/GPR49.

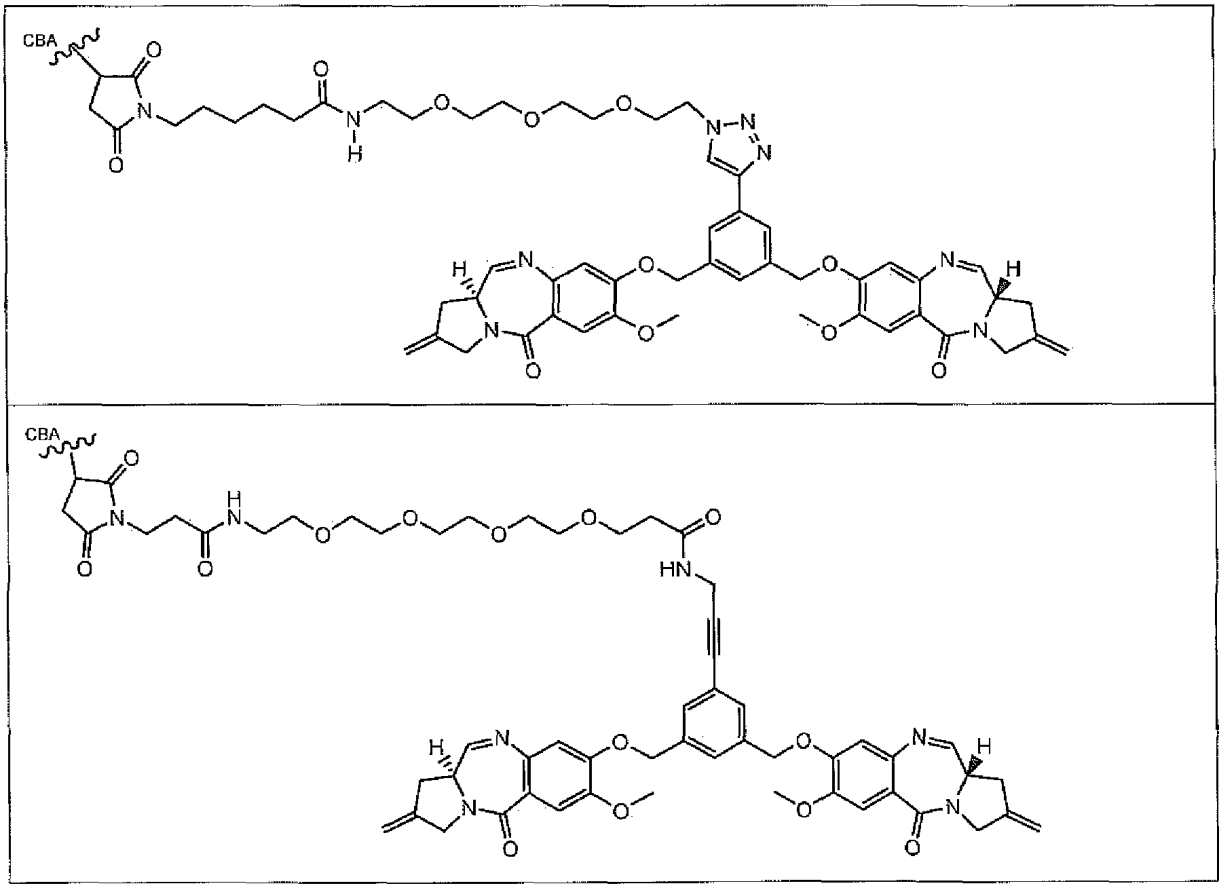
30. The conjugate of claim 29 wherein the antibody or antibody fragment is a cysteine-engineered antibody.

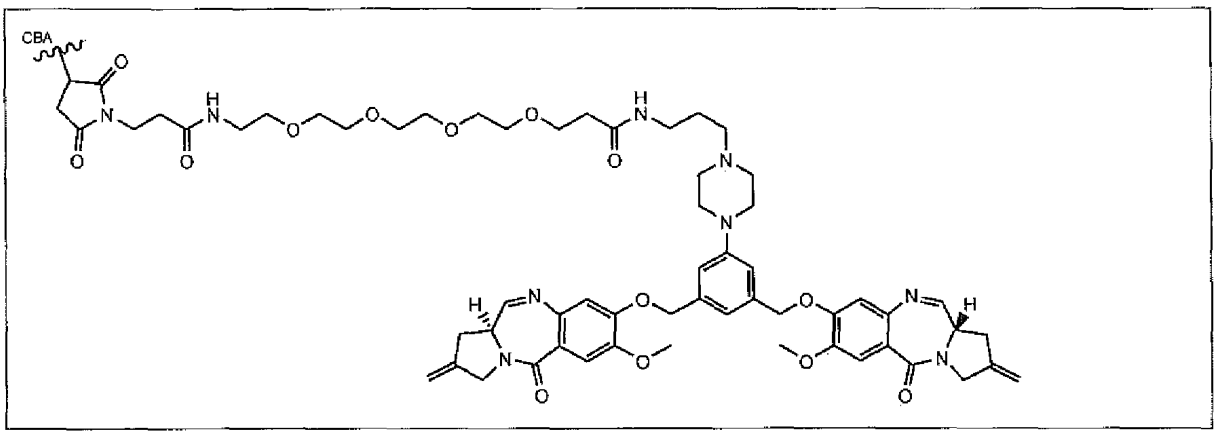
31. The conjugate of either claim 27 or claim 30 wherein the antibody or antibody fragment is an antibody which binds to an ErbB receptor.

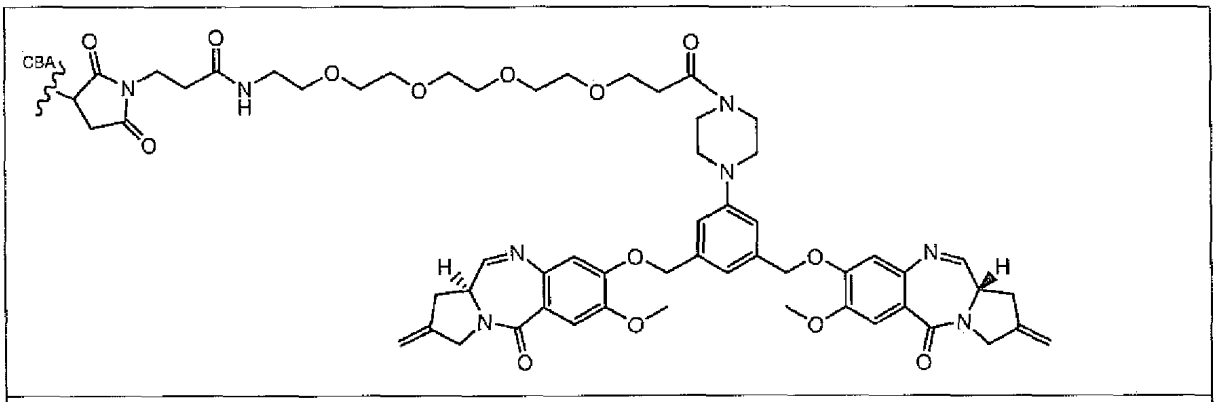
32. The conjugate of claim 31 wherein the antibody is trastuzumab.

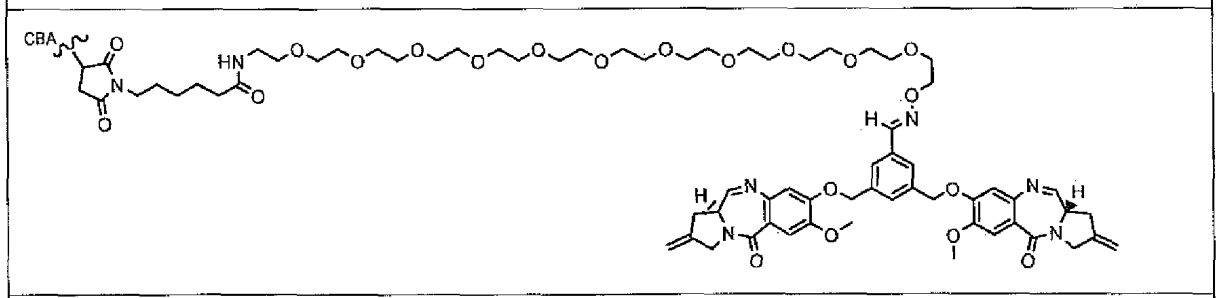
33. The conjugate of either claim 27 or claim 30 wherein Ab is an anti-HER2, an anti-Steap1, or an anti-CD22 antibody.

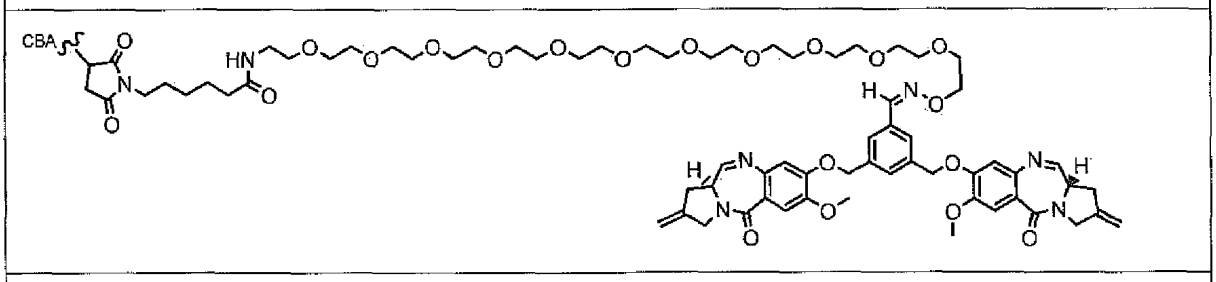
34. The conjugate according to any one of claims 29 to 33, wherein the conjugate is selected from:

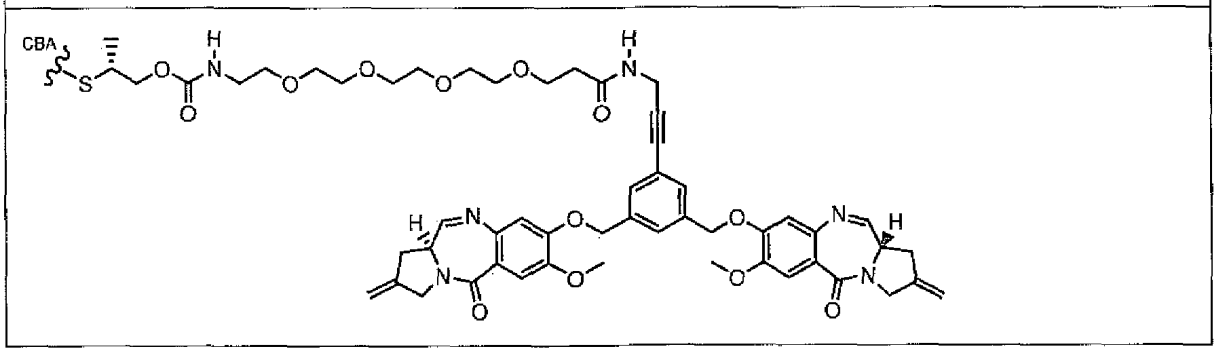


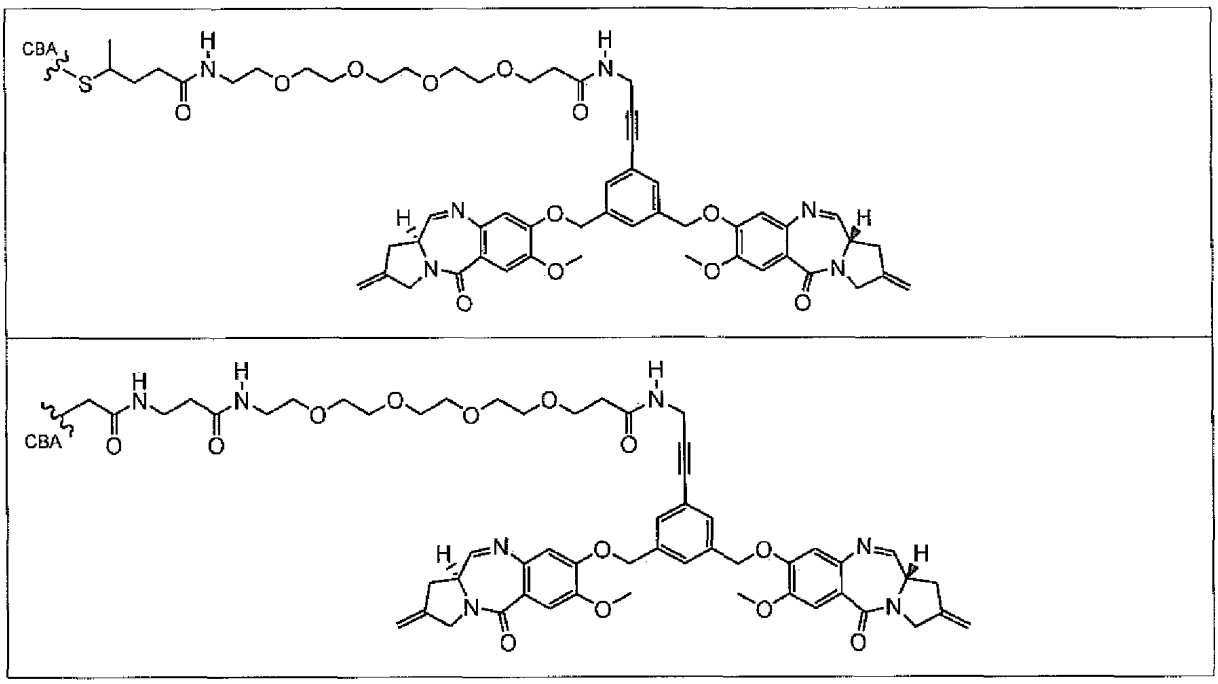












where CBA is the cell binding agent.

35. The conjugate according to either claim 27 or claim 34 wherein the drug loading (p) of drugs (D) to antibody (Ab) is an integer from 1 to about 8.

36. The conjugate according to claim 35, wherein p is 1, 2, 3, or 4.

37. The conjugate according to claim 36 comprising a mixture of the antibody-drug conjugate compounds, wherein the average drug loading per antibody in the mixture of antibody-drug conjugate compounds is about 2 to about 5.

38. The conjugate according to any one of claims 1 to 37, for use in therapy.

39. A pharmaceutical composition comprising the conjugate of any one of claims 1 to 37 and a pharmaceutically acceptable diluent, carrier or excipient.

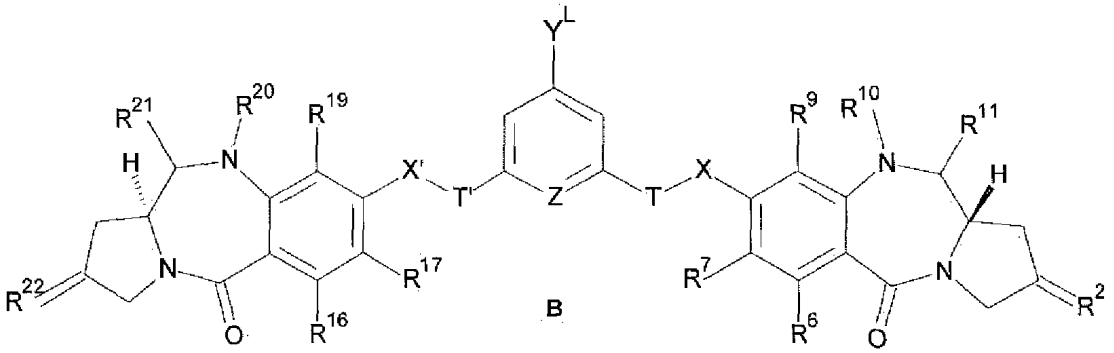
40. The conjugate according to any one of claims 1 to 37 or the pharmaceutical composition according to claim 39, for use in the treatment of a proliferative disease in a subject.

41. The conjugate according to claim 40, wherein the disease is cancer.

42. Use of a compound according to any one of claims 1 to 37 in a method of manufacture of a medicament for the treatment of a proliferative disease.

43. The use according to claim 42, wherein the disease is cancer.

44. A compound of formula (B):

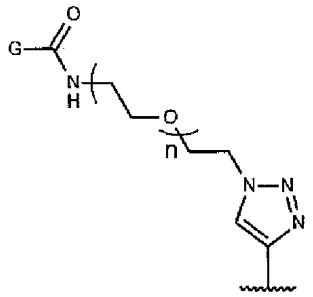


B

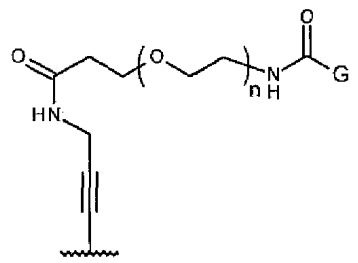
wherein:

R^2, R^6, R^7, R^9, R^{10}, R^{11}, R^{22}, R^{16}, R^{17}, R^{19}, R^{20}, R^{21}, Z, T, T', X and X' are as defined in any one of claims 1 to 15;

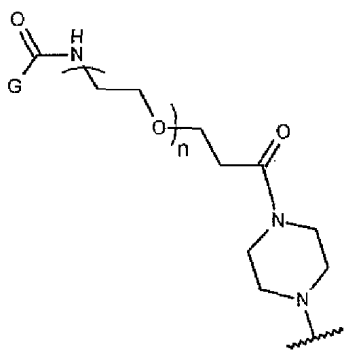
Y^L is selected from a group of formulae B1, B2, B3, B4, B5 and B6:

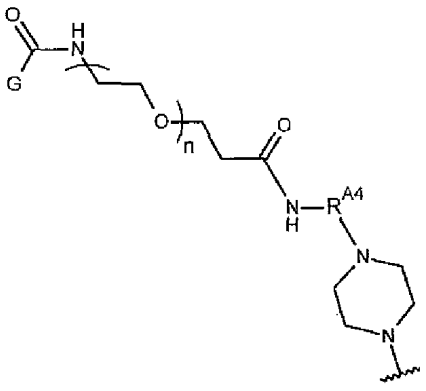


(B1)

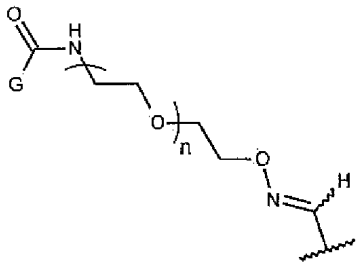


(B2)

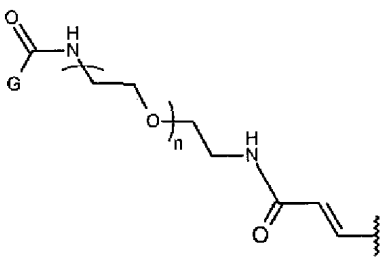




(B3)



(B4)



(B5)

(B6)

G is a reactive group for connecting to a cell binding agent

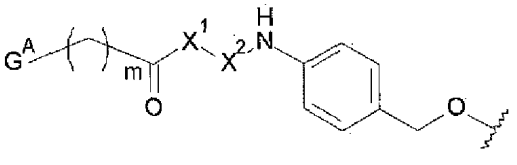
wherein n and R^{A4} are as defined in any one of claims 1 to 26 and

G is of formula selected from the group:

G^A-$(CH_2)_m$- (G1)

G^A-$(CH_2)_m$-O- (G2),

, and



(G4);

where m is from 0 to 6;

q is from 1 to 3;

p is from 1 to 3;

the group $-X_1-X_2-$ is selected from:

-Phe-Lys-,

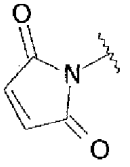
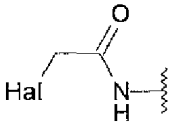
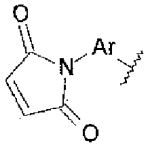
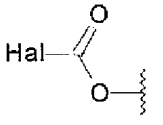
-Val-Ala-,

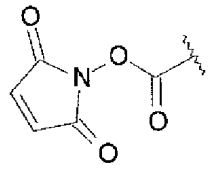
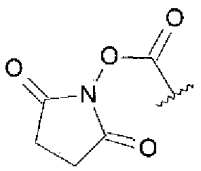
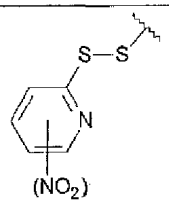
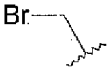
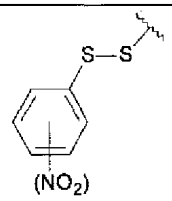
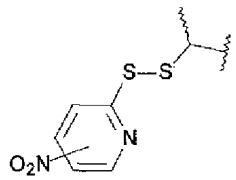
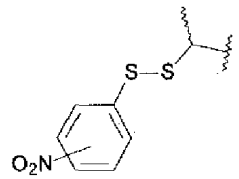
-Val-Lys-,

-Ala-Lys-,

-Val-Cit-; *and*

when G is (G4), G^A is selected from:

(G^{A1-1})		(G^{A4})	 Where Hal = I, Br, Cl
(G^{A1-2})		(G^{A5})	

(G^{A2})		(G^{A6})	
(G^{A3-1})	 where the NO_2 group is optional	(G^{A7})	
(G^{A3-2})	 where the NO_2 group is optional	(G^{A8})	
(G^{A3-3})	 where the NO_2 group is optional	(G^{A9})	
(G^{A3-4})	 where the NO_2 group is optional		

when G is (G1), G^A is selected from G^{A1-1} and G^{A3-3};

when G is (G2), G^A is selected from G^{A3-3};

where Ar represents a C_{5-6} arylene group.

45. The compound of claim 44, wherein G is of formula G1.

46. The compound according to claim 45, wherein m is 2, 3 or 5.

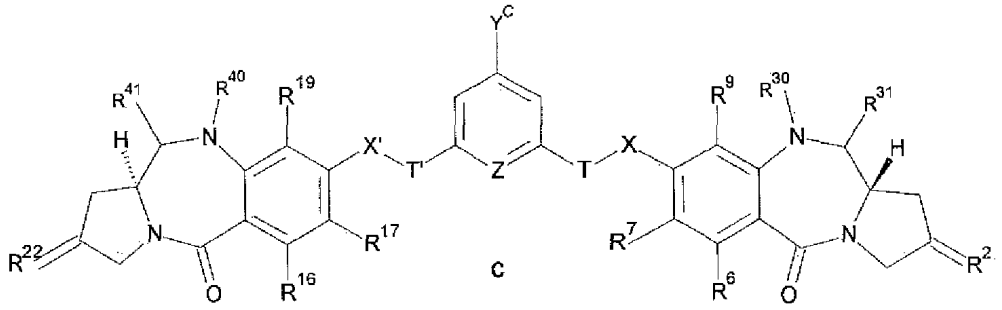
47. The compound of claim 44, wherein G is of formula G2.

48. The compound according to claim 47, wherein m is 1.

49. The compound according to any one of claims 44 to 48, wherein p is 2.

50. The compound according to claim 44 wherein G is of formula G4 and m is 5.

51. A compound of formula (C):

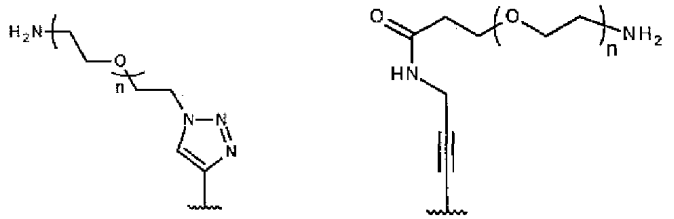


C

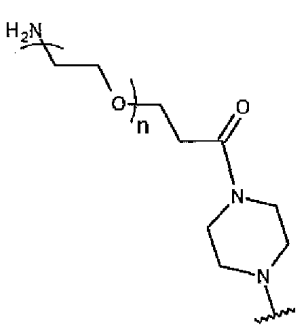
wherein:

R^2, R^6, R^7, R^9, R^{22}, R^{16}, R^{17}, R^{19}, Z, T, T', X and X' are as defined in any one of claims 1 to 15;

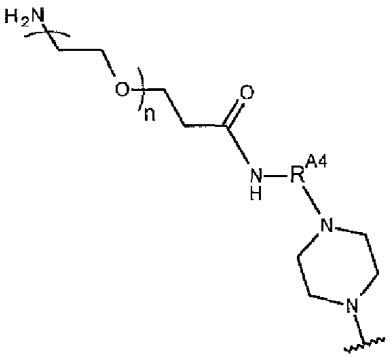
Y^C is selected from a group of formulae C1, C2, C3, C4, C5 and C6:



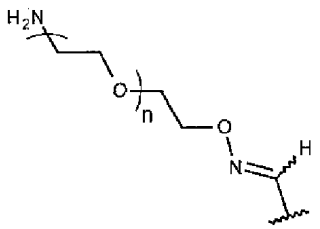
(C1)



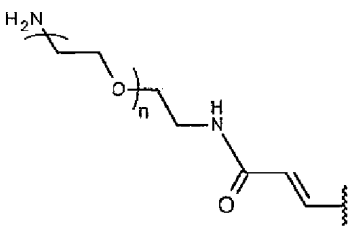
(C2)



(C3)



(C4)



(C5)

(C6)

wherein n and R^{A4} are as defined in any one of claims 1 to 31;

either

(a) R^{30} is H, and R^{31} is OH, OR^A, where R^A is C_{1-4} alkyl; or

(b) R^{30} and R^{31} form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are bound; or

(c) R^{30} is H and R^{31} is OSO_zM, where z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation; or

(d) R^{30} is a nitrogen protecting group amd R^{31} is $OProt^O$, where $Prot^O$ is a hydroxy protecting group; and

R^{40} and R^{41} are as defined for R^{30} and R^{31} respectively.

52. The compound according to claim 51, wherein R^{30} is H, and R^{31} is OH.

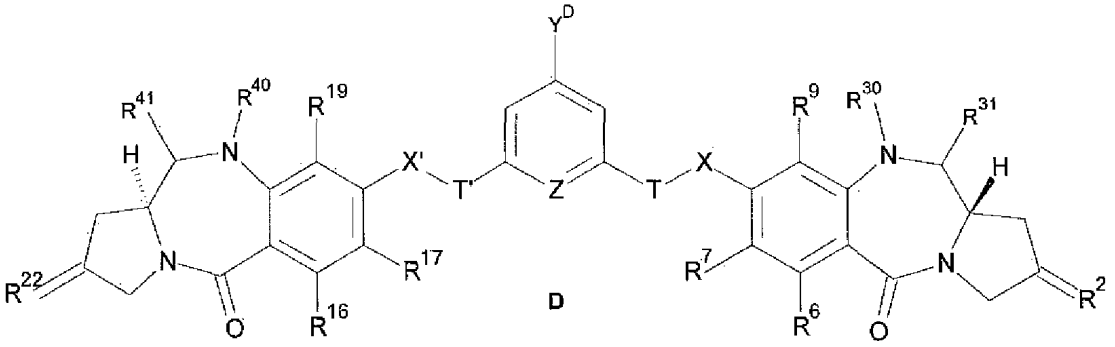
53. The compound according to claim 51, wherein R^{30} and R^{41} form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are bound.

54. The compound according to claim 51, wherein R^{30} is a nitrogen protecting group and R^{31} is $OProt^O$, where $Prot^O$ is a hydroxyl protecting group.

55. The compound according to claim 54, wherein the nitrogen protecting group is Boc.

56. The compound according to either claim 54 or claim 55, wherein the hydroxyl protecting group is THP.

57. A compound of formula (D):



D

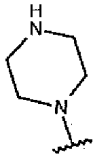
wherein:

R^2, R^6, R^7, R^9, R^{22}, R^{16}, R^{17}, R^{19}, Z, T, T', X and X' are as defined in any one of claims 1 to 15;

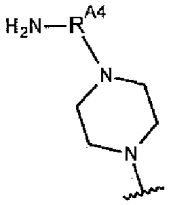
R^{30}, R^{31}, R^{40} and R^{41} are as defined in any one of claims 51 to 56;

Y^D is selected from a group of formulae D2, D3, D4 and D6:

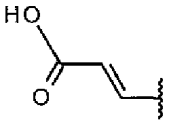
(D2)



(D3)



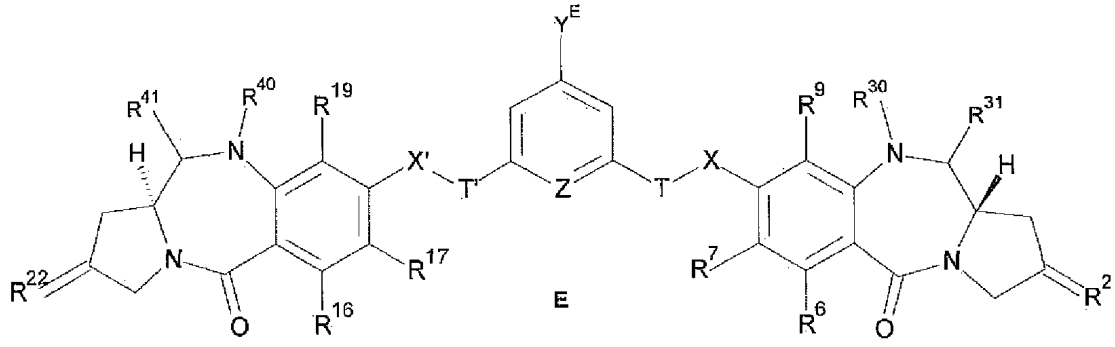
(D4)



(D6)

wherein R^{A4} is as defined in any one of claims 1 to 26.

58. A compound of formula (E):



E

wherein:

R^2, R^6, R^7, R^9, R^{22}, R^{16}, R^{17}, R^{19}, Z, T, T', X and X' are as defined in any one of claims 1 to 15;

R^{30}, R^{31}, R^{40} and R^{41} are as defined in any one of claims 51 to 56;

Y^E is selected from a group of formulae E1, E2 and E5:

(E1)

(E2)

(E5)

where

R^{E1} is selected from H and TMS; and

R^{E2} is selected from Br, Cl and I.

59. A method of synthesis of a compound according to any one of claims 1 to 37, comprising the step of conjugating a drug-linker according to any one of claims 44 to 50 with a cell-binding agent.