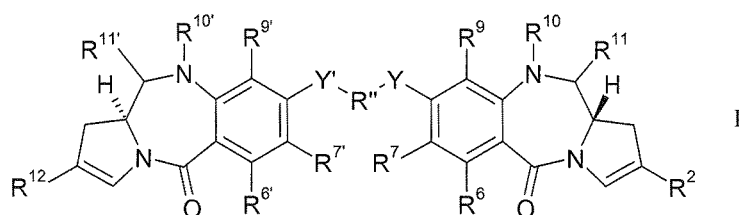
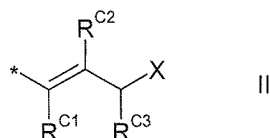


In an aspect, there is provided a compound with the formula I:

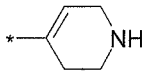
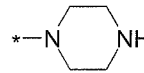


wherein:

R² is of formula II:



where X is selected from the group consisting of comprising: OH, SH, CO₂H, COH, N=C=O,

NHNH₂, CONHNH₂, ,  and, NHR^N, wherein R^N is selected from the group comprising H and C₁₋₄ alkyl;

R^{C1}, R^{C2} and R^{C3} are independently selected from H and unsubstituted C₁₋₂ alkyl;

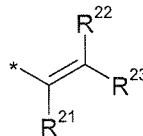
and either:

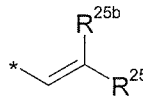
R¹² is selected from the group consisting of:

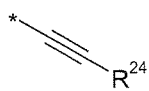
(ia) C₅₋₁₀ aryl group, optionally substituted by one or more substituents selected from the group consisting of comprising: halo, nitro, cyano, ether, C₁₋₇ alkyl, C₃₋₇ heterocyclyl and bis-oxy-C₁₋₃ alkylene;

(ib) C₁₋₅ saturated aliphatic alkyl;

(ic) C₃₋₆ saturated cycloalkyl;

(id) , wherein each of R²¹, R²² and R²³ are independently selected from H, C₁₋₃ saturated alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl and cyclopropyl, where the total number of carbon atoms in the R¹² group is no more than 5;

(ie) , wherein one of R^{25a} and R^{25b} is H and the other is selected from: phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl; and



(if) R^{24} , where R^{24} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} alkynyl; cyclopropyl; phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl;

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

where R and R' are independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups;

10 R^7 is selected from H, R, OH, OR, SH, SR, NH_2 , NHR, ~~$\text{NRR}'\text{NRR}'$~~ , nitro, Me_3Sn and halo; either:

(a) R^{10} is H, and R^{11} is OH, OR^A , where R^A is C_{1-4} alkyl;

(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 SO_zM , where z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation;

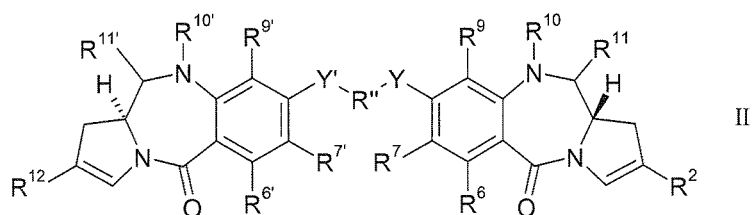
15 R'' is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, and/or aromatic rings;

Y and Y' are selected from O, S, ~~and/or~~ NH;

$\text{R}^{6'}$, $\text{R}^{7'}$, $\text{R}^{9'}$ are selected from the same groups as R^6 , R^7 and R^9 respectively and $\text{R}^{10'}$ and

20 $\text{R}^{11'}$ are the same as R^{10} and R^{11} , wherein if R^{11} and $\text{R}^{11'}$ are SO_zM , M may represent a divalent pharmaceutically acceptable cation.

In a third aspect, there is provided a compound of formula II:



wherein:

R^2 , R^6 , R^7 , R^9 , Y , R'' , Y' , R^{12} , $R^{6'}$, $R^{7'}$ and $R^{9'}$ are as defined for a compound of formula I

5 herein;

and either:

(a) R^{10} is carbamate nitrogen protecting group, and R^{11} is O-Prot^O, wherein Prot^O is an oxygen protecting group; or

(b) R^{10} is a hemi-aminal nitrogen protecting group and R^{11} is an oxo group;

10 and $R^{10'}$ and $R^{11'}$ are the same as R^{10} and R^{11} .

A third embodiment of the present disclosure comprises a compound of formula II:

In an embodiment, the present disclosure relates to Conjugates comprising dimers of PBDs linked to a targeting agent, wherein the PBD dimer is of formula I, or a pharmaceutically acceptable salt or solvate thereof (supra).

5 In an aspect, there is provided a Conjugate having formula III:



wherein L is a Ligand unit, LU is a Linker unit, p is 1 to 20; and D is a Drug unit which is a PBD dimer as disclosed herein, wherein LU is connected to D via the X substituent of R².

10 ~~In another aspect, there is provided the use of a Conjugate of the aspect above, in the manufacture of a medicament for treating a proliferative disease or an autoimmune disease.~~

In some embodiments, the Conjugates have the following formula III:



or a pharmaceutically acceptable salt or solvate thereof, wherein L is a Ligand unit (i.e., a targeting agent), LU is a Linker unit and D is a Drug unit that is a PBD dimer (see below).

The subscript p is an integer of from 1 to 20. Accordingly, the Conjugates comprise a

Ligand unit covalently linked to at least one Drug unit by a Linker unit. The Ligand unit,

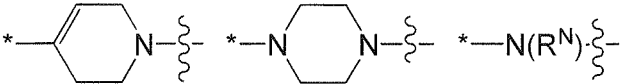
20 described more fully below, is a targeting agent that binds to a target moiety. The Ligand unit can, for example, specifically bind to a cell component (a Cell Binding Agent) or to other target molecules of interest. Accordingly, the present disclosure also provides methods for the treatment of, for example, various cancers and autoimmune disease.

These methods encompass the use of the Conjugates wherein the Ligand unit is a

25 targeting agent that specifically binds to a target molecule. The Ligand unit can be, for example, a protein, polypeptide or peptide, such as an antibody, an antigen-binding fragment of an antibody, or other binding agent, such as an Fc fusion protein.

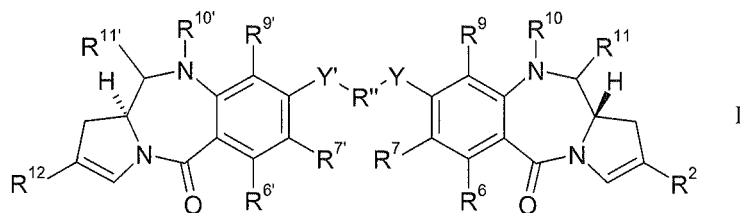
In conjugates of the present disclosure, the PBD dimer D is of formula I, or a

30 pharmaceutically acceptable salt or solvate thereof, except that X is selected from the group comprising: $^*-O^-$, $^*-S^-$, $^*-CO_2^-$, $^*-CO^-$, $^*-NH(C=O)^-$, $^*-NHNH^-$, $^*-CONHNH^-$,

, wherein R^N is selected from the group comprising H and C₁₋₄ alkyl, and the asterisk indicates the point of attachment to the

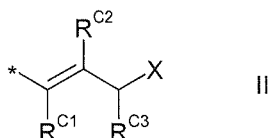
CLAIMS

1. A compound with the formula I:



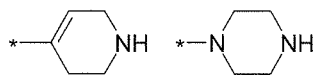
- 5 wherein:

R² is of formula II:



where X is selected from the group consisting of comprising: OH, SH, CO₂H, COH, N=C=O,

NHNH₂, CONHNH₂,



and, NHR^N, wherein R^N is selected from the

group comprising H and C₁₋₄ alkyl;

R^{C1}, R^{C2} and R^{C3} are independently selected from H and unsubstituted C₁₋₂ alkyl;

and either:

R¹² is selected from the group consisting of:

(ia) C₅₋₁₀ aryl group, optionally substituted by one or more substituents selected from the

group consisting of comprising: halo, nitro, cyano, ether, C₁₋₇ alkyl, C₃₋₇ heterocyclyl and bis-oxy-C₁₋₃ alkylene;

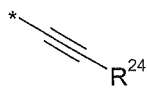
(ib) C₁₋₅ saturated aliphatic alkyl;

(ic) C₃₋₆ saturated cycloalkyl;

(id) , wherein each of R²¹, R²² and R²³ are independently selected from H, C₁₋₃

saturated alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl and cyclopropyl, where the total number of carbon atoms in the R¹² group is no more than 5;

(ie) , wherein one of R^{25a} and R^{25b} is H and the other is selected from: phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl; and



(if) R^{24} , where R^{24} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} alkynyl; cyclopropyl; phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl;

R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2 , NHR, NRR' , nitro,

5 Me_3Sn and halo;

where R and R' are independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups;

R^7 is selected from H, R, OH, OR, SH, SR, NH_2 , NHR, NRR' ~~$NHRR'$~~ , nitro, Me_3Sn and halo; either:

10 (a) R^{10} is H, and R^{11} is OH, OR^A , where R^A is C_{1-4} alkyl;

(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 SO_2M , where z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation;

15 R'' is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, and/or aromatic rings;

Y and Y' are selected from O, S, and~~or~~ NH;

R^6 , R^7 , R^9 are selected from the same groups as R^6 , R^7 and R^9 respectively and $R^{10'}$ and $R^{11'}$ are the same as R^{10} and R^{11} , wherein if R^{11} and $R^{11'}$ are SO_2M , M may represent a

20 divalent pharmaceutically acceptable cation.

2. A compound according to any claim 1, wherein R^7 is selected from H, OH and OR.

3. A compound according to claim 2, wherein R^7 is a C_{1-4} alkyloxy group.

25

4. A compound according to any one of claims 1 to 3, wherein Y is O.

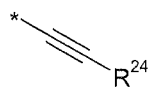
5. A compound according to any one of the preceding claims, wherein R'' is C_{3-7} alkylene.

30

6. A compound according to any one of claims 1 to 5, wherein R^9 is H.

7. A compound according to any one of claims 1 to 6, wherein R^6 is selected from H and halo.

35



30. A compound according to claim 29, wherein R^{24} is selected from H, methyl, ethyl, ethenyl and ethynyl.

5

31. A compound according to claim 30, wherein R^{24} is selected from H and methyl.

32. A compound according to any one of claims 1 to 31, wherein R^{10} and R^{11} and form a nitrogen-carbon double bond.

10

33. A compound according to any one of claims 1 to 32, wherein $R^{6'}$, $R^{7'}$, $R^{9'}$, $R^{10'}$, $R^{11'}$ and Y' are the same as R^6 , R^7 , R^9 , R^{10} , R^{11} and Y respectively.

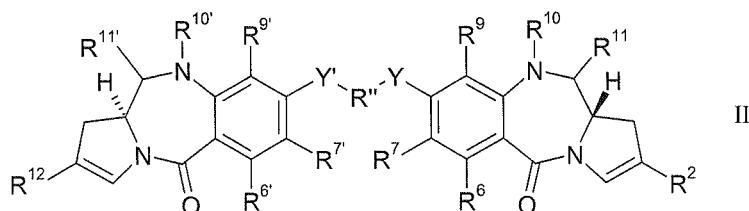
34. The use of a compound according to any one of claims 1 to 33 in the manufacture of a medicament for treating a proliferative disease.

15

35. A compound according to any one of claims 1 to 33 for use in the treatment of a proliferative disease.

36. A compound of formula II:

20



wherein:

R^2 , R^6 , R^7 , R^9 , Y , R'' , Y' , R^{12} , $R^{6'}$, $R^{7'}$ and $R^{9'}$ are as defined for a compound of formula I in any one of claims 1 to 31;

25

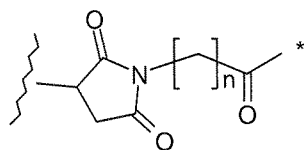
and either:

(a) R^{10} is carbamate nitrogen protecting group, and R^{11} is O-Prot^O, wherein Prot^O is an oxygen protecting group; or

(b) R^{10} is a hemi-aminal nitrogen protecting group and R^{11} is an oxo group; and $R^{10'}$ and $R^{11'}$ are the same as R^{10} and R^{11} .

30

44. The Conjugate of claim 42, wherein A¹ is:



where the asterisk indicates the point of attachment to L¹, the wavy line indicates the point of attachment to the Ligand unit, and n is 0 to 6.

45. The Conjugate of claim 44, wherein n is 5.

46. The Conjugate of any of claims 41 to 45, wherein L¹ comprises an amino acid sequence.

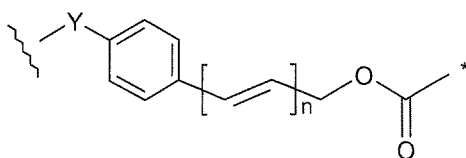
47. The Conjugate of claim 46, wherein L¹ is a dipeptide.

48. The Conjugate of claim 47, wherein L¹ is selected from the group consisting of valine-alanine, valine-citrulline and phenylalanine-lysine.

49. The Conjugate of any of claims 41 to 48, wherein y is 0.

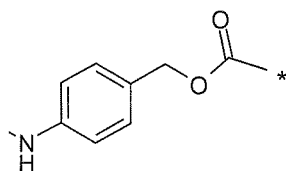
50. The Conjugate of any of claims 41 to 49, wherein y is 1 or 2.

51. The Conjugate of claim 50, wherein L² is:



where the asterisk indicates the point of attachment to the Drug unit, the wavy line indicates the point of attachment to the L¹, Y is -N(H)-, -O-, -C(=O)N(H)- or -C(=O)O-, and n is 0 to 3.

52. The Conjugate of claim 51, wherein L² is:

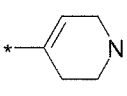


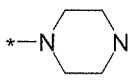
~~53. The use of a Conjugate of according to any one of claims 40 to 52, in the manufacture of a medicament for treating a proliferative disease or an autoimmune disease.~~

5 | 5354. A drug linker of formula V:

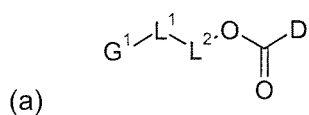
LU-D (V)

or a pharmaceutically acceptable salt or solvate thereof, wherein LU is a Linker unit and where D is a Drug unit which is a PBD dimer according to any one of claims 1 to 33, but

where X is selected from O, S, CO₂, CO, NH(C=O), NHNH, CONHNH, ,

10 | , NR^N, wherein R^N is selected from the group comprising H and C₁₋₄ alkyl.

| 5455. A drug linker according to claim 5354 of formula:



15 | , where G¹ is a Stretcher group to form a connection to a Ligand unit, L¹ is a Specificity unit, L² is a covalent bond or together with -OC(=O)- forms a self-immolative group; or

(b) G¹-L¹-L²-D, where G¹ is a Stretcher unit to form a connection to a Ligand unit, L¹ is a Specificity unit, L² is a covalent bond or a self-immolative group; where L¹ and L² are as defined in any one of claims 41 to 52.