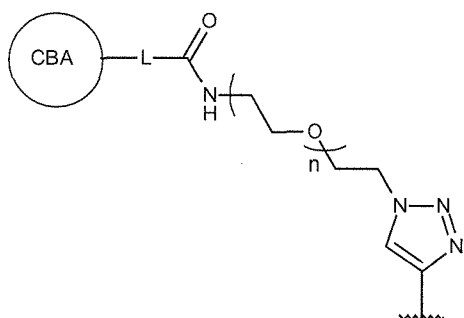
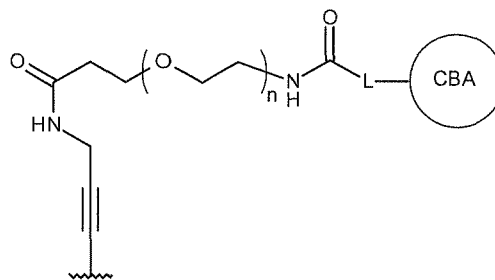


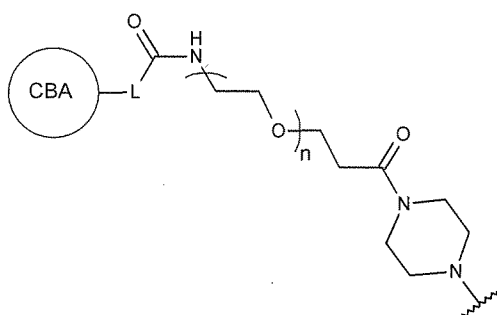
Y is selected from formulae A1, A2, A3, A4, A5 and A6:



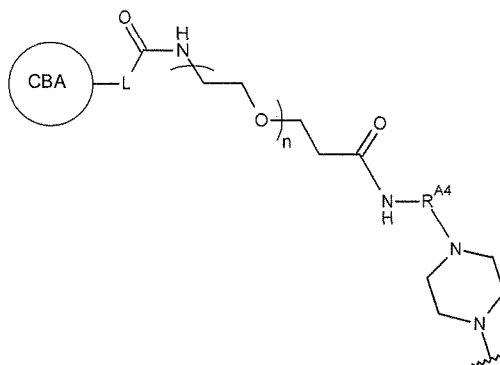
(A1)



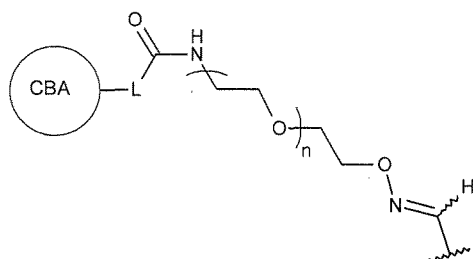
(A2)



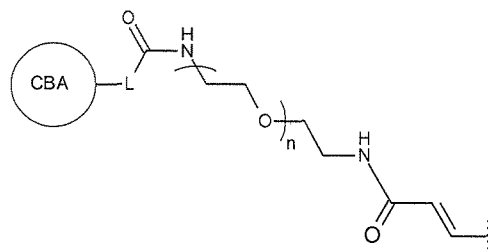
(A3)



(A4)

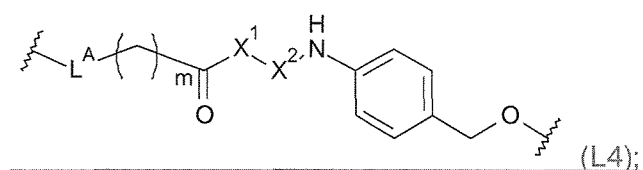
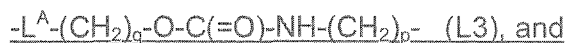
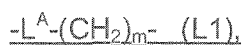


(A5)



(A6)

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



where m is from 0 to 6;

q is from 1 to 3;

p is from 1 to 3;

X^1 and X^2 are amino acid groups, selected from natural amino acids, the side chain of which may be optionally modified according to the group consisting of

(i) chemical protection of the side chain;

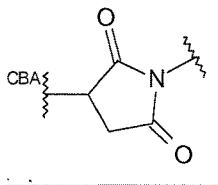
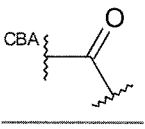
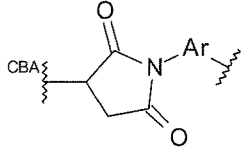
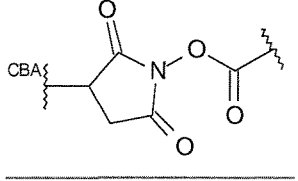
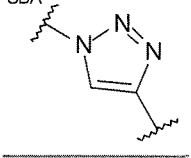
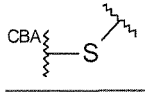
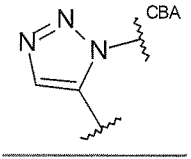
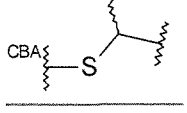
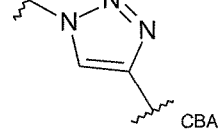
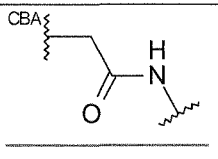
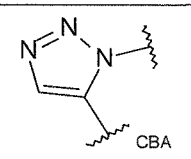
(ii) monoalkylation of an amino group NH_2 of the side chain;

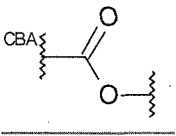
(iii) dialkylation of an amino group NH_2 of the side chain;

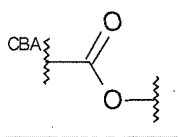
(iv) esterification of a carboxy group $COOH$ of the side chain;

(v) amidation of a carboxy group $COOH$ of the side chain; and

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}	
------------------------	---



where Ar represents a C₅₋₆ arylene group;

CBA is the cell binding agent;

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

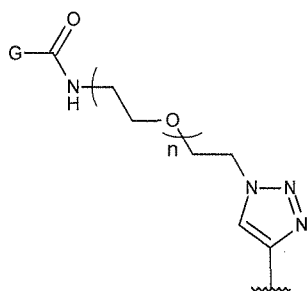
5 R^{A4} is a C₁₋₆ alkylene group;

either

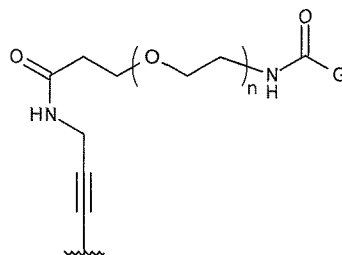
(a) R¹⁰ is H, and R¹¹ is OH, OR^A, where R^A is C₁₋₄ alkyl; or

(b) R¹⁰ and R¹¹ form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are bound; or

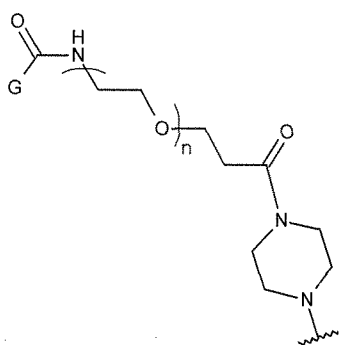
10 (c) R¹⁰ is H and R¹¹ is OSO_zM, where z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation;



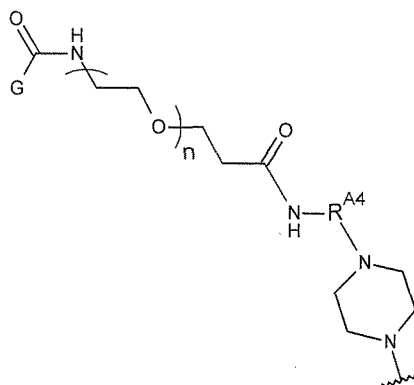
(B1)



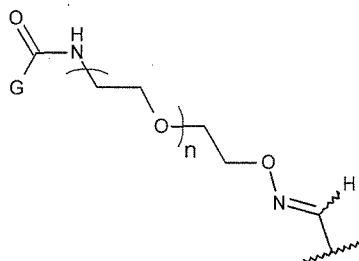
(B2)



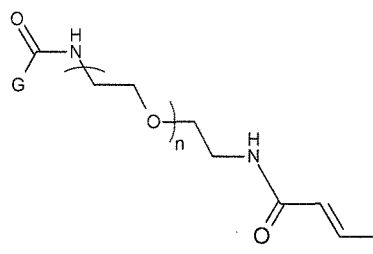
(B3)



(B4)



(B5)

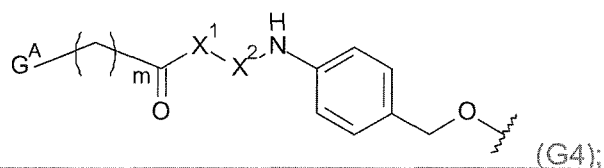
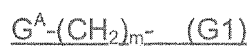


(B6)

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

wherein n and R^{A4} are as defined in the first aspect of the present disclosure and

G is of formula selected from the group:



(G4);

where m is from 0 to 6;

q is from 1 to 3;

p is from 1 to 3;

X^1 and X^2 are amino acid groups, selected from natural amino acids, the side chain of which may be optionally modified according to the group consisting of

(i) chemical protection of the side chain;

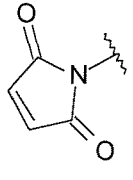
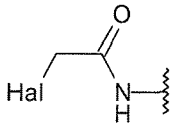
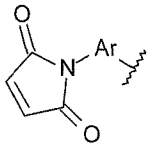
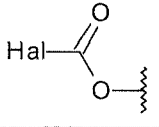
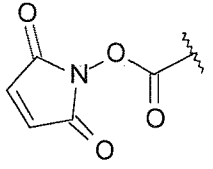
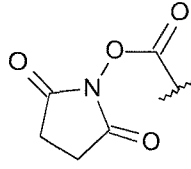
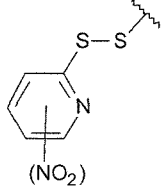
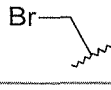
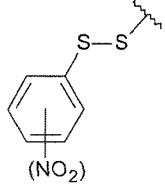
(ii) monoalkylation of an amino group NH_2 of the side chain;

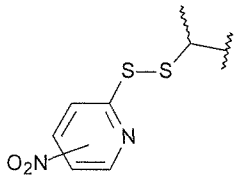
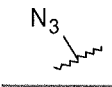
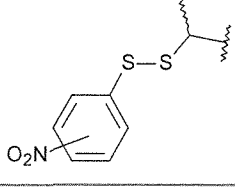
(iii) dialkylation of an amino group NH_2 of the side chain;

(iv) esterification of a carboxy group $COOH$ of the side chain;

(v) amidation of a carboxy group $COOH$ of the side chain; and

G^A is selected from:

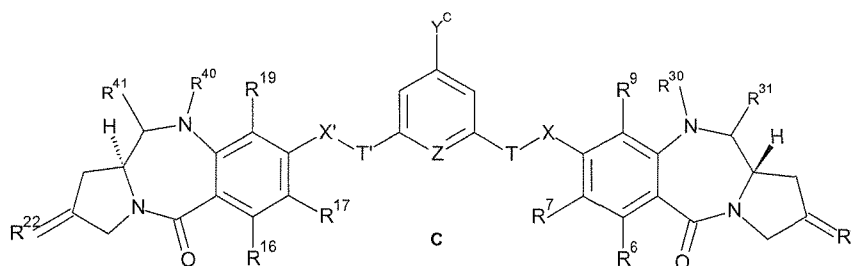
(G ^{A1-1})		(G ^{A4})	 Where Hal = I, Br, Cl
(G ^{A1-2})		(G ^{A5})	
(G ^{A2})		(G ^{A6})	
(GA3-1)	 where the NO ₂ group is optional	(GA7)	
(GA3-2)	 where the NO ₂ group is optional	(GA8)	

(GA3-3)	 <u>where the NO₂ group is optional</u>	(GA9)	
(GA3-4)	 <u>where the NO₂ group is optional</u>		

where Ar represents a C₅₋₆ 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 present

5 disclosure:





(E1)



(E2)



(E5)

where

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

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

5 all the remaining groups are as defined in the third aspect of the present disclosure.

An embodiment of the present disclosure provides the use of a compound of the first aspect of the present disclosure in a method of medical treatment. An aspect of the present disclosure provides a compound of the first aspect for use in therapy. Another aspect also provides a pharmaceutical composition comprising a compound of the first aspect, and a pharmaceutically acceptable diluent, carrier or excipient.

10

Another aspect of the present disclosure provides a compound of the first aspect of the present disclosure or a pharmaceutical composition as disclosed above for use in the treatment of a proliferative disease in a subject. Another aspect also provides the use of a compound of the first aspect in a method of manufacture of a medicament for the treatment of a proliferative disease. An embodiment provides a method of treating a mammal having a proliferative disease, comprising administering an effective amount of a compound of the first aspect or a pharmaceutical composition as disclosed above.

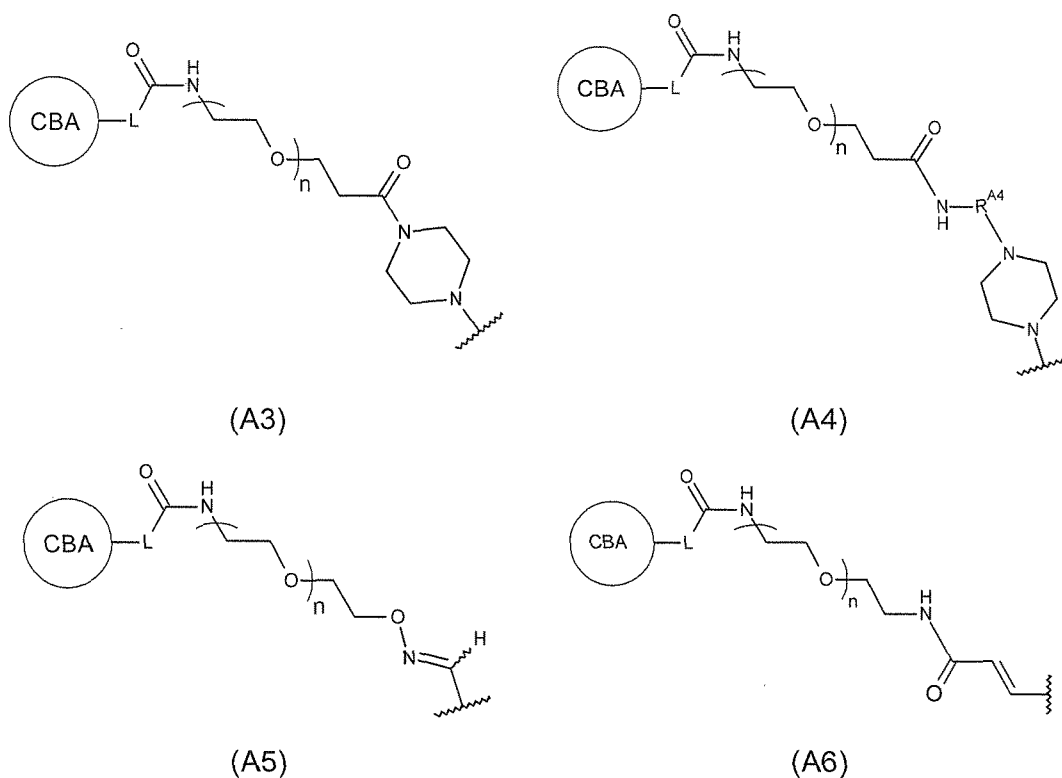
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20

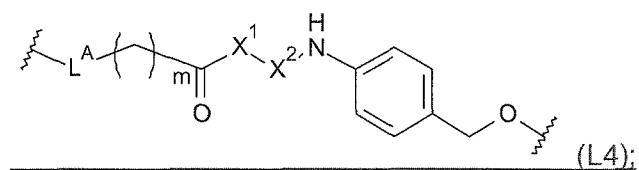
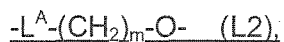
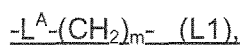
Another aspect of the present disclosure provides a method of synthesis of a compound of the first aspect of the present ~~present~~ disclosure, comprising the step of conjugating a drug-linker of the second aspect with a cell-binding agent.

25

The present disclosure also provides the synthesis of compounds of the second aspect of the present disclosure from compounds of the third, fourth or fifth aspect of the present disclosure by reacting them with suitable reagents.



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



where m is from 0 to 6;

q is from 1 to 3;

p is from 1 to 3;

X^1 and X^2 are amino acid groups, selected from natural amino acids, the side chain of which may be optionally modified according to the group consisting of

(i) chemical protection of the side chain;

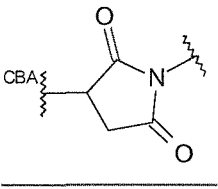
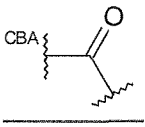
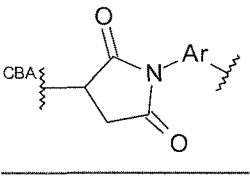
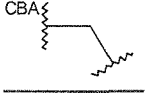
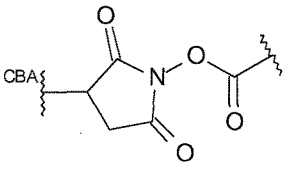
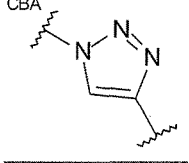
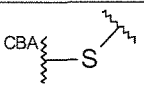
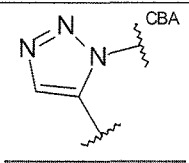
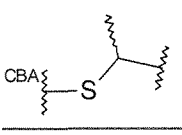
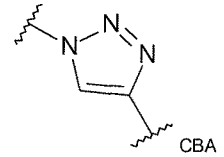
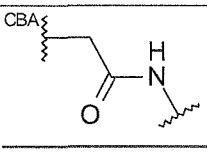
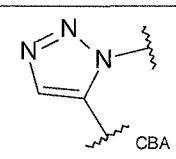
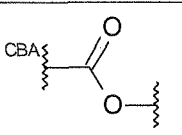
(ii) monoalkylation of an amino group NH_2 of the side chain;

(iii) dialkylation of an amino group NH_2 of the side chain;

(iv) esterification of a carboxy group $COOH$ of the side chain;

(v) amidation of a carboxy group COOH of the side chain; and

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}			

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

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.

5 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

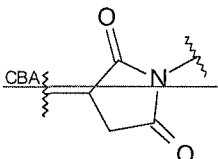
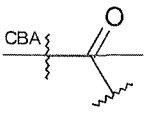
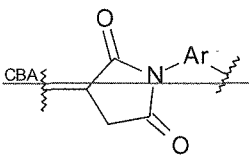
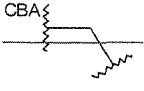
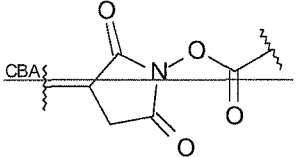
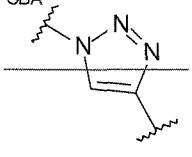
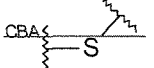
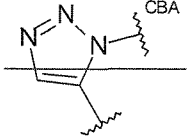
10 ~~16. The conjugate according to any one of claims 1 to 15, wherein the group L contains a moiety derived from an electrophilic functional group selected from (i) maleimide groups (ii) activated disulfides, (iii) active esters such as NHS (N-hydroxysuccinimide) esters, HOBT (N-hydroxybenzotriazole) esters, haloformates, and acid halides; (iv) alkyl and benzyl halides such as haloacetamides; and (v) aldehydes, ketones, carboxyl.~~

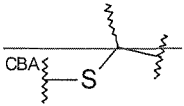
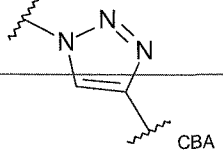
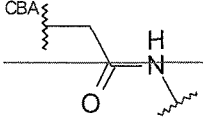
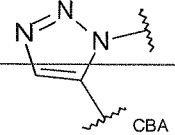
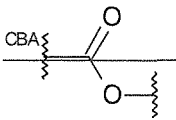
~~17. The conjugate according to any one of claims 1 to 15, wherein L is of formula:~~

15 ~~$-L^A-(CH_2)_m-(L^1)$~~

~~where m is from 0 to 6; and~~

~~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})~~	

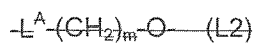
(L^{A3-2})		(L^{A9-1})	
(L^{A4})		(L^{A9-2})	
(L^{A5})			

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

4816. The conjugate of claim 17, wherein L is of formula L1 and L^A is selected from L^{A1-1} and L^{A3-2} .

5 | 4917. The conjugate according to either claim 17 or claim 4816, wherein L is of formula L1 and m is 2, 3 or 5.

20. —The conjugate according to any one of claims 1 to 15, where L is of formula:



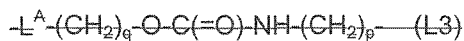
10 | Where m is from 0 to 6; and

L^A is selected from the groups as defined in claim 17.

2418. The conjugate of claim 201, wherein L is of formula L2 and L^A is L^{A3-2} .

15 | 2219. The conjugate according to either claim 201 or 2418, wherein L is of formula L2 and m is 1.

23. —The conjugate according to any one of claims 1 to 15, where L is of formula:



Where q is from 1 to 3, and p is from 1 to 3; and

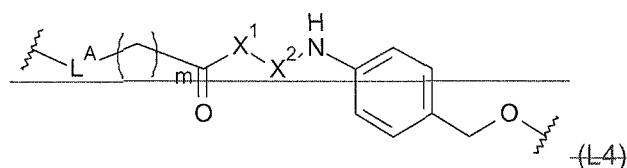
20 | L^A is selected from the groups as defined in claim 17.

2420. The conjugate of claim 231, wherein L is of formula L3 and L^A is selected from L^{A7} , L^{A8-1} and L^{A8-2} .

25 | 2521. The conjugate according to either claim 231 or 2420, wherein q is 1.

2622. The conjugate according to any one of claims 23 to 251, 20 and 21, wherein p is 2.

27. The conjugate according to any one of claims 1 to 15, where L is of formula:



Where m is from 0 to 6;

X^1 and X^2 are amino acid groups, selected from natural amino acids, which may be modified;

L^A is selected from the groups as defined in claim 17.

2823. The conjugate according to claim 271, wherein L is of formula L4 and the group $-X_1-X_2-$ is selected from:

-Phe-Lys-,

-Val-Ala-,

-Val-Lys-,

-Ala-Lys-,

-Val-Cit-.

2924. The conjugate according to either claim 271 or claim 2823, wherein L is of formula L4 and m is 5.

3025. The conjugate according to any one of claims 1 to 2924, wherein n is an integer between 0 and 16.

3426. The conjugate according to any one of claims 1 to 3025, wherein n is an integer between 0 and 8.

3227. The conjugate according to any one of claims 1 to 3426, wherein n is 3 or 4.

3328. The conjugate according to any one of claims 1 to 3227, wherein the cell binding agent is an antibody or an active fragment thereof.

3429. The conjugate according to claim 3328, wherein the antibody or antibody fragment is an antibody or antibody fragment for a tumour-associated antigen.

3530. The conjugate of claim 3429 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):

- (27) CD22 (B-cell receptor CD22-B isoform);
- (28) CD79a (CD79A, CD79 α , immunoglobulin-associated alpha);
- (29) CXCR5 (Burkitt's lymphoma receptor 1);
- (30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen));
- 5 (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);
- 10 (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
- 15 (38) LGR5/GPR49.

3631. The conjugate of claim 33-28 wherein the antibody or antibody fragment is a cysteine-engineered antibody.

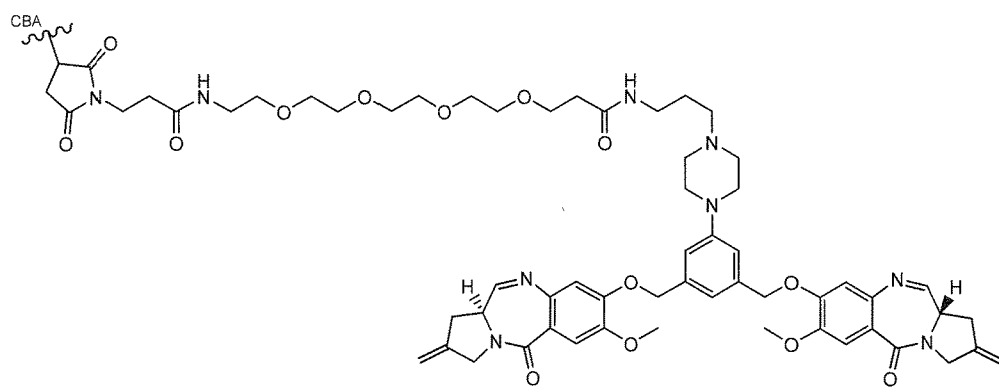
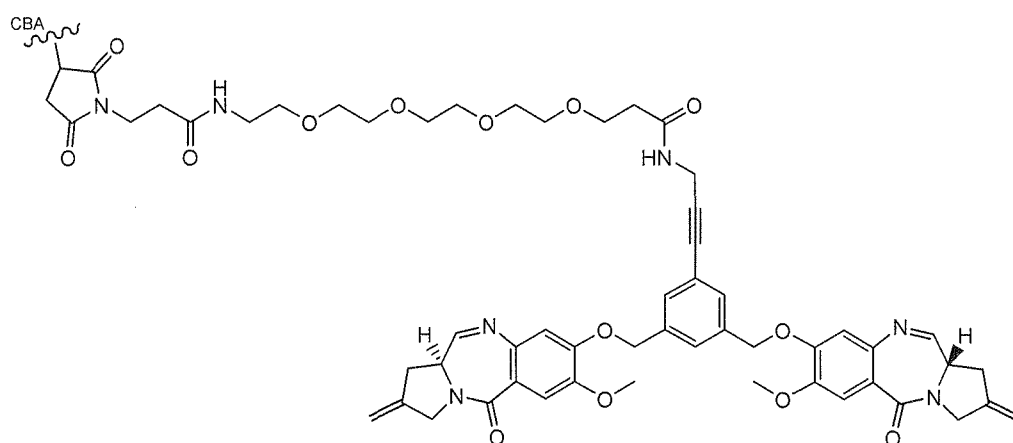
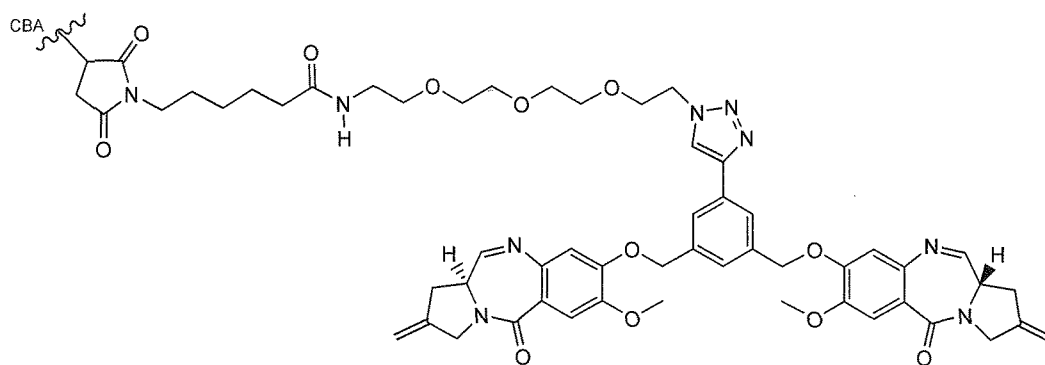
20 3732. The conjugate of either claim 33-28 or claim 3631 wherein the antibody or antibody fragment is an antibody which binds to an ErbB receptor.

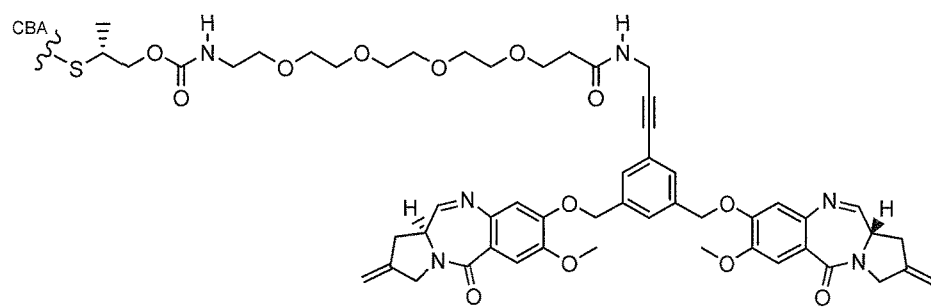
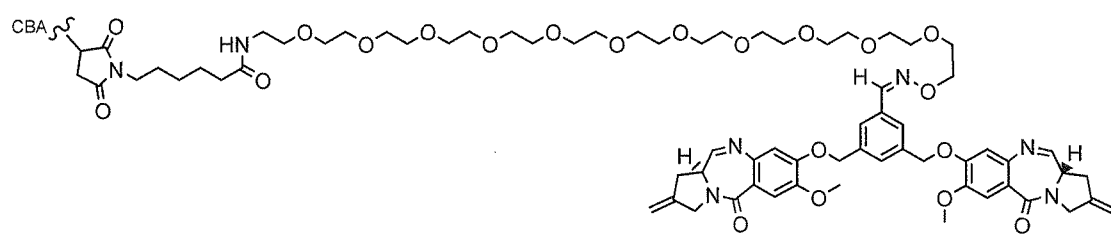
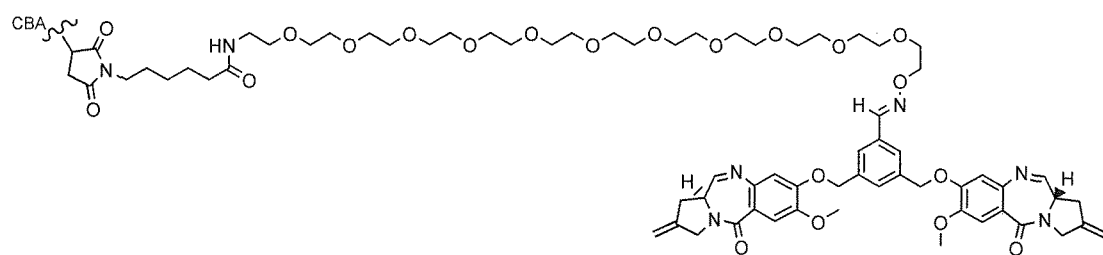
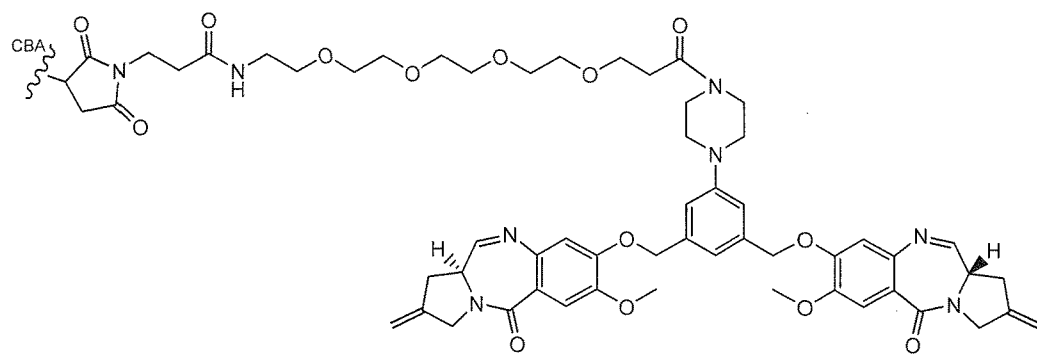
3833. The conjugate of claim 37-32 wherein the antibody is trastuzumab.

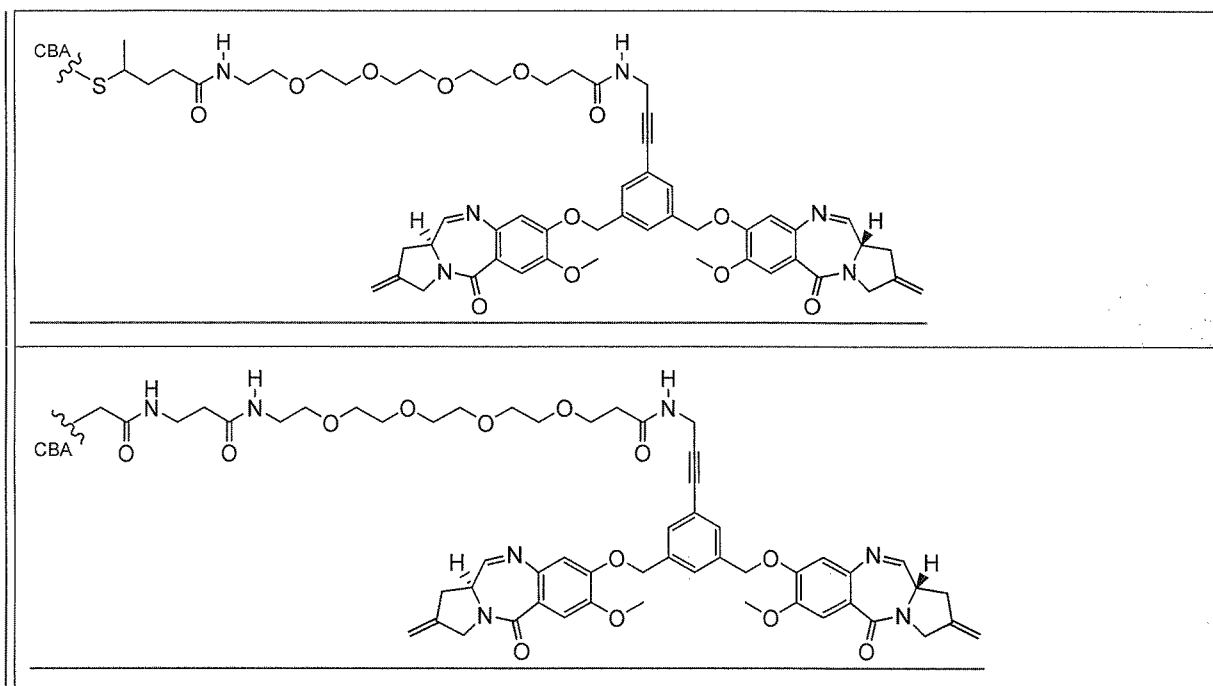
25 3934. The conjugate of either claim 33-28 or claim 3631 wherein Ab is an anti-HER2, an anti-Steap1, or an anti-CD22 antibody.

35. The conjugate according to any one of claims 30 to 34, wherein the conjugate is selected from:

157a







where CBA is the cell binding agent.

4036. The conjugate according to either claim 33-28 or claim 35 wherein the drug loading (p) of drugs (D) to antibody (Ab) is an integer from 1 to about 8.

4437. The conjugate according to claim 4036, wherein p is 1, 2, 3, or 4.

4238. The conjugate according to claim 4437 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.

4339. The conjugate according to any one of claims 1 to 4238, for use in therapy.

5 | 4440. A pharmaceutical composition comprising the conjugate of any one of claims 1 to 4238 and a pharmaceutically acceptable diluent, carrier or excipient.

4541. The conjugate according to any one of claims 1 to 4238 or the pharmaceutical composition according to claim 4440, for use in the treatment of a proliferative disease in a subject.

10

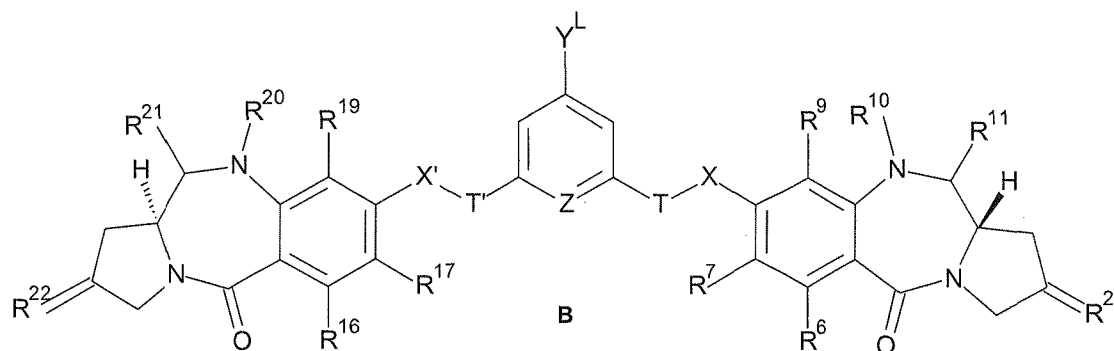
| 4642. The conjugate according to claim 4541, wherein the disease is cancer.

| 4743. Use of a compound according to any one of claims 1 to 4238 in a method of manufacture of a medicament for the treatment of a proliferative disease.

15

| 4844. The use according to claim 4743, wherein the disease is cancer.

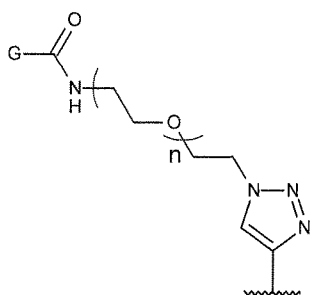
4945. A compound of formula (B):



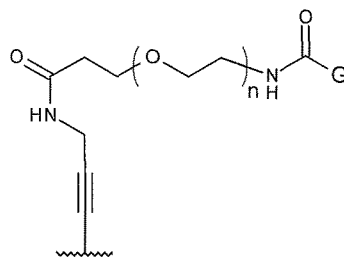
wherein:

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;

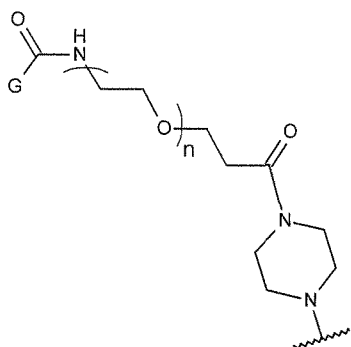
Y^L is selected from a group of formulae B1, B2, B3, B4, B5 and B6:



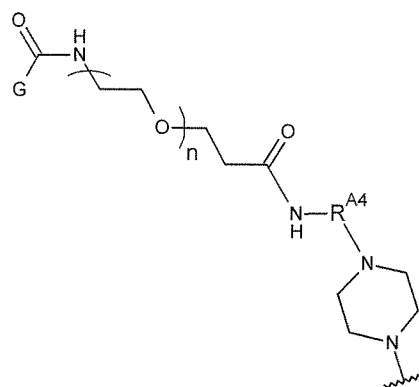
(B1)



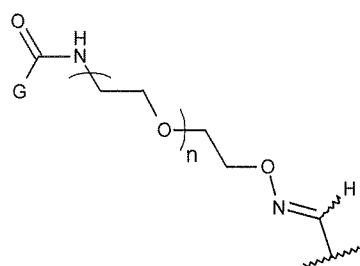
(B2)



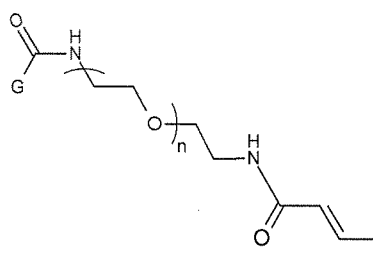
(B3)



(B4)



(B5)



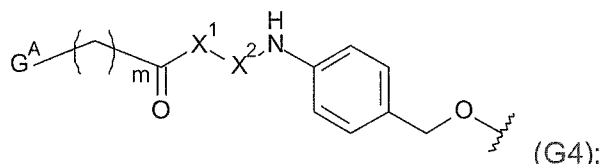
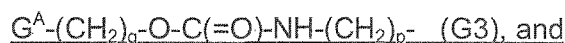
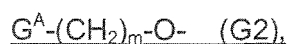
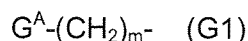
(B6)

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 32, 27 and

50. The compound according to claim 49, wherein the group G contains an electrophilic group selected from (i) maleimide groups (ii) activated disulfides, (iii) active esters such as NHS (N-hydroxysuccinimide) esters, HOBt (N-hydroxybenzotriazole) esters, haloformates, and acid halides; (iv) alkyl and benzyl halides such as haloacetamides; and (v) aldehydes, ketones, carboxyl.

51. The compound according to either claim 49 or claim 50, wherein G is of formula selected from the group:



(G4);

where m is from 0 to 6;

q is from 1 to 3;

p is from 1 to 3;

X¹ and X² are amino acid groups, selected from natural amino acids, the side chain of which may be optionally modified according to the group consisting of

(i) chemical protection of the side chain;

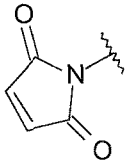
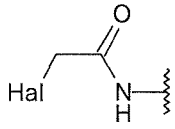
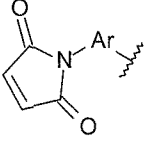
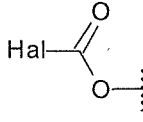
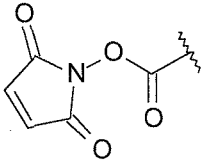
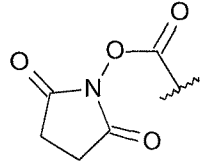
(ii) monoalkylation of an amino group NH₂ of the side chain;

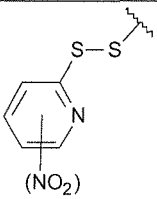
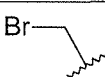
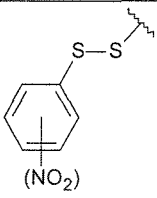
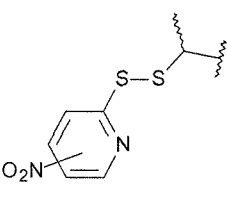
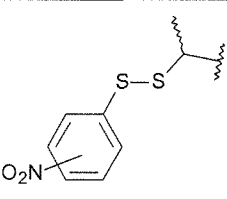
(iii) dialkylation of an amino group NH₂ of the side chain;

(iv) esterification of a carboxy group COOH of the side chain;

(v) amidation of a carboxy group COOH of the side chain; and

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			

where Ar represents a C₅₋₆ arylene group.

5246. The compound of claim 5145, wherein G is of formula G1 and G^A is selected from G^{A1-1} and G^{A3-3}.

5

5347. The compound according to either claim 51-45 or claim 5246, wherein G is of formula G1 and m is 2, 3 or 5.

54. The compound according to either claim 49 or claim 50, where G is of formula:

10

G^A-(CH₂)_m-O-(G2)

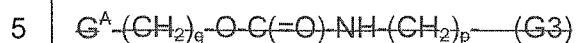
Where m is from 0 to 6; and

G^A is as defined in claim 51.

5548. The compound of claim 5445, wherein G is of formula G2 and G^A is G^{A3-2}.

5649. The compound according to either claim 5445 or 5548, wherein G is of formula G2 and m is 1.

57. The compound according to either claim 49 or claim 50, where G is of formula:



Where q is from 1 to 3, and p is from 1 to 3; and

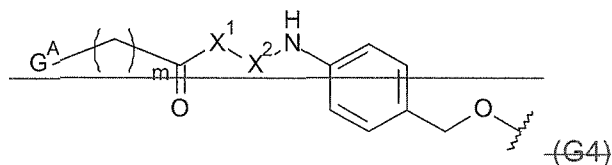
G^A is as defined in claim 51.

10 5850. The compound of claim 5745, wherein G is of formula G3 and G^A is selected from G^{A7} and G^{A8} .

5951. The compound according to either claim 5745 or 5850, wherein q is 1.

15 6052. The compound according to any one of claims 57 to 5945, 50 and 51, wherein p is 2.

61. The compound according to either claim 49 or claim 50, where G is of formula:



Where m is from 0 to 6;

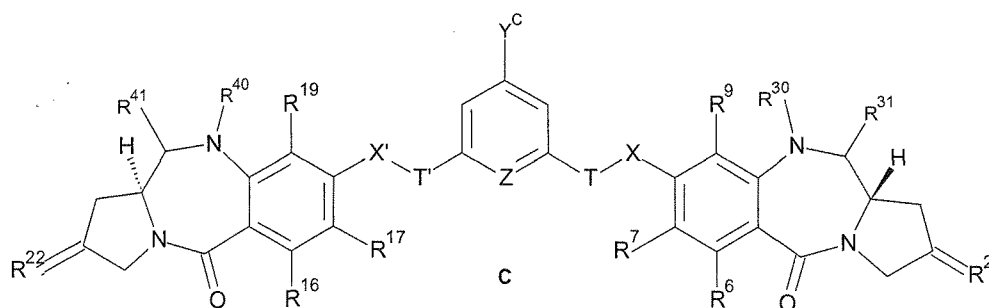
X^1 and X^2 are amino acid groups, selected from natural amino acids, which may be modified;

20 and

G^A is as defined in claim 51.)

6253. The compound according to claim 6145 wherein G is of formula G4 and m is 5.

6354. A compound of formula (C):



25 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^{40} and R^{41} are as defined for R^{30} and R^{31} respectively.

6455. The compound according to claim 6354, wherein R^{30} is H, and R^{31} is OH.

5 6556. The compound according to claim 6354, wherein R^{30} and R^{41} form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are bound.

5766. The compound according to claim 6354, wherein R^{30} is a nitrogen protecting group and R^{31} is $OProt^O$, where $Prot^O$ is a hydroxyl protecting group.

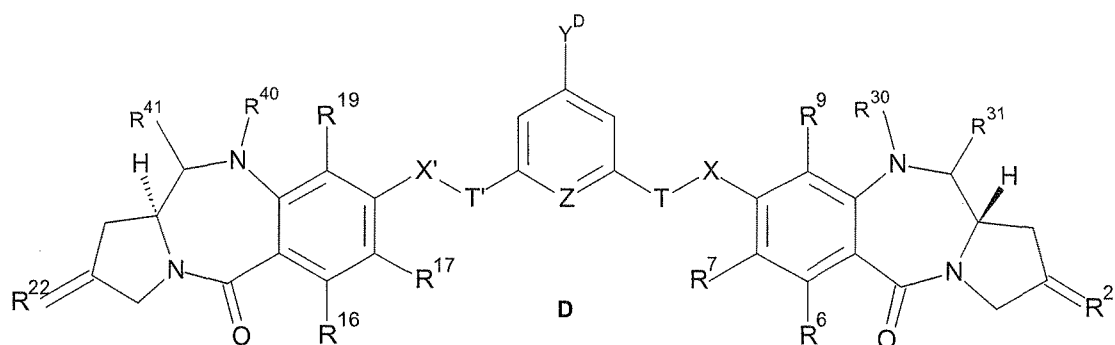
10

6758. The compound according to claim 6657, wherein the nitrogen protecting group is Boc.

15

6859. The compound according to either claim 6657 or claim 6758, wherein the hydroxyl protecting group is THP.

6960. A compound of formula (D):



wherein:

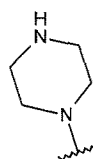
20 R^2 , R^6 , R^7 , R^9 , R^{22} , R^{16} , R^{17} , R^{19} , Z , T , T' , X and X' are as defined in any one of claims 1 to 15;

R^{30} , R^{31} , R^{40} and R^{41} are as defined in any one of claims 63-54 to 6859;

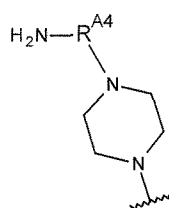
Y^D is selected from a group of formulae D2, D3, D4 and D6:



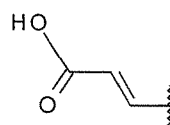
(D2)



(D3)



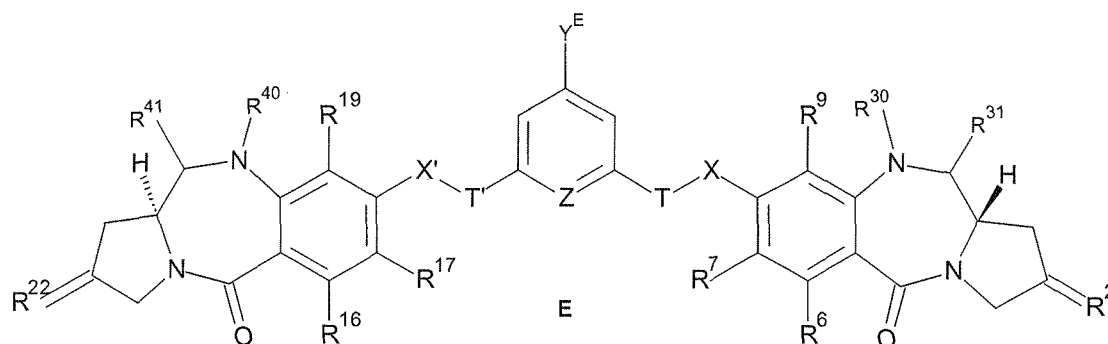
(D4)



(D6)

wherein R^{A4} are is as defined in any one of claims 1 to ~~3227~~.

~~7061~~. A compound of formula (E):



5 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 ~~63-54~~ to ~~6859~~;

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



(E1)



(E2)



(E5)

10 where

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

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

5 | ~~71~~62. A method of synthesis of a compound according to any one of claims 1 to ~~42~~38,
comprising the step of conjugating a drug-linker according to any one of claims ~~49~~45 to ~~62~~
53 with a cell-binding agent.