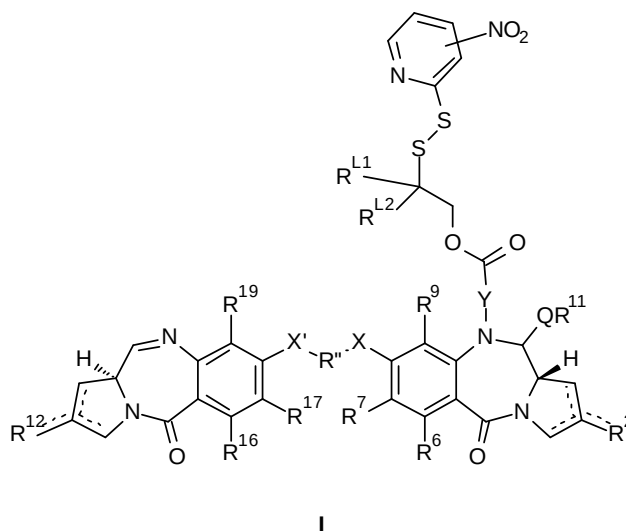


Claims

1. A compound of formula I:



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

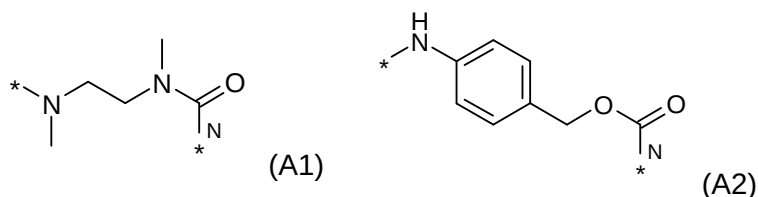
R^2 is independently selected from H, OH, =O, =CH₂, CN, R, OR, =CH-R^D, =C(R^D)₂, O-SO₂-R, CO₂R and COR, and optionally further selected from halo or dihalo;

where R^D is independently selected from R, CO₂R, COR, CHO, CO₂H, and halo;

R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH₂, NHR, NRR', NO₂, Me₃Sn and halo;

R^7 is independently selected from H, R, OH, OR, SH, SR, NH₂, NHR, NRR', NO₂, Me₃Sn and halo;

Y is selected from a single bond, and a group of formulae A1 or 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;

Q is independently selected from O, S and NH;

R^{11} is either H, or R or, where Q is O, SO₃M, where M is a metal cation;

R and R' are each independently selected from optionally substituted C₁₋₁₂ alkyl, C₃₋₂₀ heterocyclyl and C₅₋₂₀ aryl groups, and optionally in relation to the group NRR', R and

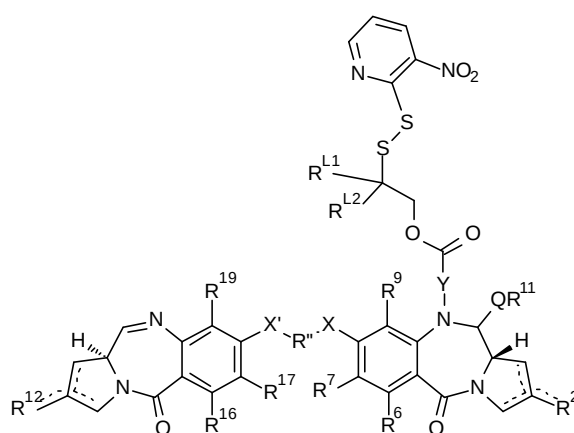
R' together with the nitrogen atom to which they are attached form an optionally substituted 4-, 5-, 6- or 7-membered heterocyclic ring;

wherein R¹², R¹⁶, R¹⁹ and R¹⁷ are as defined for R², R⁶, R⁹ and R⁷ respectively;

wherein R'' is a C₃₋₁₂ 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; and

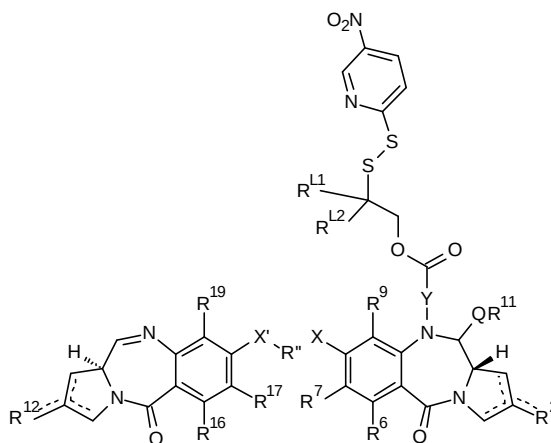
X and X' are independently selected from O, S and N(H).

2. The compound of claim 1, which is of formula II:



II

; or of formula III:

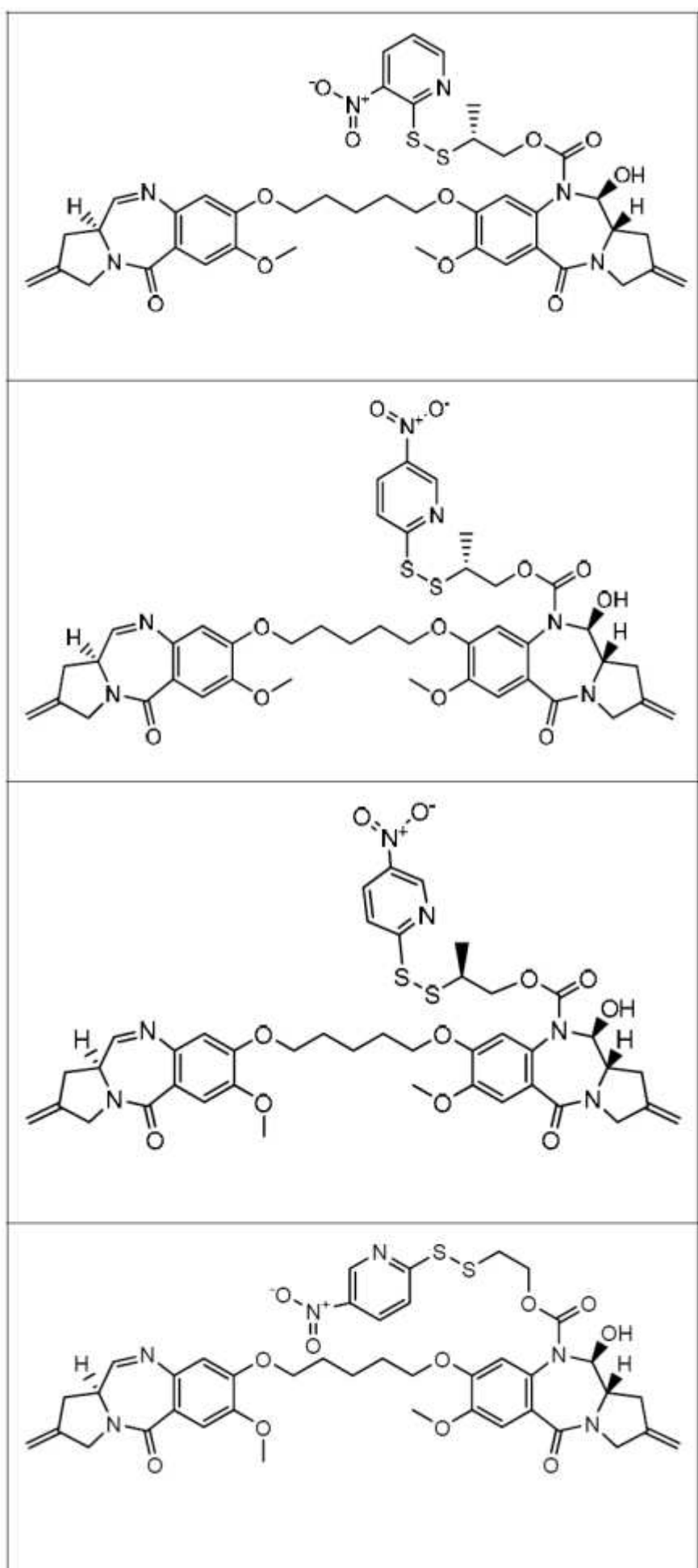


III

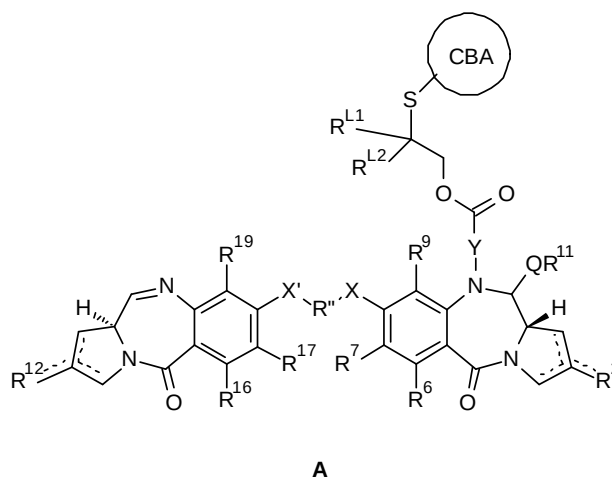
3. The compound according to either claim 1 or claim 2, wherein:

- (a) R^{L1} and R^{L2} are both H; or
- (b) R^{L1} and R^{L2} are both methyl; or
- (c) one of R^{L1} and R^{L2} is H and the other is methyl.

4. The compound according to any one of claims 1 to 3, wherein Y is a single bond.
5. The compound according to any one of claims 1 to 4, wherein R⁹ and R¹⁹ are H, R⁶ and R¹⁶ are H, and R⁷ and R¹⁷ are both OR^{7A}, where R^{7A} is optionally substituted C₁₋₄ alkyl.
6. The compound according to any one of claims 1 to 5, wherein X is O.
7. The compound according to any one of claims 1 to 6, wherein R¹¹ is H.
8. The compound according to any one of claims 1 to 7, wherein there is a double bond between C2 and C3 in each monomer unit.
9. The compound according to claim 8, wherein R² and R¹² are independently selected from H and R.
10. The compound according to claim 9, wherein R² and R¹² are independently optionally substituted C₅₋₂₀ aryl.
11. The compound according to any one of claims 1 to 8, wherein R² and R¹² are =CH₂.
12. The compound according to any one of claims 1 to 11, wherein R" is a C₃ alkylene group or a C₅ alkylene group.
13. The compound according to claim 1, which is selected from:



14. A method of making a conjugate of formula A:



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

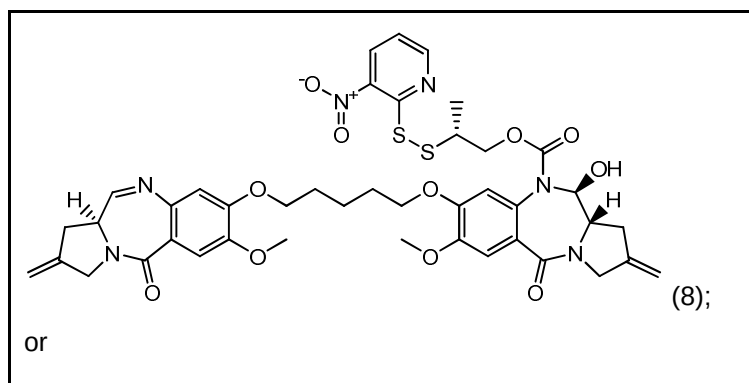
CBA represents a cell binding agent;

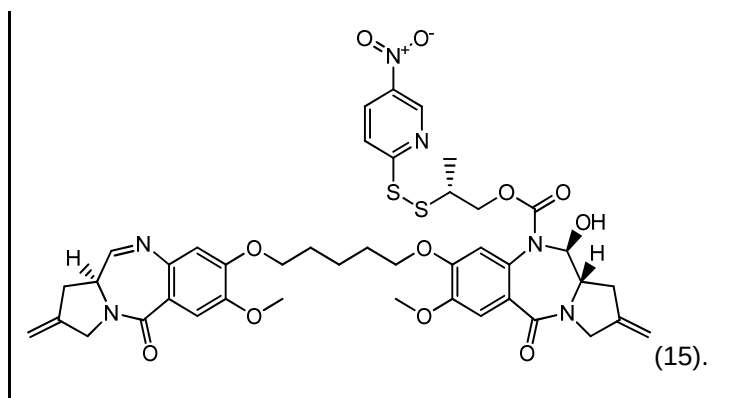
by reacting a compound according to any one of claims 1 to 13 with a cell binding agent, wherein the groups Y, R^{L1}, R^{L2}, R², R⁶, R⁷, R⁹, Q, R¹¹, X, X', R'', R¹², R¹⁶, R¹⁹ are as defined in any one of claims 1 to 13.

15. The method of claim 14, wherein the antibody or antibody fragment is an antibody or antibody fragment for a tumour-associated antigen.

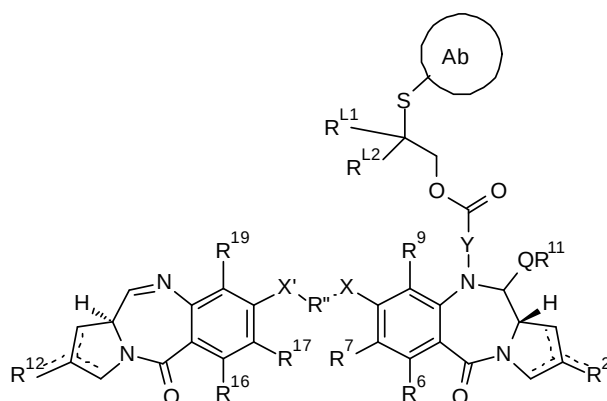
16. The method of either claim 14 or claim 15 wherein Ab is anti-HER2 4D5, anti-CD22, anti-CD33, anti-Napi3b, anti-HER2 7C2, or anti-CLL-1 antibody.

17. The method of any one of claims 14 to 16, wherein Ab is a Thio Hu anti-CLL-1 LC A118C antibody or Thio Hu anti-CLL-1 LC K149C antibody and the compound is either:





18. A conjugate of formula A1:



A1

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

Ab represents a cysteine-engineered antibody mutant (THIOMAB™) which binds to CLL-1 selected from the group consisting of:

- (a) LC K149C cysteine-engineered antibody mutant (THIOMAB™);
- (b) HC A140C cysteine-engineered antibody mutant (THIOMAB™);
- (c) LC V205C cysteine-engineered antibody mutant (THIOMAB™); and
- (d) HC S239C cysteine-engineered antibody mutant (THIOMAB™);

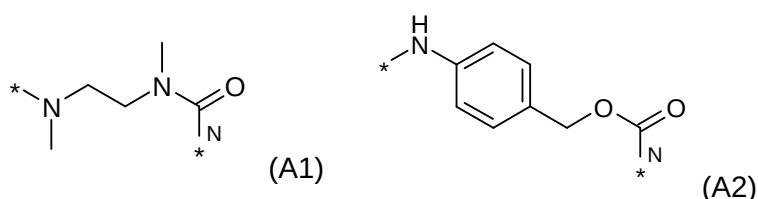
wherein R^2 is independently selected from H, OH, =O, =CH₂, CN, R, OR, =CH-R^D, =C(R^D)₂, O-SO₂-R, CO₂R and COR, and optionally further selected from halo or dihalo;

where R^D is independently selected from R, CO₂R, COR, CHO, CO₂H, and halo;

R⁶ and R⁹ are independently selected from H, R, OH, OR, SH, SR, NH₂, NHR, NRR', NO₂, Me₃Sn and halo;

R⁷ is independently selected from H, R, OH, OR, SH, SR, NH₂, NHR, NRR', NO₂, Me₃Sn and halo;

Y is selected from a single bond, and a group of formulae A1 or 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;

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; and

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

19. The conjugate according to claim 18, wherein

- (a) R^{L1} and R^{L2} are both H; or
- (b) R^{L1} and R^{L2} are both methyl; or
- (c) one of R^{L1} and R^{L2} is H and the other is methyl.

20. The conjugate according to either claim 18 or claim 19, wherein Y is a single bond.

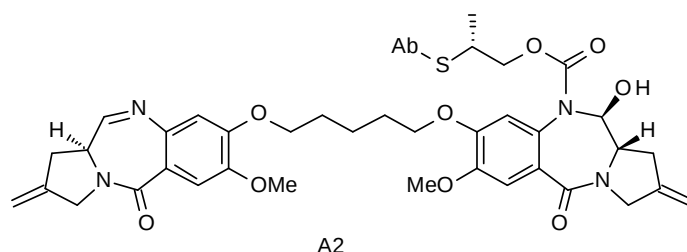
21. The conjugate according to any one of claims 18 to 20, wherein R^9 and R^{19} are H, R^6 and R^{16} are H, R^7 and R^{17} are both OR^{7A} , where R^{7A} is optionally substituted C_{1-4} alkyl.

22. The conjugate according to any one of claims 18 to 21, wherein X is O.

23. The conjugate according to any one of claims 18 to 22, wherein R^{11} is H.

24. The conjugate according to any one of claims 18 to 23, wherein there is a double bond between C2 and C3 in each monomer unit.

25. The conjugate according to claim 24, wherein R^2 and R^{12} are independently selected from H and R.
26. The conjugate according to claim 24, wherein R^2 and R^{12} are independently optionally substituted C_{5-20} aryl.
27. The conjugate according to any one of claims 18 to 23, wherein R^2 and R^{12} are $=CH_2$.
28. The conjugate according to any one of claims 18 to 27, wherein R'' is a C_3 alkylene group or a C_5 alkylene group.
29. A conjugate of formula A2:



Ab represents a HC A118C or LC K149C cysteine-engineered antibody mutant (THIOMAB™) which binds to CLL-1.

30. The conjugate according to any one of claims 18 to 29 for use in therapy.
31. The conjugate according to any one of claims 18 to 29 for use in the treatment of a proliferative disease in a subject.
32. The conjugate according to claim 31, wherein the disease is cancer.
33. A pharmaceutical composition comprising the conjugate according to any one of claims 18 to 29, and a pharmaceutically acceptable diluent, carrier or excipient.
34. The pharmaceutical composition of claim 33 further comprising a therapeutically effective amount of a chemotherapeutic agent.