CLAIMS

1. An auristatin-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 an auristatin 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:

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

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 $C_{1\text{-}4}$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;

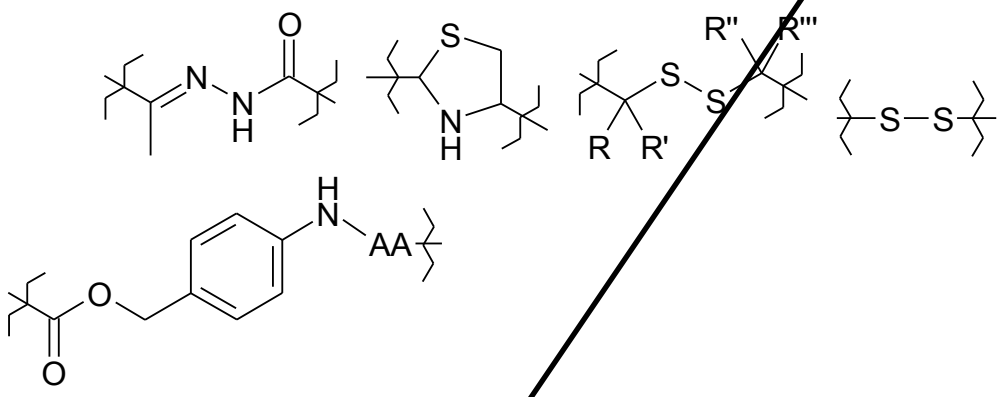
the meanings of m, n, p, q, y and z being chosen such that the conjugate contains from 1 to 10 D groups.

2. A conjugate according to Claim 1, in which the auristatin is monomethylauristatin E or monomethylauristatin F bonded via its terminal nitrogen atom.

3. A conjugate according to Claim 1 or 2, in which the auristatin is monomethylauristatin E bonded via its terminal nitrogen atom.

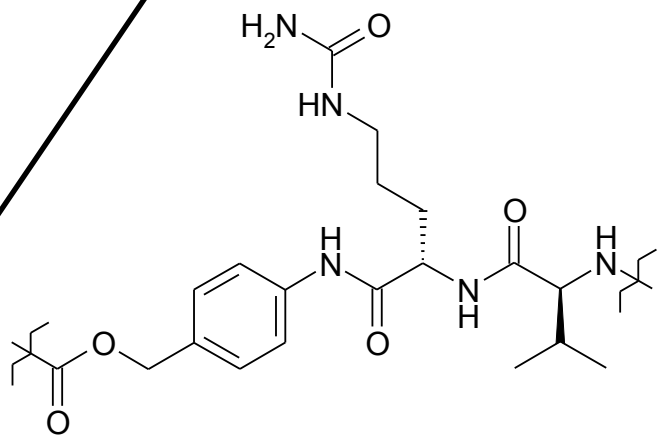
4. A conjugate according to Claim 1, 2 or 3, in which Lk^1 is a degradable linker.

5. A conjugate according to Claim 4, 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.

6. A conjugate according to Claim 5, in which Lk^1 includes:



(V)

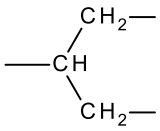
7. A conjugate according to any of Claims 1 to 3, in which q is an integer from 2 to 10 and Lk^1 is a multivalent linker incorporating one or more aspartate or glutamate residues.

8. A conjugate according to any preceding claim, in which P represents a bond, or P represents $–P^1$-NH- in which P^1 contains from 2 to 10 ethylene glycol units.

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

10. A conjugate according to any preceding claim, in which the phenyl group Ph in Lk^3 is unsubstituted.

11. A conjugate according to any preceding claim, in which Y has the formula:



12. A conjugate according to any preceding claim, in which Ab represents a full length antibody or an antibody fragment comprising an antigen-binding region of the full length antibody.

13. A conjugate according to Claim 12, in which Ab represents IgG1 or IgG4 or a fragment of IgG1 or IgG4.

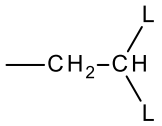
14. A process for the preparation of a conjugate according to any preceding claim, which comprises reducing one or more disulfide bonds in a binding protein and subsequently reacting with a conjugating reagent of the general formula:

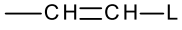
$$((D_q\text{-}Lk^1)_m\text{-}P)_p\text{-}Lk^2\text{-}Lk^{3a} \qquad \text{(VIII)}$$

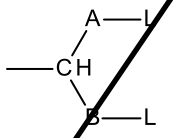
in which D, Lk^1, P, Lk^2 and m, p and q have the meanings given in claim 1, and Lk^{3a} represents a group of formula:

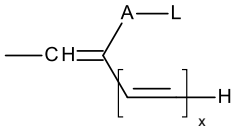
$$\text{-CO-Ph-}X^a\text{-}Y^a \qquad \text{(IX)}$$

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


(X),

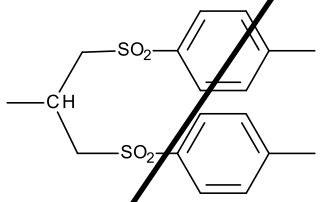

(XI),




(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.

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


(XIIa)

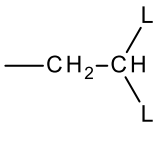
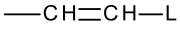
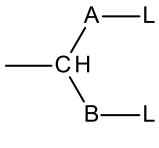
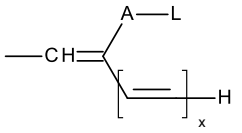
16. A compound of the general formula:

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

in which D has the meaning given in any one of claims 1 to3; 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:

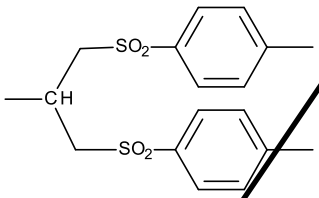
$$\text{-CO-Ph-}X^a\text{-}Y^a \qquad \text{(IX)}$$

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.

17. A compound according to Claim 16, in which Y^a represents:


(XIIa)

18. A pharmaceutical composition comprising a conjugate according to any of Claims 1 to 13, together with a pharmaceutically acceptable carrier, optionally together with an additional therapeutic agent.

19. A conjugate according to any of Claims 1 to 13 or a composition according to Claim 18 for use in therapy.

20. Use of a conjugate according to any of Claims 1 to 13 or a composition according to Claim 18 in the preparation of a medicament for the treatment or prevention of cancer.

CLAIMS

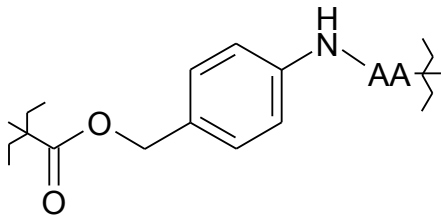
1. An auristatin-containing conjugate of the general formula:

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

in which D represents an auristatin moiety;

q represents an integer from 1 to 10;

Lk^1 represents a linker which includes the group:



in which AA represents a protease-specific amino acid sequence;

m represents an integer from 1 to 10;

P represents a bond or a z-valent group $-P^1\text{-}NH-$ 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 $-O\text{-}CH_2\text{-}CH_2-$;

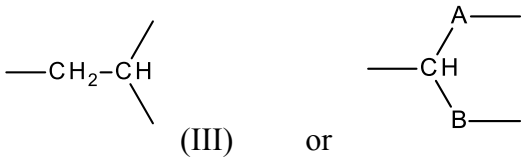
p represents an integer from 1 to 10;

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:

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

in which Ph is a phenyl group which may be unsubstituted or substituted by one or more of the same or different substituents selected from alkyl optionally substituted by OH or CO_2H, -CN, $-NO_2$, $-CO_2R^4$, -COH, $-CH_2OH$, $-COR^4$, $-OR^4$, $-OCOR^4$, $-OCO_2R^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-NHCOR^4$, $-NR^4COR^4$, $NHCO_2R^4$, $-NR^4.CO_2R^4$, -NO, -NHOH, $-NR^4.OH$, $-C=N\text{-}NHCOR^4$, $-C=N\text{-}NR^4.COR^4$, $-N^+R^4{}_3$, $-N^+H_3$, $-N^+HR^4{}_2$, $-N^+H_2R^4$, halogen, $-C\equiv CR^4$, $-C=CR^4{}_2$ and $-C=CHR^4$, in which each R^4 independently represents a hydrogen atom or an alkyl, aryl, or alkyl-aryl 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

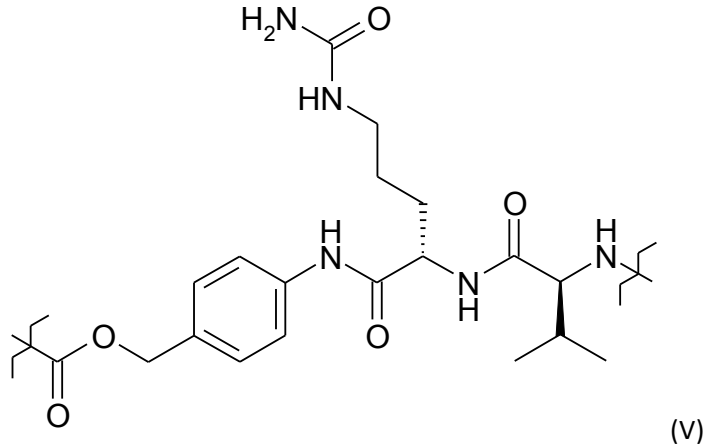
n represents an integer from 1 to s where s is the number of disulfide bonds present in the binding protein or peptide prior to conjugation to Lk^3;

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 according to Claim 1, in which the auristatin is monomethylauristatin E or monomethylauristatin F bonded via its terminal nitrogen atom.

3. A conjugate according to Claim 1 or 2, in which the auristatin is monomethylauristatin E bonded via its terminal nitrogen atom.

4. A conjugate according to Claim 1, 2 or 3, in which Lk^1 includes:



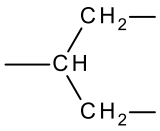
(V)

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

6. A conjugate according to any of Claims 1 to 4, in which P represents polyethylene glycol.

7. A conjugate according to any preceding claim, in which the phenyl group Ph in Lk^3 is unsubstituted.

8. A conjugate according to any preceding claim, in which Y has the formula:



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

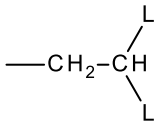
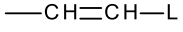
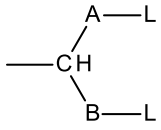
10. A conjugate according to Claim 9, in which Ab represents IgG1 or IgG4 or a fragment of IgG1 or IgG4.

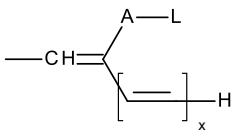
11. A process for the preparation of a conjugate according to any preceding claim, which comprises reducing one or more disulfide bonds in a binding protein and subsequently reacting with a conjugating reagent of the general formula:

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

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:

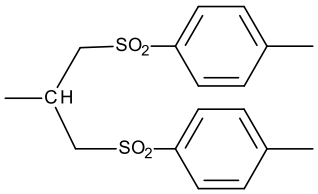
$$\text{-CO-Ph-}X^a\text{-}Y^a \qquad \text{(IX)}$$

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.

12. A process according to Claim 11, in which Y^a represents:



(XIIa)

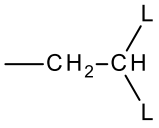
13. A compound of the general formula:

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

in which D has the meaning given in any of Claims 1 to 3; Lk^1 has the meaning given in either Claim 1 or Claim 4; P has the meaning given in any of Claims 1, 5 and 6; Lk^2, m, p and q have the meanings given in Claim 1, and Lk^{3a} represents a group of formula:

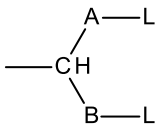
$$\text{-CO-Ph-}X^a\text{-}Y^a \qquad \text{(IX)}$$

in which Ph has the meaning given in either Claim 1 or Claim 7, X^a represents a CO group, and Y^a represents a group:

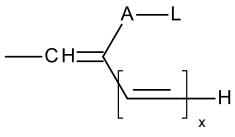


(X),

(XI),



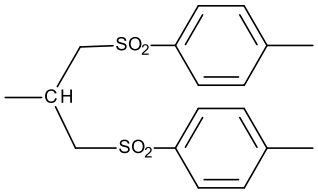
(XII) or



(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.

14. A compound according to Claim 13, in which Y^a represents:



(XIIa)

15. A pharmaceutical composition comprising a conjugate according to any of Claims 1 to 10, together with a pharmaceutically acceptable carrier, optionally together with an additional therapeutic agent.

16. A conjugate according to any of Claims 1 to 10 or a composition according to Claim 15 for use in therapy.

17. Use of a conjugate according to any of Claims 1 to 10 or a composition according to Claim 15 in the preparation of a medicament for the treatment or prevention of cancer.