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 $-P^1\text{-}NH-$ 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 $-O\text{-}CH_2\text{-}CH_2-$;

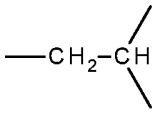
p represents an integer from 1 to 10;

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;

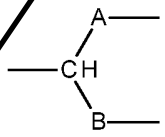
Lk^3 represents a linker of the general formula:

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

in which Ph is 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;

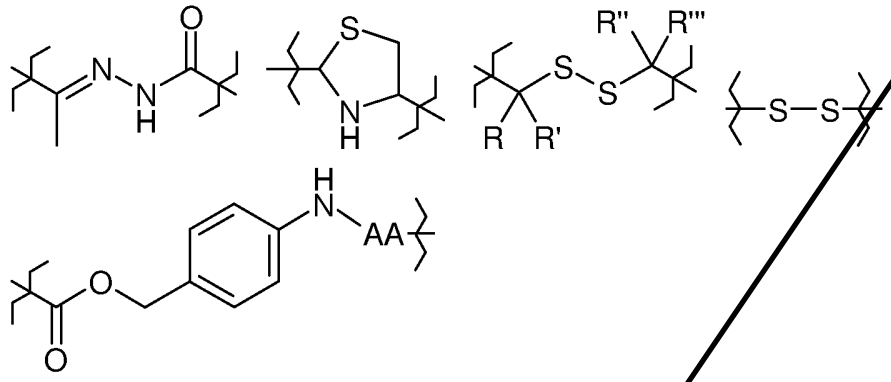
the meanings of m, n, p, q, y and z being chosen such that the conjugate contains from 1 to 10 D groups.

2. A conjugate as claimed in claim 1, wherein the auristatin is monomethylauristatin E or monomethylauristatin F bonded via its terminal nitrogen atom.

3. A conjugate as claimed in either claim 1 or claim 2, wherein the auristatin is monomethylauristatin E bonded via its terminal nitrogen atom.

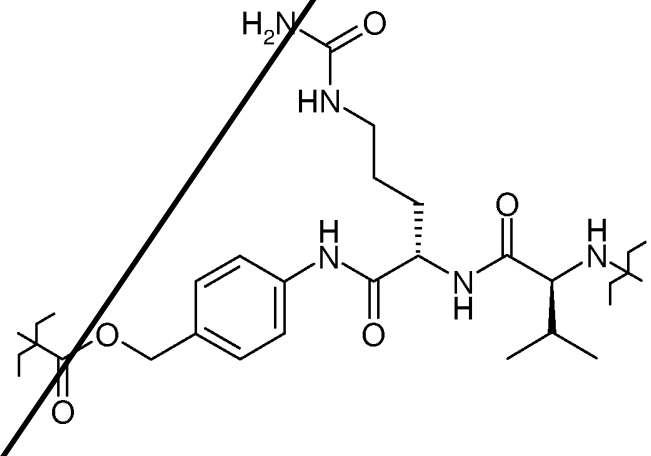
4. A conjugate as claimed in any one of the preceding claims, in which Lk^1 is a degradable linker.

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



(V)

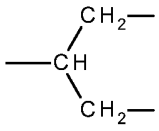
7. A conjugate as claimed in any one of claims 1 to 3, in which q is an integer from 2 to 10 and Lk^1 is a multivalent linker incorporating one or more aspartate or glutamate residues.

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

9. A conjugate as claimed in any one of claims 1 to 7, in which P represents polyethylene glycol.

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

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



12. A conjugate as claimed in any one of claims 1 to 11, 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 as claimed in claim 12, in which Ab represents IgG1 or IgG4 or a fragment of IgG1 or IgG4.

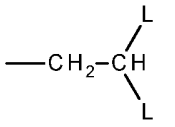
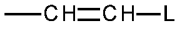
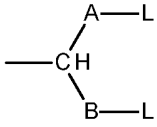
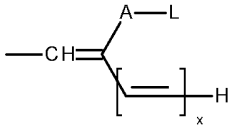
14. A process for the preparation of a conjugate as claimed in any one of claims 1 to 13, which comprises reducing one or more disulfide bonds in a binding protein and subsequently reacting with a conjugating reagent of the general formula:

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

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:

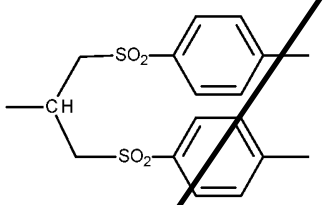
$$\text{-CO-Ph-}X^a\text{-}Y^a \qquad \text{(IX)}$$

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 as claimed in claim 14, in which Y^a represents:


(XIIa)

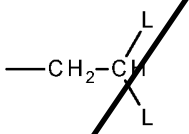
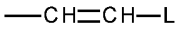
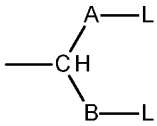
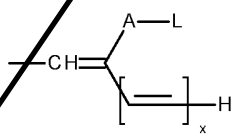
16. A compound of the general formula:

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

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:

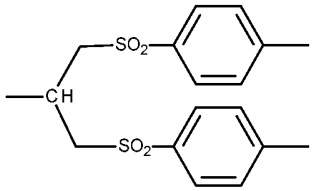
$$\text{-CO-Ph-}X^a\text{-}Y^a \qquad \text{(IX)}$$

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 as claimed in claim 16, in which Y^a represents:



(XIIa)

18. A pharmaceutical composition comprising a conjugate as claimed in any one of claims 1 to 13, together with a pharmaceutically acceptable carrier, optionally together with an additional therapeutic agent.

19. A conjugate as claimed in any one of claims 1 to 13 or a composition as claimed in claim 18 for use in therapy.

20. 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 13 or a pharmaceutical composition as claimed in claim 18 to a patient

21. A conjugate which has 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 drug moiety;

q' represents an integer from 2 to 10;

$Lk^{1'}$ represents a linker;

m represents an integer from 1 to 10;

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

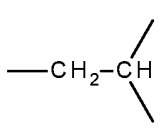
p represents an integer from 1 to 10;

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;

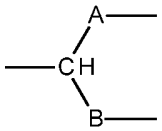
Lk^3 represents a linker of the general formula:

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

in which Ph is 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 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.

22. A compound of the formula:

$$((D'_{q'}\text{-}Lk^{1'})_m\text{-}P)_p\text{-}Lk^2\text{-}Lk^{3a} \qquad \text{(VIII')}$$

in which D', q', $Lk^{1'}$, m, P, p, Lk^2 and Lk^3 have the meanings given in claim 21, and Lk^{3a} has the meaning given in claim 16.

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 $–CH_2$-CH_2- or ethylene glycol unit -O-CH_2-CH_2-;

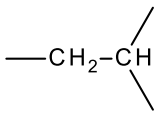
p represents an integer from 1 to 10;

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;

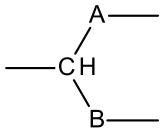
Lk^3 represents a linker of the general formula:

-CO-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;

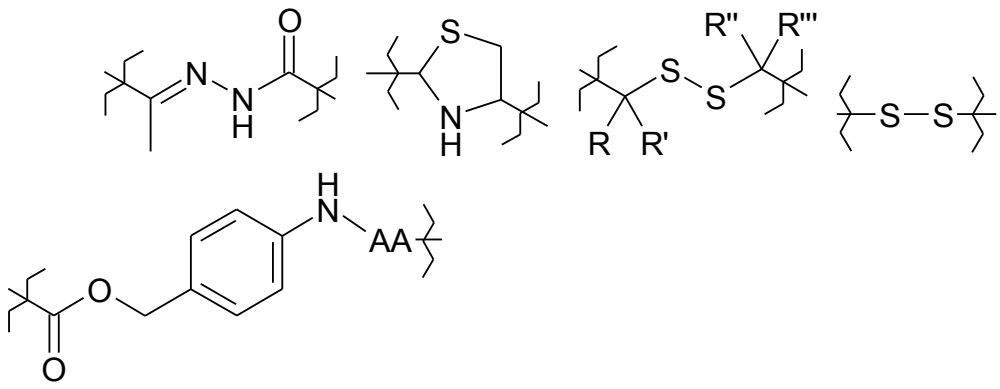
the meanings of m, n, p, q, y and z being chosen such that the conjugate contains from 1 to 10 D groups.

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

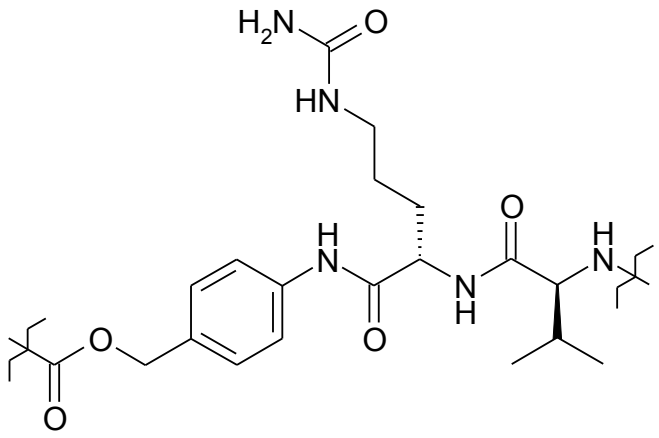
4. A conjugate according to Claim 1, 2 or 3, in which Lk^1 is a degradable linker.

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)

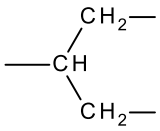
7. A conjugate according to any of Claims 1 to 3, in which q is an integer from 2 to 10 and Lk^1 is a multivalent linker incorporating one or more aspartate or glutamate residues.

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.

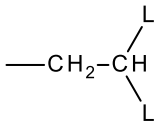
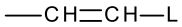
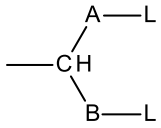
13. A conjugate according to Claim 12, in which Ab represents IgG1 or IgG4 or a fragment of IgG1 or IgG4.

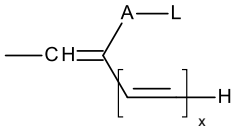
14. A process for the preparation of a conjugate according to any preceding claim, which comprises reducing one or more disulfide bonds in a binding protein and subsequently reacting with a conjugating reagent of the general formula:

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

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:

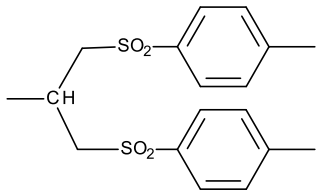
$$\text{-CO-Ph-}X^a\text{-}Y^a \qquad \text{(IX)}$$

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)

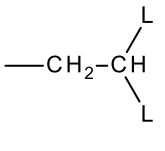
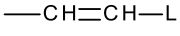
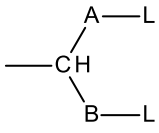
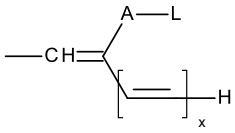
16. A compound of the general formula:

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

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:

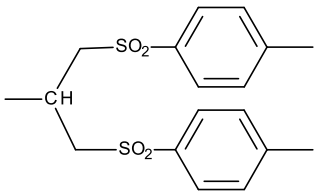
$$\text{-CO-Ph-}X^a\text{-}Y^a \qquad \text{(IX)}$$

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.