Claims

1. A maytansine-containing conjugate of the general formula:

$$(((D_q\text{-}Lk^1)_m\text{-}P)_p\text{-}Lk^2\text{-}Lk^3)_n\text{-}Ab \qquad (I)$$

in which D represents a maytansine moiety;

q represents an integer from 1 to 10;

Lk^1 represents a linker;

m represents an integer from 1 to 10;

P represents a bond or a z-valent group $-P^1-NH-$ where z is from 2 to 11 and P^1 is a group containing at least one ethylene unit $–CH_2-CH_2-$ or ethylene glycol unit $-O-CH_2-CH_2-$;

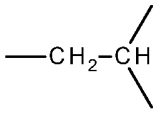
p represents an integer from 1 to 10;

Lk^2 represents a bond or a y-valent linker where y is from 2 to 11 and which consists of from 1 to 9 aspartate and/or glutamate residues;

Lk^3 represents a linker of the general formula:

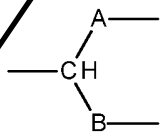
$$-CO\text{-}Ph\text{-}X\text{-}Y- \qquad (II)$$

in which Ph is an optionally substituted phenyl group; X represents a CO group or a CH.OH group; and Y represents a group of formula:



(III)

or



(IV)

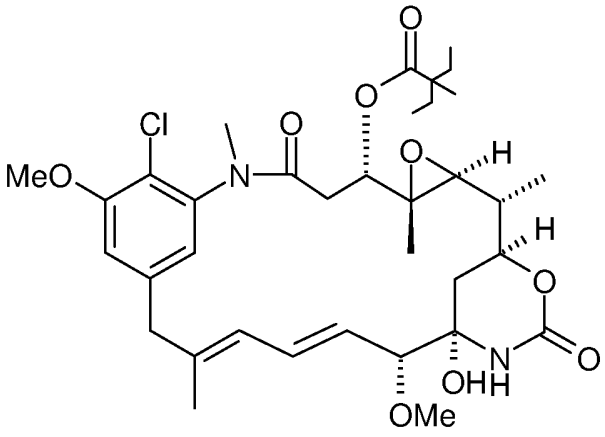
in which each of A and B represents a C_{1-4}alkylene or alkenylene group;

Ab represents a binding protein or peptide capable of binding to a binding partner on a target, said binding protein or peptide being bonded to Lk^3 via two sulfur atoms derived from a disulfide bond in the binding protein or peptide; and

n represents an integer from 1 to s where s is the number of disulfide bonds present in the binding protein or peptide prior to conjugation to Lk^3;

the meanings of m, n, p, q, y and z being chosen such that the conjugate contains from 1 to 10 D groups.

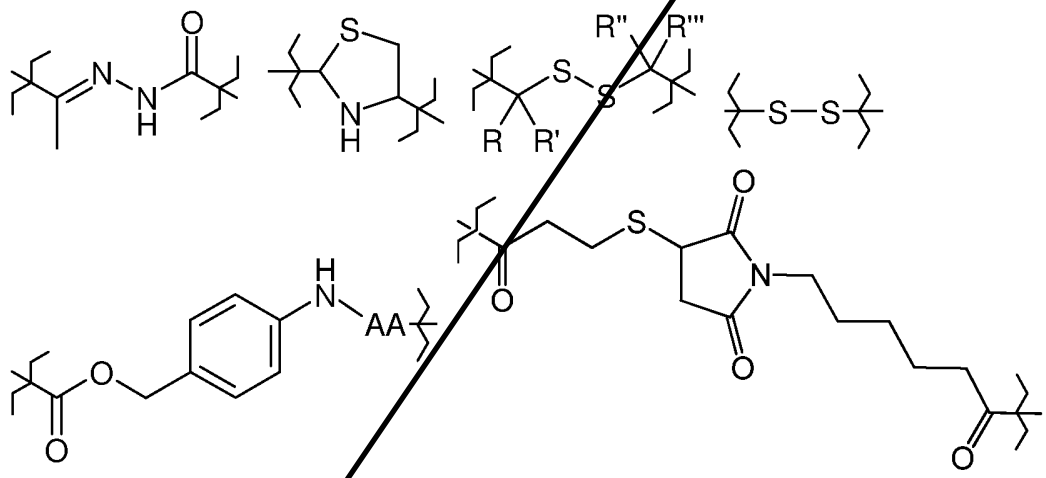
2. A conjugate as claimed in claim 1, wherein the maytansine moiety comprises



(C).

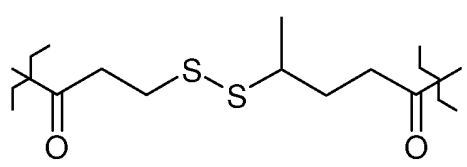
3. A conjugate as claimed in any one of the preceding claims, in which Lk^1 is a degradable linker.

4. A conjugate as claimed in claim 3, in which Lk^1 includes one of the following groups:

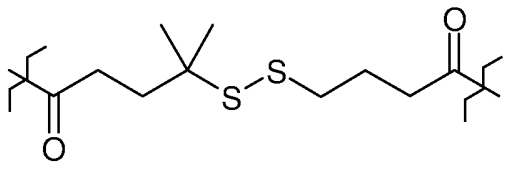


in which each of R, R', R" and R"' represents a hydrogen atom or an alkyl group and AA represents a protease-specific amino acid sequence.

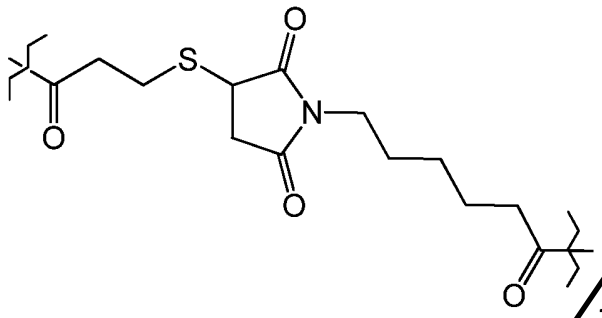
5. A conjugate as claimed in claim 4, in which Lk^1 includes:



(Vb)



(Vc), or



.

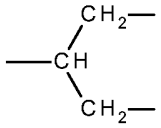
6. A conjugate as claimed in claim 1 or claim 2, in which q is an integer from 2 to 10 and Lk^1 is a multivalent linker incorporating one or more aspartate or glutamate residues.

7. A conjugate as claimed in any one of claims 1 to 6, in which P represents a bond, or P represents $–P^1$-NH- wherein P^1 contains from 2 to 10 ethylene glycol units.

8. A conjugate as claimed in any one of claims 1 to 6, in which P represents polyethylene glycol.

9. A conjugate as claimed in any one of claims 1 to 8, in which the phenyl group Ph in Lk^3 is unsubstituted.

10. A conjugate as claimed in any one of claims 1 to 9, in which Y has the formula:



11. A conjugate as claimed in any one of claims 1 to 10, in which Ab represents a full length antibody or an antibody fragment comprising an antigen-binding region of the full length antibody.

12. A conjugate as claimed in claim 11, in which Ab represents IgG1 or IgG4 or a fragment of IgG1 or IgG4.

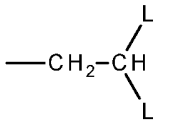
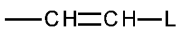
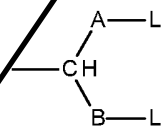
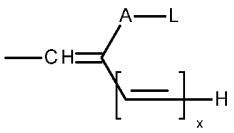
13. A process for the preparation of a conjugate as claimed in any one of claims 1 to 12, which comprises reducing one or more disulfide bonds in a binding protein and subsequently reacting with a conjugating reagent of the general formula:

$$((D_q\text{-}Lk^1)_m\text{-}P)_p\text{-}Lk^2\text{-}Lk^{3a} \qquad (VIII)$$

in which D, Lk^1, P, Lk^2 and m, p and q have the meanings given in claim 1, and Lk^{3a} represents a group of formula:

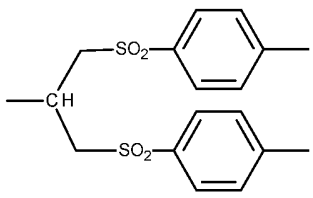
$$\text{-CO-Ph-}X^a\text{-}Y^a \qquad (IX)$$

in which Ph has the meaning given in claim 1, X^a represents a CO group, and Y^a represents a group:


(X),

(XI),

(XII) or

(XIII)

in which A and B have the meanings given in claim 1, each L independently represents a leaving group, and x represents an integer from 1 to 4, to produce a conjugate of formula I in which X represents CO; and optionally reducing said initially-formed CO group X to give a conjugate having a CHOH group X.

14. A process as claimed in claim 13, in which Y^a represents:


(XIIa)

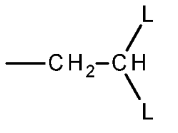
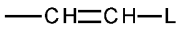
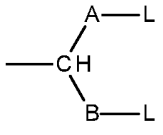
15. A compound of the general formula:

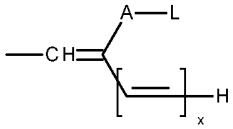
$$((D_q\text{-}Lk^1)_m\text{-}P)_p\text{-}Lk^2\text{-}Lk^{3a} \qquad \text{(VIII)}$$

in which D has the meaning given in any one of claims 1 to 3; Lk^1 has the meaning given in any one of claims 1 and 4 to 7; P has the meaning given in any one of claims 1, 8 and 9; Lk^2, m, p and q have the meanings given in claim 1, and Lk^{3a} represents a group of formula:

$$\text{-CO-Ph-}X^a\text{-}Y^a \qquad \text{(IX)}$$

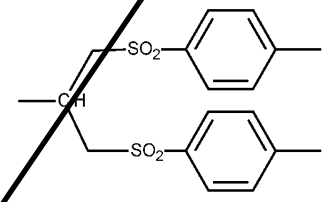
in which Ph has the meaning given in either claim 1 or claim 10, X^a represents a CO group, and Y^a represents a group:


(X),

(XI),

(XII) or


(XIII)

in which A and B have the meanings given in claim 1, each L independently represents a leaving group, and x represents an integer from 1 to 4.

16. A compound as claimed in claim 15, in which Y^a represents:


(XIIa)

17. A pharmaceutical composition comprising a conjugate as claimed in any one of claims 1 to 12, together with a pharmaceutically acceptable carrier, optionally together with an additional therapeutic agent.

18. A conjugate as claimed in any one of claims 1 to 12 or a composition as claimed in claim 17 for use in therapy.

19. A method of treating a patient which comprises administering a pharmaceutically-effective amount of a conjugate as claimed in any one of claims 1 to 12 or a pharmaceutical composition as claimed in claim 17 to a patient.

CLAIMS

1. A maytansine-containing conjugate of the general formula:

$(((D_q\text{-}Lk^1)_m\text{-}P)_p\text{-}Lk^2\text{-}Lk^3)_n\text{-}Ab$ (I)

in which D represents a maytansine moiety;

q represents an integer from 1 to 10;

Lk^1 represents a linker;

m represents an integer from 1 to 10;

P represents a bond or a z-valent group $-P^1$-NH- where z is from 2 to 11 and P^1 is a group containing at least one ethylene unit $–CH_2\text{-}CH_2$- or ethylene glycol unit $-O\text{-}CH_2\text{-}CH_2$-;

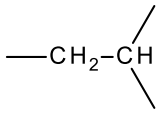
p represents an integer from 1 to 10;

Lk^2 represents a bond or a y-valent linker where y is from 2 to 11 and which consists of from 1 to 9 aspartate and/or glutamate residues;

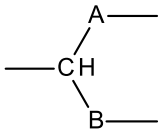
Lk^3 represents a linker of the general formula:

-CO-Ph-X-Y- (II)

in which Ph is an optionally substituted phenyl group; X represents a CO group or a CH.OH group; and Y represents a group of formula:



(III) or



(IV)

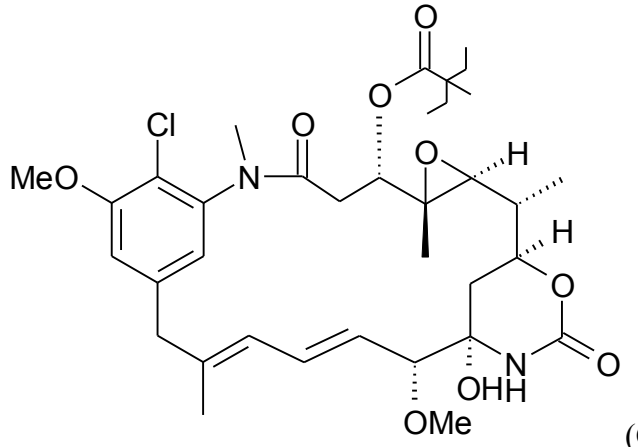
in which each of A and B represents a $C_{1\text{-}4}$alkylene or alkenylene group;

Ab represents a binding protein or peptide capable of binding to a binding partner on a target, said binding protein or peptide being bonded to Lk^3 via two sulfur atoms derived from a disulfide bond in the binding protein or peptide; and

n represents an integer from 1 to s where s is the number of disulfide bonds present in the binding protein or peptide prior to conjugation to Lk^3;

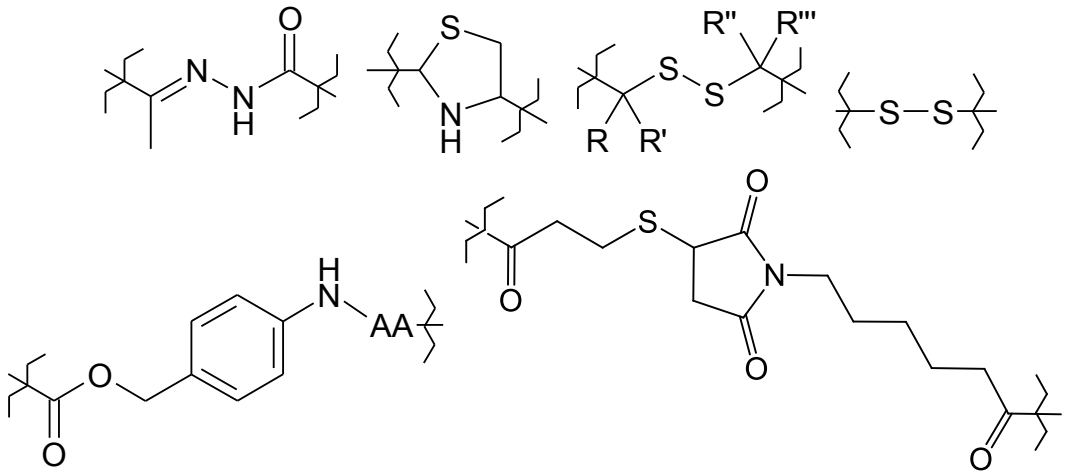
the meanings of m, n, p, q, y and z being chosen such that the conjugate contains from 1 to 10 D groups.

2. A conjugate according to Claim 1, in which the maytansine moiety comprises



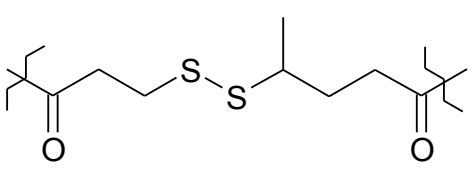
(C).

3. A conjugate according to any preceding claim, in which Lk^1 includes one of the following groups:

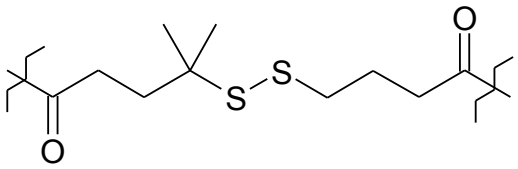


in which each of R, R', R" and R''' represents a hydrogen atom or an alkyl group and AA represents a protease-specific amino acid sequence.

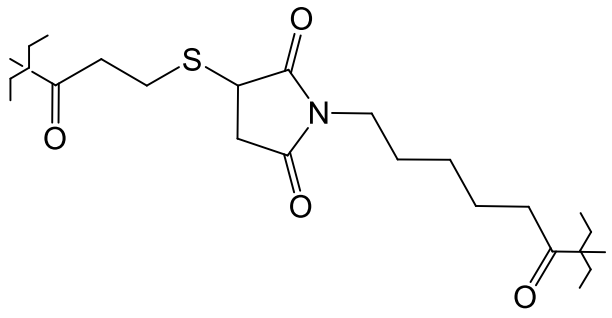
4. A conjugate according to Claim 3, in which Lk^1 includes:



(Vb)



(Vc), or



.

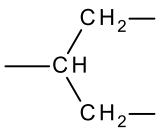
5. A conjugate according to Claim 1 or 2, in which q is an integer from 2 to 10 and Lk^1 is a multivalent linker incorporating one or more aspartate or glutamate residues.

6. A conjugate according to any of Claims 1 to 5, in which P represents a bond, or P represents $–P^1$-NH- in which P^1 contains from 2 to 10 ethylene glycol units.

7. A conjugate according to any of Claims 1 to 5, in which P represents polyethylene glycol.

8. A conjugate according to any of Claims 1 to 7, in which the phenyl group Ph in Lk^3 is unsubstituted.

9. A conjugate according to any of Claims 1 to 8, in which Y has the formula:



10. A conjugate according to any of Claims 1 to 9, in which Ab represents a full length antibody or an antibody fragment comprising an antigen-binding region of the full length antibody.

11. A conjugate according to Claim 10, in which Ab represents IgG1 or IgG4 or a fragment of IgG1 or IgG4.

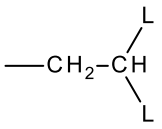
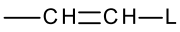
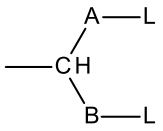
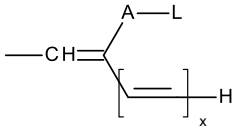
12. A process for the preparation of a conjugate according to any of Claims 1 to 11, which comprises reducing one or more disulfide bonds in a binding protein and subsequently reacting with a conjugating reagent of the general formula:

$$((D_q\text{-}Lk^1)_m\text{-}P)_p\text{-}Lk^2\text{-}Lk^{3a} \qquad \text{(VIII)}$$

in which D, Lk^1, P, Lk^2 and m, p and q have the meanings given in Claim 1, and Lk^{3a} represents a group of formula:

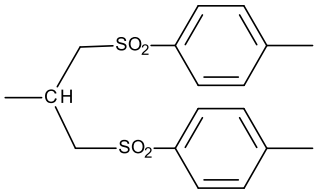
$$\text{-CO-Ph-}X^a\text{-}Y^a \qquad \text{(IX)}$$

in which Ph has the meaning given in Claim 1, X^a represents a CO group, and Y^a represents a group:


(X),

(XI),

(XII) or

(XIII)

in which A and B have the meanings given in Claim 1, each L independently represents a leaving group, and x represents an integer from 1 to 4, to produce a conjugate of formula I in which X represents CO; and optionally reducing said initially-formed CO group X to give a conjugate having a CH.OH group X.

13. A process according to Claim 12, in which Y^a represents:



(XIIa)

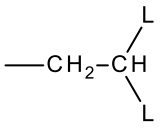
14. A compound of the general formula:

$((D_q\text{-}Lk^1)_m\text{-}P)_p\text{-}Lk^2\text{-}Lk^{3a}$ (VIII)

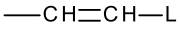
in which D has the meaning given in of Claim 1 or 2; Lk^1 has the meaning given in any of Claims 1 and 3 to 6; P has the meaning given in any of Claims 1, 7 and 8; Lk^2, m, p and q have the meanings given in Claim 1, and Lk^{3a} represents a group of formula:

$-CO\text{-}Ph\text{-}X^a\text{-}Y^a$ (IX)

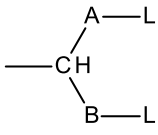
in which Ph has the meaning given in either Claim 1 or Claim 9, X^a represents a CO group, and Y^a represents a group:



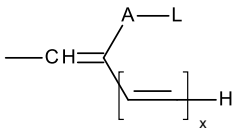
(X),



(XI),



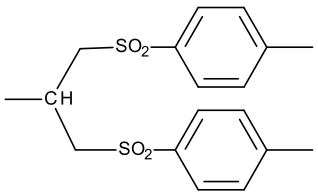
(XII) or



(XIII)

in which A and B have the meanings given in Claim 1, each L independently represents a leaving group, and x represents an integer from 1 to 4.

15. A compound according to Claim 14, in which Y^a represents:



(XIIa)

16. A pharmaceutical composition comprising a conjugate according to any of Claims 1 to 11, together with a pharmaceutically acceptable carrier, optionally together with an additional therapeutic agent.

17. A conjugate according to any of Claims 1 to 11 or a composition according to Claim 16 for use in therapy.