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.

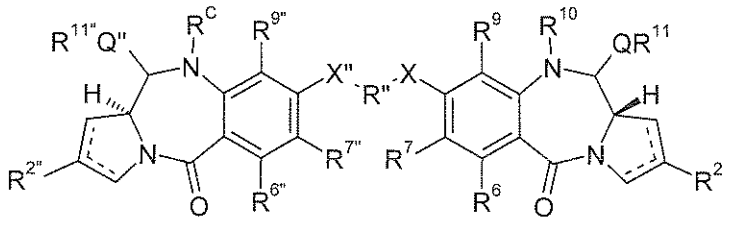
The present inventors have developed a novel approach to forming PBD conjugates with cell binding agents, and in particular PBD antibody conjugates.

Summary ~~of the Invention~~

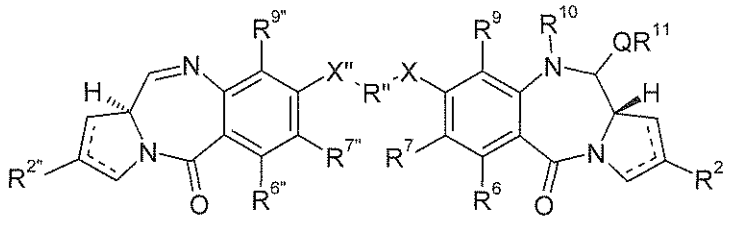
In a general ~~aspect~~embodiment the present ~~invention~~disclosure provides a conjugate comprising a PBD compound connected through the N10 position via a linker to a cell binding agent. The linker is a labile linker, and may be an enzyme labile linker. The cell binding agent is preferably an antibody.

In one embodiment, the conjugate comprises a cell binding agent connected to a spacer, the spacer connected to a trigger, the trigger connected to a self-immolative linker, and the self-immolative linker connected to the N10 position of the PBD compound.

In an aspect, there is provided a conjugate of Formula (AB) or (AC):



AB



AC

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;

R^{10} is a linker connected to a cell binding agent selected from an antibody, a fragment of an antibody that contains at least one binding site and a cyclic polypeptide;

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;

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 by NH_2;

each X is O, S or N(H); and

wherein $R^{2''}$, $R^{6''}$, $R^{7''}$, $R^{9''}$, X'', Q'' and $R^{11''}$ are as defined according to R^2, R^6, R^7, R^9, X, Q and R^{11} respectively, and R^C is a capping group.

In another aspect, there is provided the conjugate as defined above for use in therapy.

In another aspect, there is provided the conjugate as defined above, for use in the treatment of a proliferative disease in a subject, wherein the disease is cancer.

In another aspect, there is provided a conjugate having the formula:

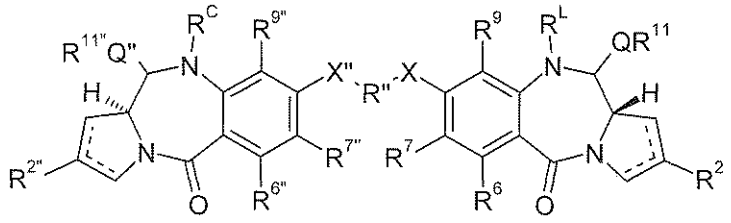
$$Ab\text{--}(L\text{--}D)_p$$

where Ab is an antibody attached by a linker moiety (L) to the formula (AB) or (AC) PBD drug moiety (D), and p is an integer from 1 to about 8, wherein the linker moiety (L) and the PBD drug moiety (D) of formula (AB) or (AC) as defined above.

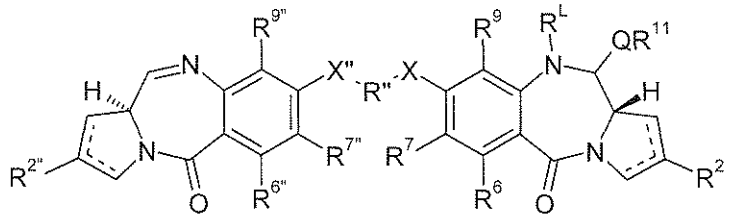
In another aspect, there is provided a pharmaceutical composition comprising the conjugate as defined above a pharmaceutically acceptable diluent, carrier or excipient.

In another aspect, there is provided the use of a conjugate as defined above in the preparation of a medicament for use in the treatment of a proliferative disease in a subject.

In another aspect, there is provided a compound of formula (EB) or (EC):



EB



EC

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;

R^L is a linker for connection to a cell binding agent selected from an antibody, a fragment of an antibody that contains at least one binding site and a cyclic polypeptide;

Q is independently selected from O, S and NH;

R^{11} is either H, or R or, where Q is O, R^{11} is 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;

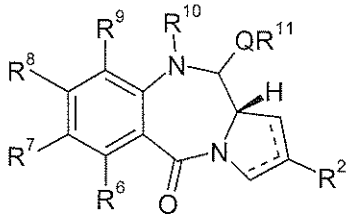
R″ is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, e.g. O, S, N(H), NMe and/or aromatic rings, e.g. benzene or pyridine, which rings are optionally substituted by NH_2;

each X is O, S or N(H); and

wherein $R^{2''}$, $R^{6''}$, $R^{7''}$, $R^{9''}$, $R^{11''}$, Q″ and X″ are as defined according to R^2, R^6, R^7, R^9, R^{11}, Q and X respectively, and R^C is a capping group;

wherein R^L is different to R^C.

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;

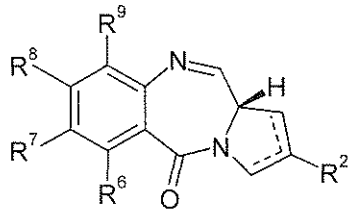
where R^D is independently selected from R, CO_2R, COR, CHO, CO_2H, and halo;

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;

R^8 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

The present ~~invention~~disclosure also pertains to the use of a conjugate to provide a compound of formula (C) at a target location:



C

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;

R^8 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

R and R' are 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;

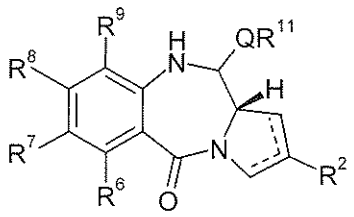
or any pair of adjacent groups from R^6 to R^9 together form a group $-O\text{-}(CH_2)_p\text{-}O-$, where p is 1 or 2

or the compound is a dimer with each monomer being of formula (C), and the R^7 groups or R^8 groups of each monomer form together a dimer bridge having the formula -X-R"-X- linking the monomers;

wherein R" is a $C_{3\text{-}12}$ 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 by NH_2;

and each X is O, S or N(H).

The present ~~invention~~disclosure also pertains to the use of a conjugate to provide a compound of formula (D) at a target location:



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 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;

R^8 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

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;

or any pair of adjacent groups from R^6 to R^9 together form a group $-O\text{-}(CH_2)_p\text{-}O-$, where p is 1 or 2;

or the compound is a dimer with each monomer being of formula (D), or with one monomer being of formula (D) and the other being of formula (C);

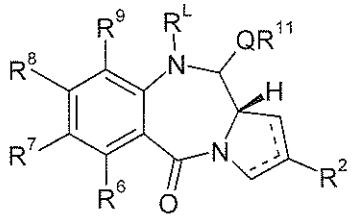
and the R^7 groups or R^8 groups of each monomer form together a dimer bridge having the formula -X-R''-X- linking the monomers;

wherein R'' is a $C_{3\text{-}12}$ 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 by NH_2;

and each X is O, S or N(H);

wherein the monomer unit of formula (C) is as defined above.

The present ~~invention~~disclosure also provides compounds of formula (E) for use in the preparation of the conjugate compounds of the ~~invention~~present disclosure:



E

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;

R^8 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

R^L is a linker for connection to 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, R^{11} is 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;

or any pair of adjacent groups from R^6 to R^9 together form a group $-O\text{-}(CH_2)_p\text{-}O-$, where p is 1 or 2;

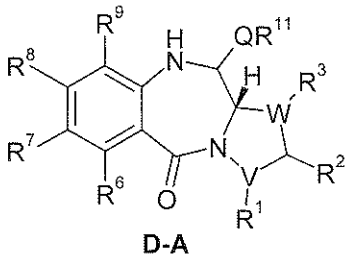
or the compound is a dimer with each monomer being of formula (C), each monomer being of formula (C-I), or with one monomer being of formula (C) and the other being of formula (C-I), and the R^7 groups or R^8 groups of each monomer form together a dimer bridge having the formula -X-R″-X- linking the monomers;

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 by NH_2;

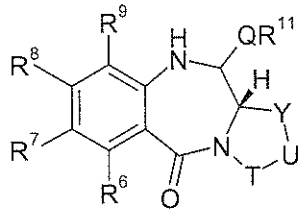
and each X is O, S or N(H).

The present ~~invention~~disclosure also pertains to the use of a conjugate to provide a compound at a target location, wherein the compound is a compound of formula (D) as described above or formula (D-I);

where (D-I) is selected from (D-A) and (D-B):



D-A



D-B

and salts and solvates thereof, wherein:

R^6, R^9, R and R' are as defined according to the compounds of formula (D);

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

R^8 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

or any pair of adjacent groups from R^6 to R^9 together form a group $-O-(CH_2)_p-O-$, where p is 1 or 2,

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^2 with either of R^1 or R^3, together with 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 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 carbon atoms of the C ring to which they are attached, form an optionally substituted benzene ring;

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;

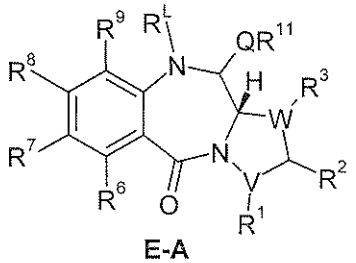
or the compound is a dimer with each monomer being of formula (D), each monomer being of formula (D-I), or with one monomer being of formula (D) and the other being of formula (D-I), and the R^7 groups or R^8 groups of each monomer form together a dimer bridge having the formula -X-R″-X- linking the monomers;

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 by NH_2;

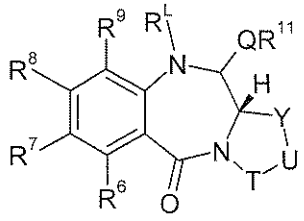
and each X is O, S or N(H).

Alternatively, the present ~~invention~~disclosure also provides compounds of formula (E) as described above and (E-I) for use in the preparation of the conjugate compounds of the ~~invention~~present disclosure;

where (E-I) is selected from (E-A) and (E-B):



E-A



E-B

and salts and solvates thereof, wherein:

R^6, R^9, R and R' are as defined according to the compounds of formula (D);

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

R^8 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

or any pair of adjacent groups from R^6 to R^9 together form a group $-O-(CH_2)_p-O-$, where p is 1 or 2,

R^L is a linker for connection to 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^2 with either of R^1 or R^3, together with carbon atoms of the C ring to which they are attached, form an optionally substituted benzene ring;