

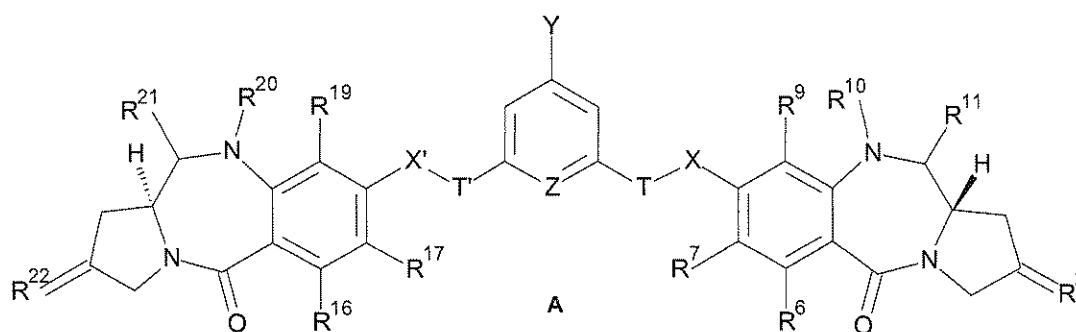
group is attached to the tether between the tomamycin units, and are generally cleaved by action of an enzyme on the linker group.

The present inventors have developed a novel approach to forming PBD conjugates with cell binding agents, and in particular PBD antibody conjugates.

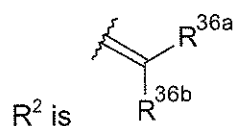
### Summary of the Invention

In a general aspect, the present invention provides a conjugate comprising a PBD dimer compound with a linker for connecting to a cell binding agent, wherein the linker has a triazole, piperazine, propargylene or oxime group attached to a phenylene or pyridylene in the bridge linking the two PBD monomers. The cell binding agent is preferably an antibody.

In a first aspect, the present invention provides novel conjugate compounds of formula (A):



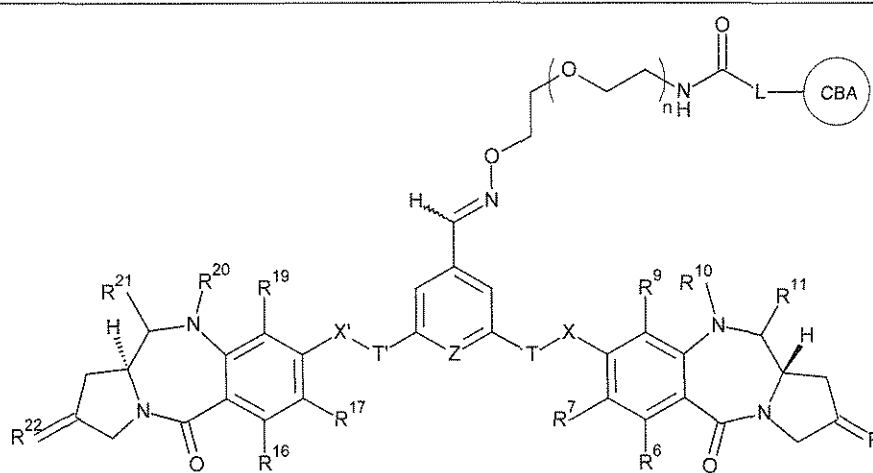
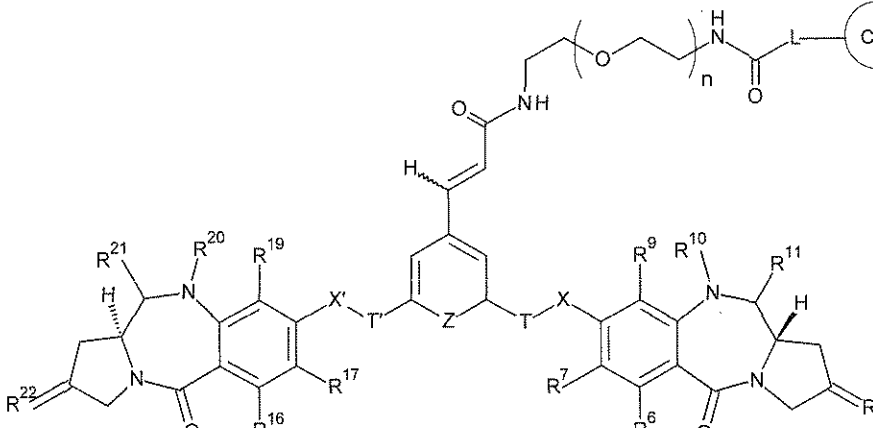
wherein:



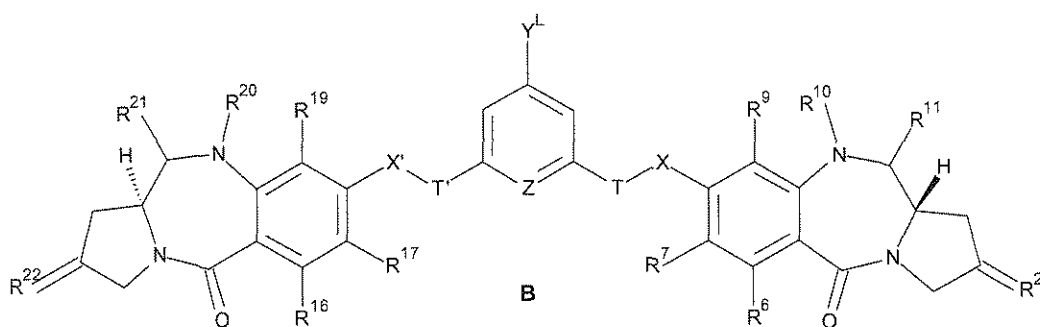
$R^2$  is  $\begin{matrix} \text{---} & \text{---} & R^{36a} \\ & \diagdown & \\ & C & \\ & \diagup & \\ R^{36b} & & \end{matrix}$ , where  $R^{36a}$  and  $R^{36b}$  are independently selected from H, F,  $C_{1-4}$  saturated alkyl,  $C_{2-3}$  alkenyl, which alkyl and alkenyl groups are optionally 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;

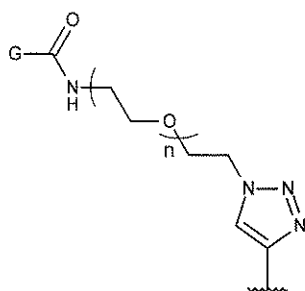
| Y  | A                                                                                                                           |
|----|-----------------------------------------------------------------------------------------------------------------------------|
| A5 |  <p style="text-align: center;">(A-V)</p> |
| A6 |                                          |

A second aspect of the present ~~invention~~disclosure provides novel drug-linker compounds of formula (B):

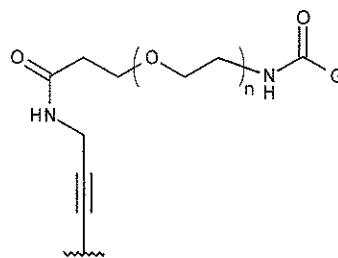


- 5 | Where all the groups are as defined in the first aspect of the ~~invention~~present disclosure;  
and

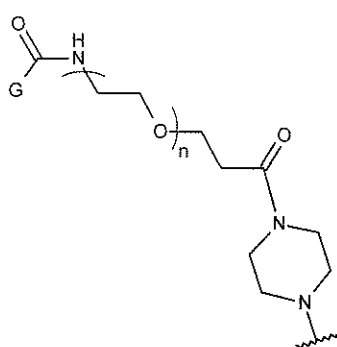
$Y^L$  is selected from a group of formulae B1, B2, B3, B4, B5 and B6:



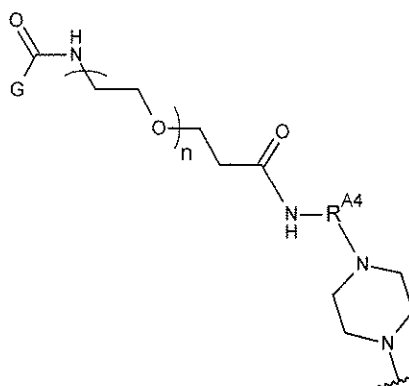
(B1)



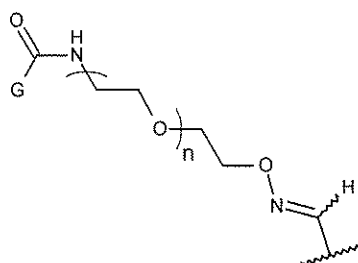
(B2)



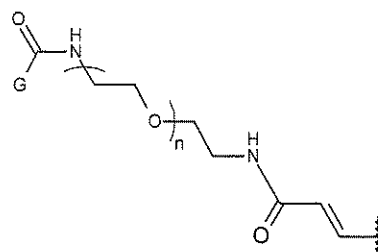
(B3)



(B4)



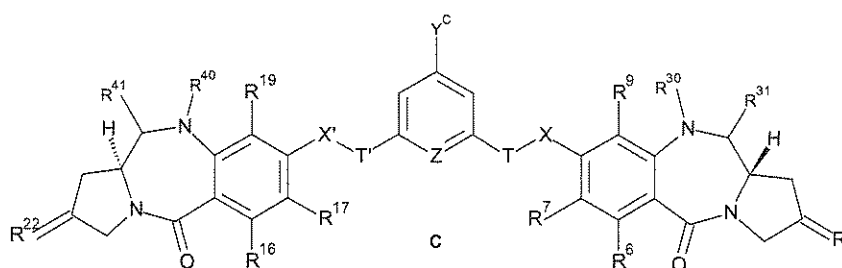
(B5)



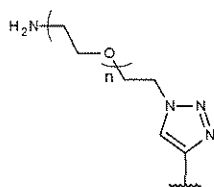
(B6)

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

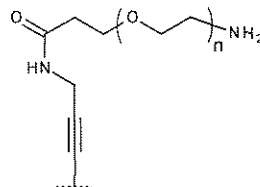
5 | A third aspect of the present invention ~~disclosure~~ provides compounds of formula (C) which may be used in the preparation of the compounds and conjugate compounds of the ~~invention~~ present disclosure:



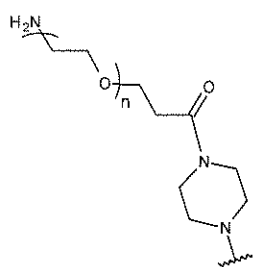
where  $Y^C$  is selected from a group of formulae C1, C2, C3, C4, ~~C5~~ and C6:



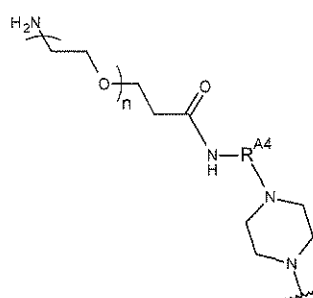
(C1)



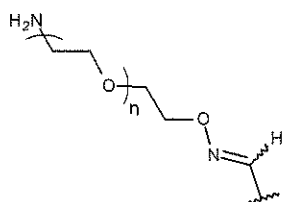
(C2)



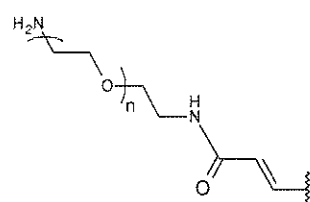
(C3)



(C4)



(C5)



(C6)

either

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

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

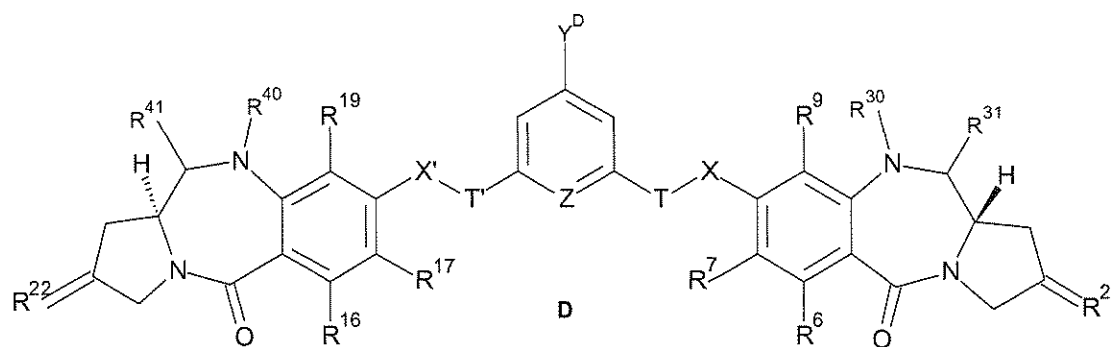
(c)  $R^{30}$  is H and  $R^{31}$  is  $OSO_2M$ , where z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation; or

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

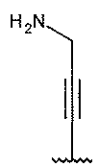
$R^{40}$  and  $R^{41}$  are as defined for  $R^{30}$  and  $R^{31}$  respectively; and

all the remaining groups are as defined in the first aspect of the ~~invention~~present disclosure.

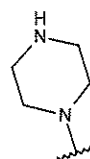
15 A fourth aspect of the present ~~invention~~disclosure provides compounds of formula (D) which may be used in the preparation of the compounds of the second and third aspects of the ~~invention~~present disclosure:



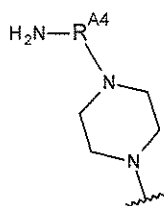
$Y^D$  is selected from a group of formulae D2, D3, D4 and D6:



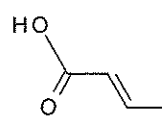
(D2)



(D3)



(D4)

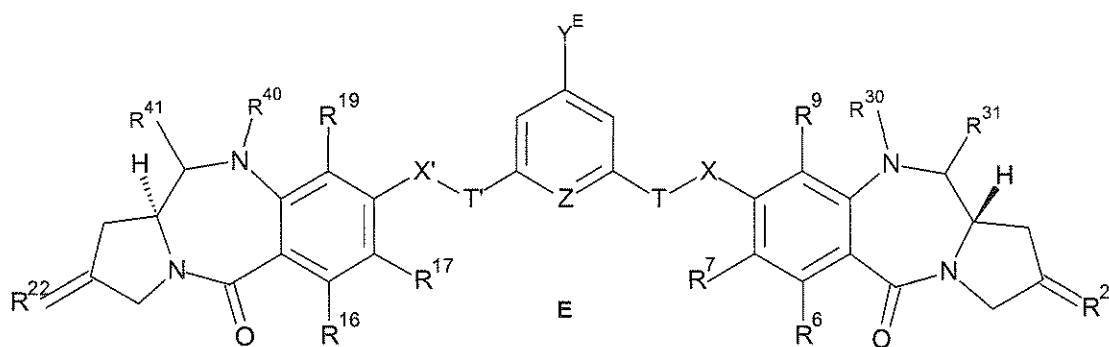


(D6)

and all the remaining groups are as defined in the third aspect of the ~~invention~~present disclosure.

5

A fifth aspect of the present ~~invention~~disclosure provides compounds of formula (E) which may be used in the preparation of the compounds of the second, third and fourth aspects of the ~~invention~~present disclosure:



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



(E1)



(E2)



(E5)

where

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

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

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

10 | ~~An embodiment sixth aspect of the present invention-disclosure~~ provides the use of a compound of the first aspect of the ~~invention-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. The fourth-~~Another aspect also provides a pharmaceutical composition comprising a compound of the first aspect, and a pharmaceutically acceptable diluent, carrier or excipient.

15 | ~~Another seventh aspect of the present invention-disclosure~~ provides a compound of the first aspect of the ~~invention-present disclosure~~ or a pharmaceutical composition as disclosed above of the ~~fourth aspect of the invention for use in a method of the~~ treatment of a proliferative disease in a subject. ~~Another~~ The ~~fifth~~ 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, and a method of treating a mammal having a proliferative disease, comprising administering an effective amount of a compound of the first aspect or a  
20 | pharmaceutical composition as disclosed above ~~of the fourth aspect~~.

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

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

43. The conjugate according to any one of claims 1 to 42, for use in therapy.

44. A pharmaceutical composition comprising the conjugate of any one of claims 1 to 42  
5 | and a pharmaceutically acceptable diluent, carrier or excipient.

45. The conjugate according to any one of claims 1 to 42 or the pharmaceutical  
composition according to claim 44, for use in the treatment of a proliferative disease in a  
subject.

10 | 46. The conjugate according to claim 45, wherein the disease is cancer.

~~47. Use of a conjugate according to any one of claims 1 to 42 or a pharmaceutical  
according to claim 45 or 46 in a method of medical treatment.~~

15 | ~~48. A method of medical treatment comprising administering to a patient the  
pharmaceutical composition of claim 45 or claim 46.~~

~~49. The method of claim 48 wherein the method of medical treatment is for treating  
20 | cancer.~~

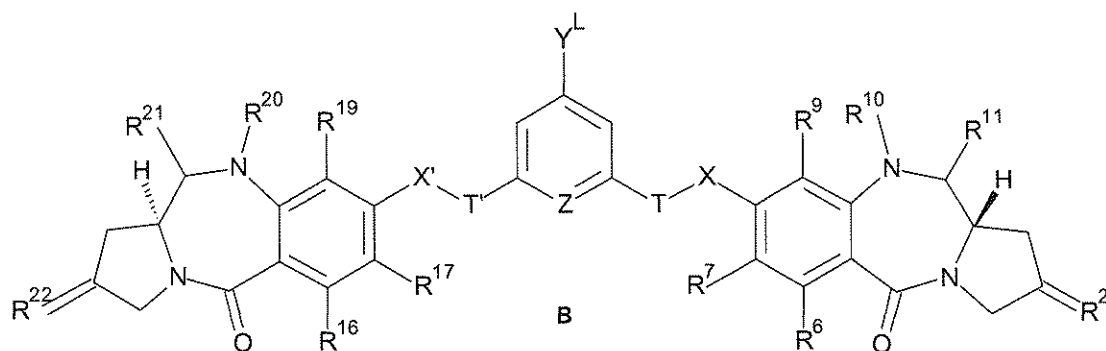
~~50. The method of claim 49, wherein the patient is administered a chemotherapeutic  
agent, in combination with the conjugate.~~

25 | ~~51~~47. Use of a compound according to any one of claims 1 to 42 in a method of  
manufacture of a medicament for the treatment of a proliferative disease.

48. The use according to claim 47, wherein the disease is cancer.

30 | ~~52. A method of treating a mammal having a proliferative disease, comprising  
administering an effective amount of a compound according to any one of claims 1 to 42 or a  
pharmaceutical composition according to claim 45 or claim 46.~~

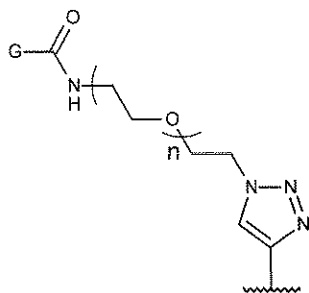
5349. A compound of formula (B):



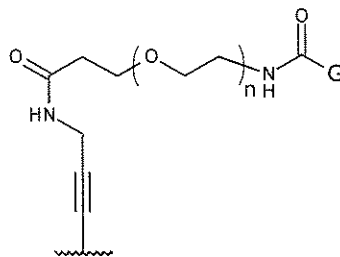
wherein:

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

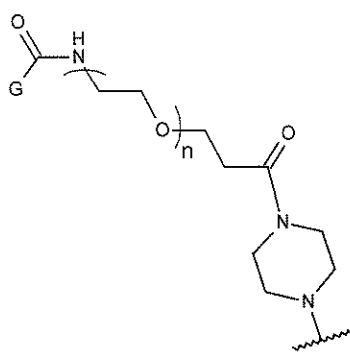
$Y^L$  is selected from a group of formulae B1, B2, B3, B4, B5 and B6:



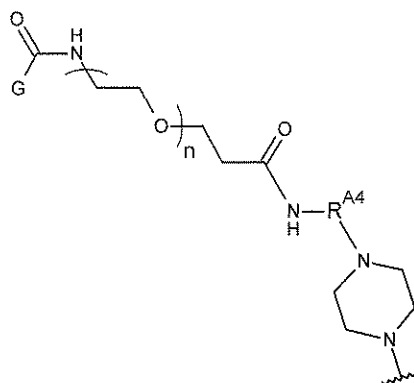
(B1)



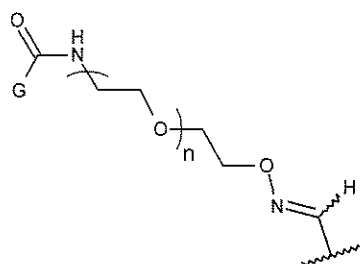
(B2)



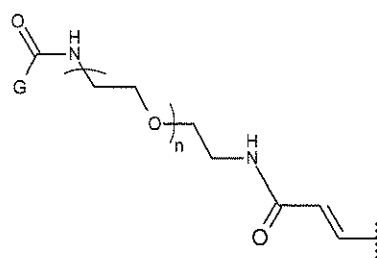
(B3)



(B4)



(B5)

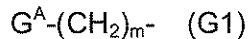


(B6)

G is a reactive group for connecting to a cell binding agent  
wherein n and R<sup>A4</sup> are as defined in any one of claims 1 to 32.

5 | 5450. The compound according to claim 5349, 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.

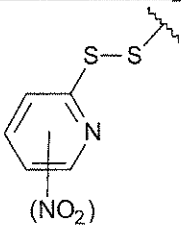
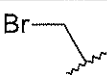
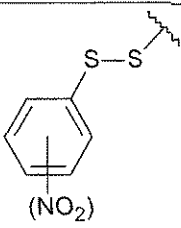
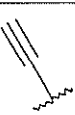
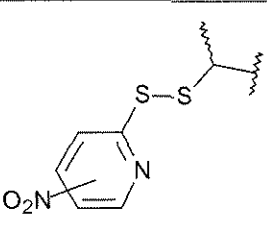
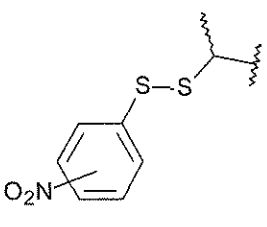
10 | 5551. The compound according to either claim 5349 or claim 5450, wherein G is of  
formula:



where m is from 0 to 6; and

G<sup>A</sup> is selected from:

|                      |  |                    |                           |
|----------------------|--|--------------------|---------------------------|
| (G <sup>A1-1</sup> ) |  | (G <sup>A4</sup> ) | <br>Where Hal = I, Br, Cl |
| (G <sup>A1-2</sup> ) |  | (G <sup>A5</sup> ) |                           |
| (G <sup>A2</sup> )   |  | (G <sup>A6</sup> ) |                           |

|                      |                                                                                                                                       |                    |                                                                                    |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------|--------------------|------------------------------------------------------------------------------------|
| (G <sup>A3-1</sup> ) |  <p>where the NO<sub>2</sub> group is optional</p>   | (G <sup>A7</sup> ) |  |
| (G <sup>A3-2</sup> ) |  <p>where the NO<sub>2</sub> group is optional</p>   | (G <sup>A8</sup> ) |  |
| (G <sup>A3-3</sup> ) |  <p>where the NO<sub>2</sub> group is optional</p>  | (G <sup>A9</sup> ) |  |
| (G <sup>A3-4</sup> ) |  <p>where the NO<sub>2</sub> group is optional</p> |                    |                                                                                    |

where Ar represents a C<sub>5-6</sub> arylene group.

5652. The compound of claim 4551, wherein G<sup>A</sup> is selected from G<sup>A1-1</sup> and G<sup>A3-3</sup>.

5 5753. The compound according to either claim 5551 or claim 5652, wherein m is 2, 3 or 5.

5854. The compound according to either claim 5349 or claim 5450, where G is of formula:  
G<sup>A</sup>-(CH<sub>2</sub>)<sub>m</sub>-O- (G2)

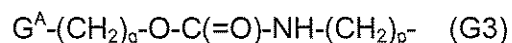
Where m is from 0 to 6; and

10 G<sup>A</sup> is as defined in claim 5551.

5955. The compound of claim 5854, wherein G<sup>A</sup> is G<sup>A3-2</sup>.

6056. The compound according to either claim 58-54 or 5955, wherein m is 1.

6157. The compound according to either claim 53-49 or claim 5450, where G is of formula:



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

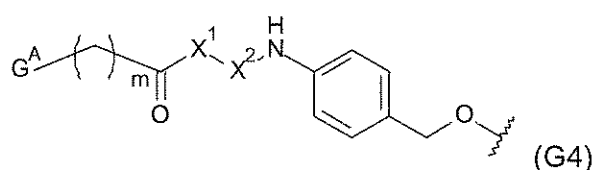
G<sup>A</sup> is as defined in claim 5551.

6258. The compound of claim 6157, wherein G<sup>A</sup> is selected from G<sup>A7</sup> and G<sup>A8</sup>.

6359. The compound according to either claim 61-57 or 6258, wherein q is 1.

6460. The compound according to any one of claims 61-57 to 6359, wherein p is 2.

6561. The compound according to either claim 53-49 or claim 5450, where G is of formula:



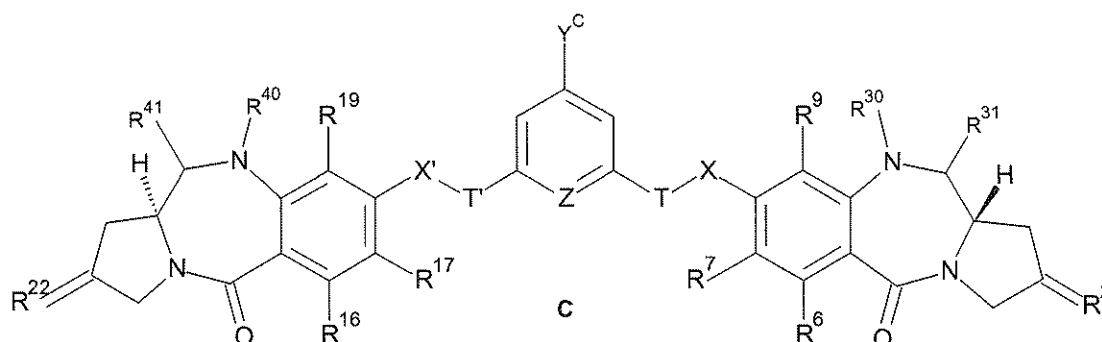
Where m is from 0 to 6;

X<sup>1</sup> and X<sup>2</sup> are amino acid groups, selected from natural amino acids, which may be modified;  
and

G<sup>A</sup> is as defined in claim 5551.

6662. The compound according to claim 65-61 wherein m is 5.

6763. A compound of formula (C):



wherein:

R<sup>2</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>9</sup>, R<sup>22</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>19</sup>, 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.

6864. The compound according to claim 6763, wherein  $R^{30}$  is H, and  $R^{31}$  is OH.

5 6965. The compound according to claim 6763, wherein  $R^{30}$  and  $R^{41}$  form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are bound.

7066. The compound according to claim 6763, wherein  $R^{30}$  is a nitrogen protecting group and  $R^{31}$  is OProt<sup>O</sup>, where Prot<sup>O</sup> is a hydroxyl protecting group.

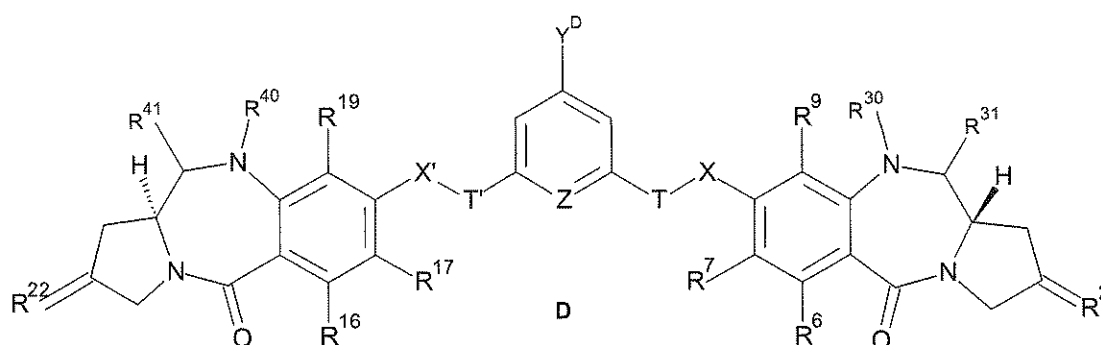
10

7167. The compound according to claim 7066, wherein the nitrogen protecting group is Boc.

15

7268. The compound according to either claim 7066 or claim 7167, wherein the hydroxyl protecting group is THP.

7369. A compound of formula (D):

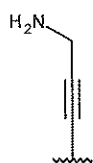


wherein:

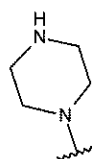
20  $R^2$ ,  $R^6$ ,  $R^7$ ,  $R^9$ ,  $R^{22}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{19}$ , Z, T, T', X and X' are as defined in any one of claims 1 to 15;

$R^{30}$ ,  $R^{31}$ ,  $R^{40}$  and  $R^{41}$  are as defined in any one of claims 47-63 to 5268;

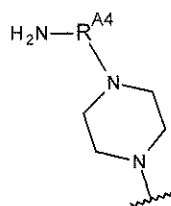
$Y^D$  is selected from a group of formulae D2, D3, D4 and D6:



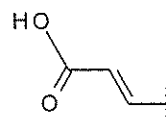
(D2)



(D3)



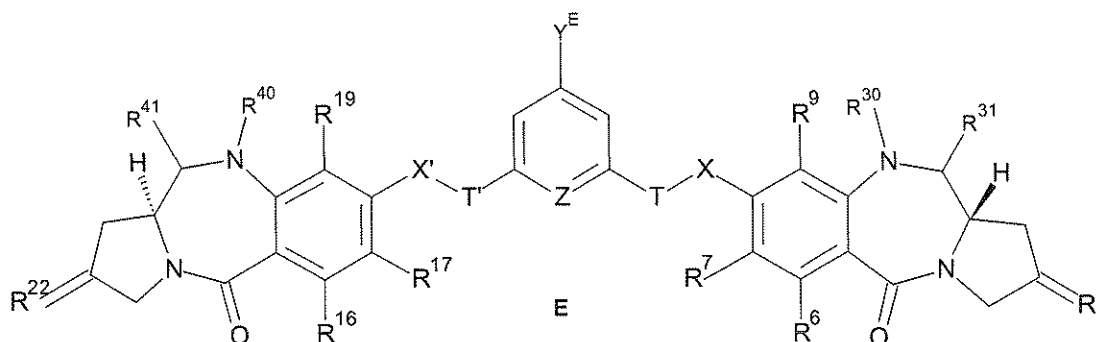
(D4)



(D6)

wherein  $R^{A4}$  are as defined in any one of claims 1 to 32.

7470. 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 67-63 to 7268;

$Y^E$  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 | ~~75~~71. A method of synthesis of a compound according to any one of claims 1 to ~~52~~42,  
comprising the step of conjugating a drug-linker according to any one of claims ~~53-49~~ to ~~66~~  
62 with a cell-binding agent.