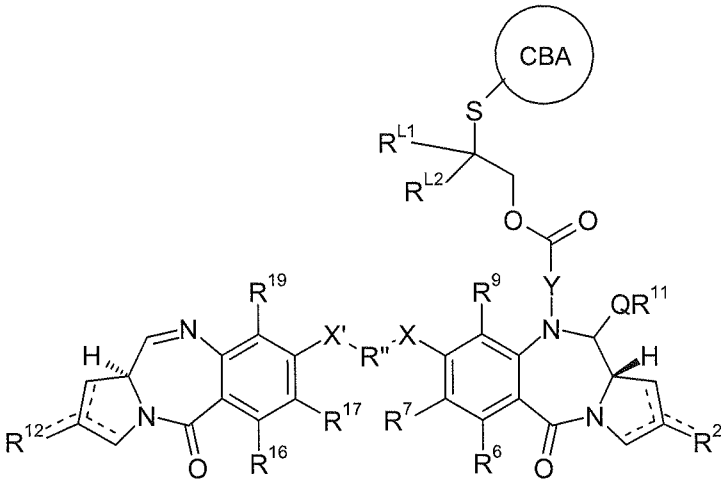
19(7): 299-307; Doronina *et al* (2006) Bioconj. Chem. 17:114-124; Erickson *et al* (2006) *Cancer Res.* 66(8):1-8; Sanderson *et al* (2005) *Clin. Cancer Res.* 11:843-852; Jeffrey *et al* (2005) *J. Med. Chem.* 48:1344-1358; Hamblett *et al* (2004) *Clin. Cancer Res.* 10:7063-7070). Drug moieties may impart their cytotoxic and cytostatic effects by mechanisms including tubulin binding, DNA binding, or topoisomerase inhibition. Some cytotoxic drugs tend to be inactive or less active when conjugated to large antibodies or protein receptor ligands.

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~~ embodiment, the present ~~invention~~ disclosure provides a conjugate comprising a PBD dimer compound connected through the N10 position via a specific sulfur linker to a cell binding agent. The cell binding agent is preferably an antibody.

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



A

and salts and solvates thereof, wherein:

the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;

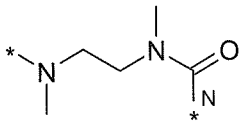
R^2 is independently selected from H, OH, =O, $=CH_2$, CN, R, OR, $=CH\text{-}R^D$, $=C(R^D)_2$, $O\text{-}SO_2\text{-}R$, CO_2R and COR, and optionally further selected from halo or dihalo;

where R^D is independently selected from R, CO_2R, COR, CHO, CO_2H, and halo;

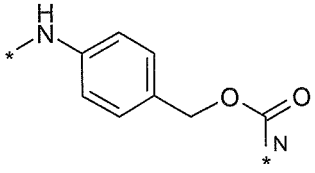
R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

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 a single bond, and a group of formulae A1 or A2:



(A1)



(A2)

where N shows where the group binds to the N10 of the PBD moiety;

R^{L1} and R^{L2} are independently selected from H and methyl, or together with the carbon atom to which they are bound form a cyclopropylene group;

CBA represents a cell binding agent;

Q is independently selected from O, S and NH;

R^{11} is either H, or R or, where Q is O, SO_3M, where M is a metal cation;

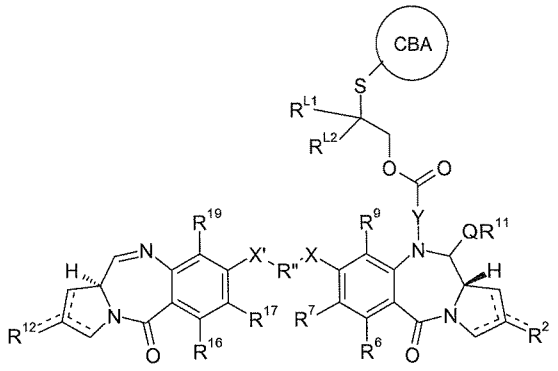
R and R' are each independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups, and optionally in relation to the group NRR', R and R' together with the nitrogen atom to which they are attached form an optionally substituted 4-, 5-, 6- or 7-membered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

wherein R^{12}, R^{16}, R^{19} and R^{17} are as defined for R^2, R^6, R^9 and R^7 respectively;

wherein R'' is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, e.g. O, S, N(H), NMe and/or aromatic rings, e.g. benzene or pyridine, which rings are optionally substituted;

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

In a first aspect, there is provided a conjugate of formula (A):



A

the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;

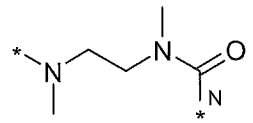
R^2 is independently selected from H, OH, =O, $=CH_2$, CN, R, OR, $=CH\text{-}R^D$, $=C(R^D)_2$, $O\text{-}SO_2\text{-}R$, CO_2R and COR, and optionally further selected from halo or dihalo;

where R^D is independently selected from R, CO_2R, COR, CHO, CO_2H, and halo;

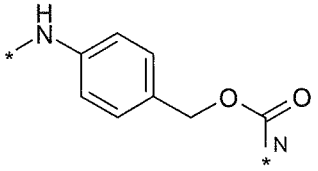
R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

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 a single bond, and a group of formulae A1 or A2:



(A1)



(A2)

where N shows where the group binds to the N10 of the PBD moiety;

R^{L1} and R^{L2} are independently selected from H and methyl, or together with the carbon atom to which they are bound form a cyclopropylene group;

CBA represents a cell binding agent;

Q is independently selected from O, S and NH;

R^{11} is either H, or R or, where Q is O, SO_3M, where M is a metal cation;

R and R' are each independently selected from optionally substituted $C_{1\text{-}12}$ alkyl, $C_{3\text{-}20}$ heterocyclyl and $C_{5\text{-}20}$ 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;

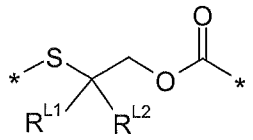
wherein R^{12}, R^{16}, R^{19} and R^{17} are as defined for R^2, R^6, R^9 and R^7 respectively;

wherein R″ is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, e.g. O, S, N(H), NMe and/or aromatic rings, e.g. benzene or pyridine, which rings are optionally substituted;

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

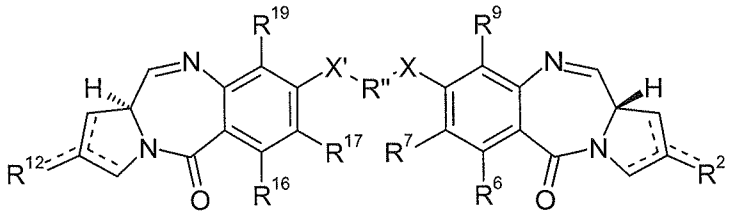
Thus formula A is selected from the following formulae A-I, A-II and A-III, depending on Y:

In compounds of formula A:

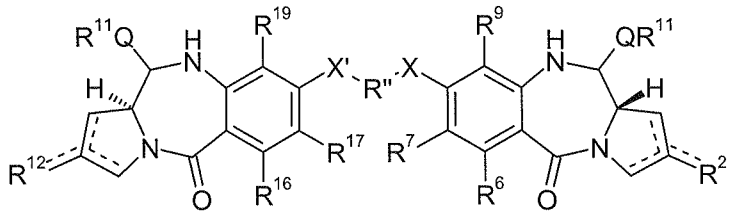


is the sulfur linking group.

A second ~~aspect~~ embodiment of the present ~~invention~~ disclosure pertains to the use of a conjugate of the first aspect to provide a compound of formula (B) or (C) at a target location:



B



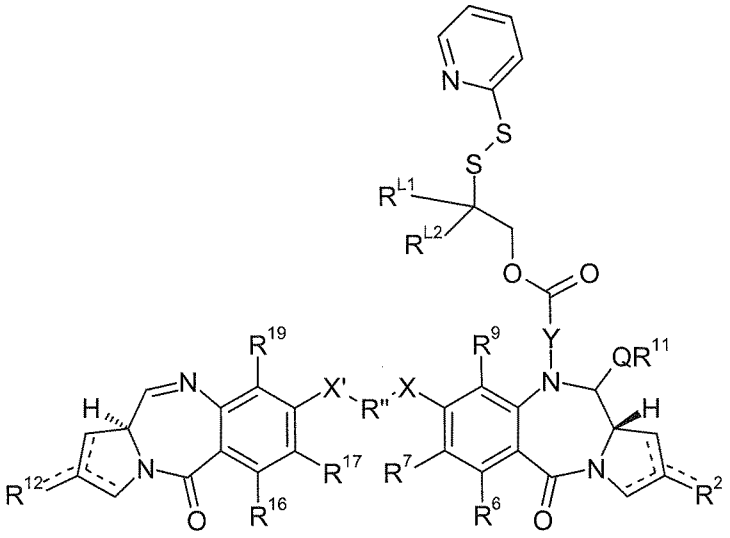
C

and salts and solvates thereof, wherein the groups are as for the first aspect, except that

Q is independently selected from O, S and NH; and

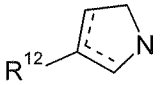
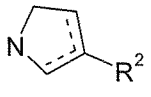
R^{11} is either H, or R or, where Q is O, SO_3M, where M is a metal cation.

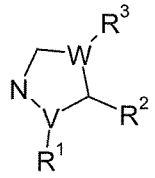
A third ~~aspect~~ embodiment of the present ~~invention~~ disclosure also provides compounds of formula (D) for use in the preparation of the conjugate compounds of the ~~invention~~disclosure:



D

and salts and solvates thereof, wherein the groups are as defined in the first aspect of the ~~invention~~disclosure.

In the compounds above, the 5-membered rings represented by  and , may be replaced by a ring selected from:



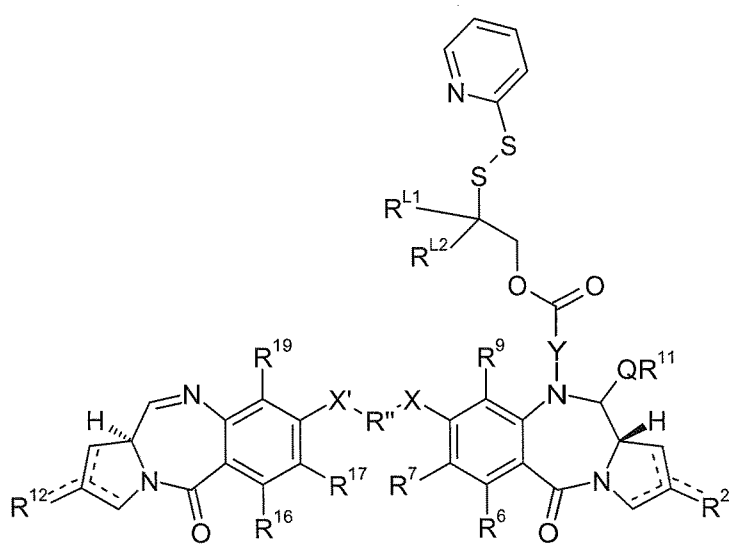
(a) (E), where R^2 with either of R^1 or R^3, together with the carbon atoms of the C ring to which they are attached, form an optionally substituted benzene ring;
V and W are each selected from $(CH_2)_n$, O, S, NR, CHR, and CRR' where n is 1, 2 or 3, except that V is C when R^1 and R^2, together with the carbon atoms of the C ring to which they are attached, form an optionally substituted benzene ring, and W is C when R^3 and R^2, together with the carbon atoms of the C ring to which they are attached, form an optionally substituted benzene ring; and

(b) (F), where T is selected from CH_2, NR, CO, BH, SO, and SO_2;
U is selected from CH_2, NR, O and S;

Y is $(CH_2)_n$, where n is 1, 2, 3 or 4;

except that T, U and Y are not all CH_2.

In an aspect, there is provided a compound of formula (D):



D

and salts and solvates thereof, wherein

the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;

R^2, R^6, R^7, R^9, R^{12}, R^{16}, R^{17}, R^{19}, X, X', R'', Y, R^{L1} and R^{L2} are as defined herein.

In an aspect, there is provided a method of preparing a conjugate according to the first aspect, the method comprising the step of reacting a cell binding agent with compound (D) as defined herein.

In another aspect, there is provided the conjugate according to the first aspect, for use in therapy. In yet another aspect, there is provided the conjugate according to the first aspect, for use in the treatment of a proliferative disease in a subject. In still another aspect, there is provided the use of the conjugate according to the first aspect in the preparation of a medicament for use in the treatment of a proliferative disease in a subject.

In a further aspect, there is provided a pharmaceutical composition comprising the conjugate of the first aspect, a pharmaceutically acceptable diluent, carrier or excipient.

Detailed Description of the Invention

The present invention provides a conjugate comprising a PBD dimer connected through the N10 position on one of the PBD moieties via the specified linker to a cell binding agent.

The present invention is suitable for use in providing a PBD compound to a preferred site in a subject. The conjugate allows the release of an active PBD compound that does not retain any part of the linker. There is no stub present that could affect the reactivity of the PBD compound.

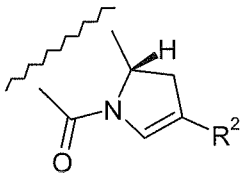
Preferences

The following preferences may apply to all aspects of the invention as described above, or may relate to a single aspect. The preferences may be combined together in any combination.

Double Bond

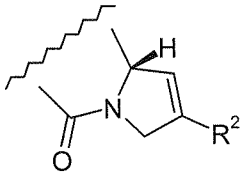
In one embodiment, there is no double bond present between C1 and C2, and C2 and C3.

In one embodiment, the dotted lines indicate the optional presence of a double bond between C2 and C3, as shown below:



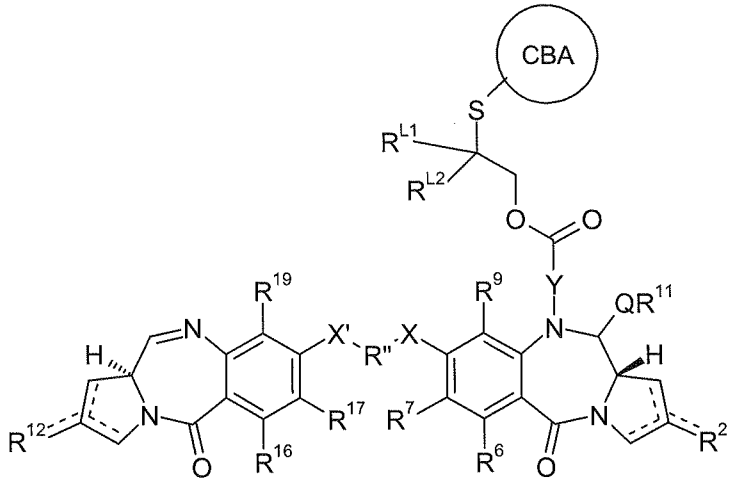
In one embodiment, a double bond is present between C2 and C3 when R^2 is C_{5-20} aryl or C_{1-12} alkyl.

In one embodiment, the dotted lines indicate the optional presence of a double bond between C1 and C2, as shown below:



Claims

1. A conjugate of formula (A):



A

the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;

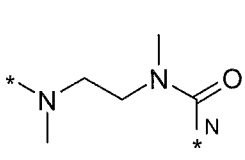
R^2 is independently selected from H, OH, =O, $=CH_2$, CN, R, OR, $=CH\text{-}R^D$, $=C(R^D)_2$, $O\text{-}SO_2\text{-}R$, CO_2R and COR, and optionally further selected from halo or dihalo;

where R^D is independently selected from R, CO_2R, COR, CHO, CO_2H, and halo;

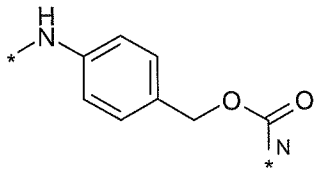
R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

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 a single bond, and a group of formulae A1 or A2:



(A1)



(A2)

where N shows where the group binds to the N10 of the PBD moiety;

R^{L1} and R^{L2} are independently selected from H and methyl, or together with the carbon atom to which they are bound form a cyclopropylene group;

CBA represents a cell binding agent;

Q is independently selected from O, S and NH;

R^{11} is either H, or R or, where Q is O, SO_3M, where M is a metal 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^{12}, R^{16}, R^{19} and R^{17} are as defined for R^2, R^6, R^9 and R^7 respectively;

wherein R" is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, e.g. O, S, N(H), NMe and/or aromatic rings, e.g. benzene or pyridine, which rings are optionally substituted;

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

2. The conjugate according to claim 1, wherein R^{L1} and R^{L2} are both H.

3. The conjugate according to claim 1, wherein one of R^{L1} and R^{L2} is H and the other is methyl.

4. The conjugate according to any one of claims 1 to 3, wherein Y is a single bond.

5. The conjugate according to any one of claims 1 to 4, wherein R^9 and R^{19} are H, and/or R^6 and R^{16} are H.

6. The conjugate according to any one of claims 1 to 5, wherein R^7 are R^{17} are both OR^{7A}, where R^{7A} is optionally substituted C_{1-4} alkyl.

7. The conjugate of claim 6, wherein R^{7A} is Me.

8. The conjugate according to any one of claims 1 to 7, wherein X is O.

9. The conjugate according to any one of claims 1 to 8, wherein R^{11} is H.

10. The conjugate according to any one of claims 1 to 9, wherein there is a double bond between C2 and C3 in each monomer unit, and wherein R^2 and R^{12} are independently R.

11. The conjugate according to claim 10, wherein R^2 and R^{12} are independently optionally substituted C_{5-20} aryl.

12. The conjugate according to any one of claims 1 to 9, wherein R^2 and R^{12} are independently selected from =O, $=CH_2$, $=CH\text{-}R^D$, and $=C(R^D)_2$.

13. The conjugate according to claim 12, wherein R^2 and R^{12} are $=CH_2$.

14. The conjugate according to any one of claims 1 to 13, wherein R'' is a C_3 alkylene group or a C_5 alkylene group.

15. The conjugate according to any one of claims 1 to 14, wherein the cell binding agent is an antibody or an active fragment thereof, and wherein the antibody or antibody fragment is an antibody or antibody fragment for a tumour-associated antigen.

16. The conjugate of claim 15 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)-(36):

(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, 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); and

(36) TENB2 (putative transmembrane proteoglycan).

17. The conjugate of claim 15 wherein the antibody or antibody fragment is a cysteine-engineered antibody.

18. The conjugate of either claim 15 or claim 17 wherein the antibody is trastuzumab.

19. The conjugate of either claim 15 or claim 17 wherein Ab is an anti-HER2, an anti-Steap1, or an anti-CD22 antibody.

20. The conjugate according to claim 15 wherein the drug loading (p) of drugs (D) to antibody (Ab) is an integer from 1 to about 8.

21. The conjugate according to claim 20 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.

22. The conjugate according to any one of claims 1 to 21, for use in therapy.

23. The conjugate according to any one of claims 1 to 21, for use in the treatment of a proliferative disease in a subject.

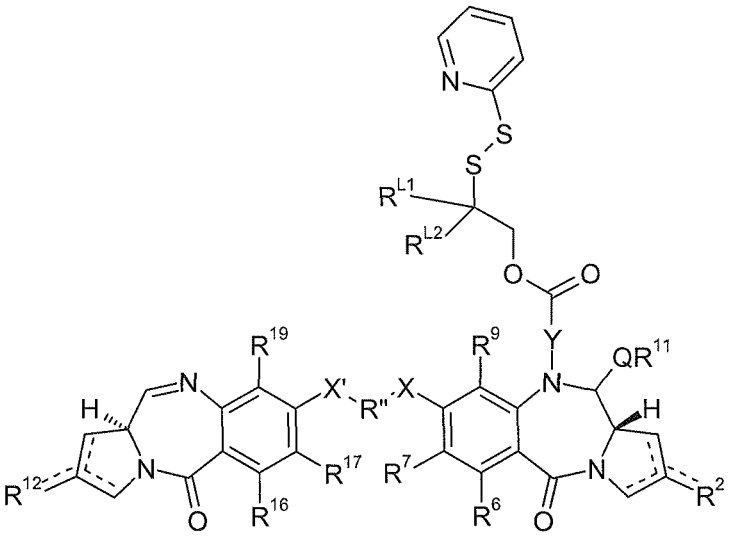
24. The conjugate according to claim 23, wherein the disease is cancer.

25. Use of the conjugate according to any one of claims 1 to 21 in the preparation of a medicament for use in the treatment of a proliferative disease in a subject.

26. A pharmaceutical composition comprising the conjugate of any one of claims 1 to 21, a pharmaceutically acceptable diluent, carrier or excipient.

27. The pharmaceutical composition of claim 26 further comprising a therapeutically effective amount of a chemotherapeutic agent.

28. A compound of formula (D):



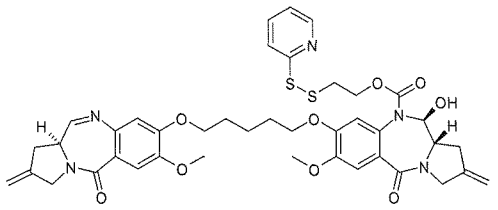
D

and salts and solvates thereof, wherein

the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;

R^2, R^6, R^7, R^9, R^{12}, R^{16}, R^{17}, R^{19}, X, X', R'', Y, R^{L1} and R^{L2} are as defined in any one of claims 1 to 14.

29. The compound of claim 28, which is:



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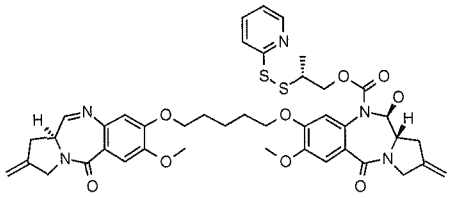
30. The compound of claim 28, which is:



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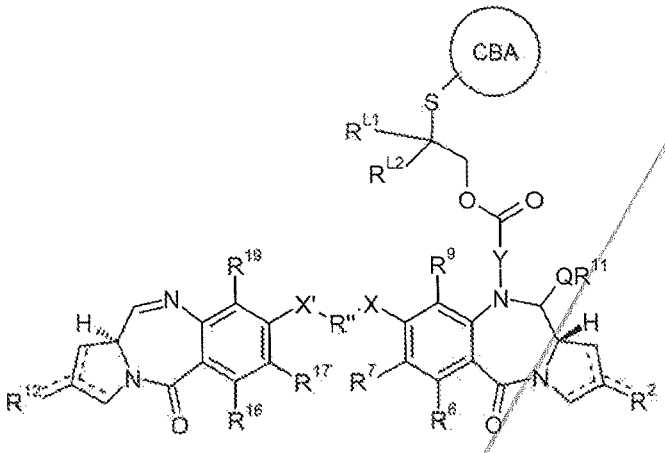
31. A method of preparing a conjugate according to any one of claims 1 to 14, the method comprising the step of reacting a cell binding agent with compound (D) as defined in any one of claims 28 to 30.

Claims

1. A conjugate of formula (A):



A

the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;

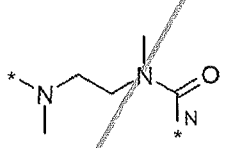
R^2 is independently selected from H, OH, =O, $=CH_2$, CN, R, OR, $=CH\text{-}R^D$, $=C(R^D)_2$, $O\text{-}SO_2\text{-}R$, CO_2R and COR, and optionally further selected from halo or dihalo;

where R^D is independently selected from R, CO_2R, COR, CHO, CO_2H, and halo;

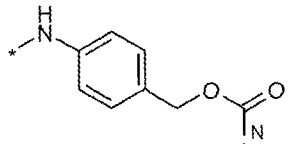
R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

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 a single bond, and a group of formulae A1 or A2:



(A1)



(A2)

where N shows where the group binds to the N10 of the PBD moiety;

R^{L1} and R^{L2} are independently selected from H and methyl, or together with the carbon atom to which they are bound form a cyclopropylene group;

CBA represents a cell binding agent;

Q is independently selected from O, S and NH;

R^{11} is either H, or R or, where Q is O, SO_3M, where M is a metal 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^{12}, R^{16}, R^{19} and R^{17} are as defined for R^2, R^6, R^9 and R^7 respectively;

wherein R'' is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, e.g. O, S, N(H), NMe and/or aromatic rings, e.g. benzene or pyridine, which rings are optionally substituted;

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

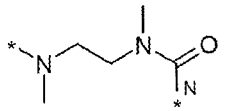
2. The conjugate according to claim 1, wherein R^{L1} and R^{L2} are both H.

3. The conjugate according to claim 1, wherein R^{L1} and R^{L2} are both methyl.

4. The conjugate according to claim 1, wherein one of R^{L1} and R^{L2} is H and the other is methyl.

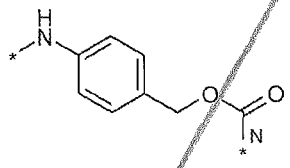
5. The conjugate according to any one of claims 1 to 4, wherein Y is a single bond.

6. The conjugate according to any one of claims 1 to 4, wherein Y is:



(A1).

7. The conjugate according to any one of claims 1 to 4, wherein Y is:



(A2).

8. The conjugate according to any one of claims 1 to 7, wherein R^9 and R^{19} are H.

9. The conjugate according to any one of claims 1 to 8, wherein R^6 and R^{16} are H.

10. The conjugate according to any one of claims 1 to 9, wherein R^7 are R^{17} are both OR^{7A}, where R^{7A} is optionally substituted C_{1-4} alkyl.

11. The conjugate of claim 10, wherein R^{7A} is Me.

12. The conjugate according to any one of claims 1 to 11, wherein X is O.

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

14. The conjugate according to any one of claims 1 to 13, wherein there is a double bond between C2 and C3 in each monomer unit.

15. The conjugate according to claim 14, wherein R^2 and R^{12} are independently selected from H and R.

16. The conjugate according to claim 15, wherein R^2 and R^{12} are independently R.

17. The conjugate according to claim 16, wherein R^2 and R^{12} are independently optionally substituted C_{5-20} aryl.

18. The conjugate according to any one of claims 1 to 13, wherein R^2 and R^{12} are independently selected from =O, $=CH_2$, $=CH\text{-}R^D$, and $=C(R^D)_2$.

19. The conjugate according to claim 18, wherein R^2 and R^{12} are $=CH_2$.

20. The conjugate according to any one of claims 1 to 19, wherein R" is a C_3 alkylene group or a C_5 alkylene group.

21. The conjugate according to any one of claims 1 to 20, wherein the cell binding agent is an antibody or an active fragment thereof.

22. The conjugate according to claim 21, wherein the antibody or antibody fragment is an antibody or antibody fragment for a tumour-associated antigen.

23. The conjugate of claim 21 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)-(36):

(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, 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); and

(36) TENB2 (putative transmembrane proteoglycan).

24. The conjugate of claim 21 wherein the antibody or antibody fragment is a cysteine-engineered antibody.

25. The conjugate of either claim 21 or claim 24 wherein the antibody or antibody fragment is an antibody which binds to an ErbB receptor.

26. The conjugate of claim 25 wherein the antibody is trastuzumab.

27. The conjugate of either claim 21 or claim 24 wherein Ab is an anti-HER2, an anti-Steap1, or an anti-CD22 antibody.

28. The conjugate according to claim 21 wherein the drug loading (p) of drugs (D) to antibody (Ab) is an integer from 1 to about 8.

29. The conjugate according to claim 28, wherein p is 1, 2, 3, or 4.

30. The conjugate according to claim 28 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.

31. The conjugate according to any one of claims 1 to 30, for use in therapy.

32. The conjugate according to any one of claims 1 to 30, for use in the treatment of a proliferative disease in a subject.

33. The conjugate according to claim 31, wherein the disease is cancer.

34. A pharmaceutical composition comprising the conjugate of any one of claims 1 to 30 a pharmaceutically acceptable diluent, carrier or excipient.

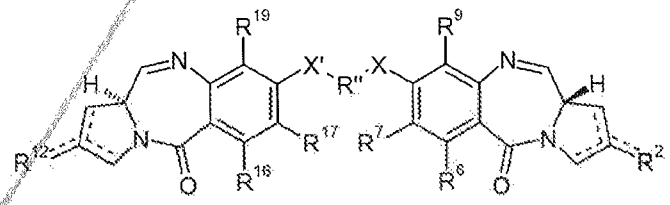
35. The pharmaceutical composition of claim 34 further comprising a therapeutically effective amount of a chemotherapeutic agent.

36. Use of a conjugate according to any one of claims 1 to 30 in the preparation of a medicament for use in the treatment of a proliferative disease in a subject.

37. A method of treating cancer comprising administering to a patient the pharmaceutical composition of claim 36.

38. The method of claim 37 wherein the patient is administered a chemotherapeutic agent, in combination with the conjugate.

39. Use of a conjugate according to any one of claims 1 to 30 to provide a compound of formula (B) at a target location.

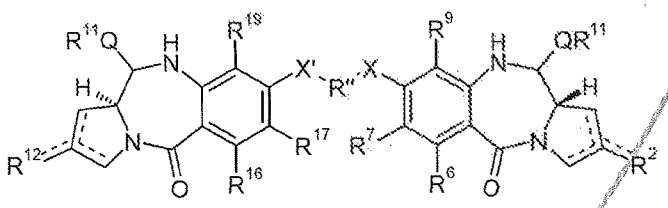


B

and salts and solvates thereof.

40. The use according to claim 39, wherein the target location is a proliferative cell population.

41. Use of a conjugate according to any one of claims 1 to 30 to provide a compound of formula (C) at a target location:



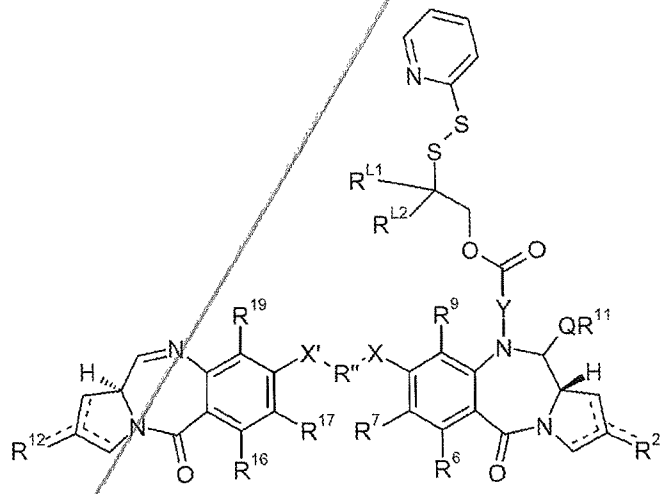
C

and salts and solvates thereof, wherein

Q is independently selected from O, S and NH; and

R^{11} is either H, or R or, where Q is O, SO_3M, where M is a metal cation.

42. A compound of formula (E):



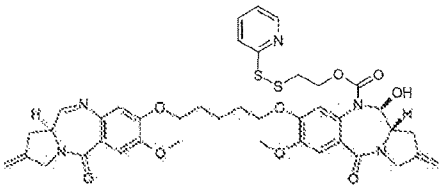
D

and salts and solvates thereof, wherein

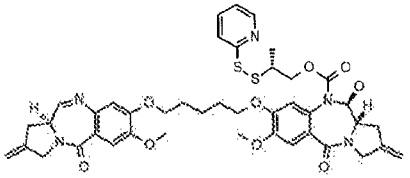
the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;

R^2, R^6, R^7, R^9, R^{12}, R^{16}, R^{17}, R^{19}, X, X', R'', Y, R^{L1} and R^{L2} are as defined in any one of claims 1 to 20.

43. The compound of claim 42, which is:



44. The compound of claim 43, which is:



45. A method of preparing a conjugate according to any one of claims 1 to 30, the method comprising the step of reacting a cell binding agent with compound (D) as defined in any one of claims 42 to 44.

46. An article of manufacture comprising a pharmaceutical composition of claim 35; a container; and a package insert or label indicating that the pharmaceutical composition can be used to treat cancer.