

CLAIMS

1. A peptide ligand specific for MT1-MMP comprising a polypeptide comprising at least three cysteine residues, separated by at least two loop sequences, and a molecular scaffold which forms covalent bonds with the cysteine residues of the polypeptide such that at least two polypeptide loops are formed on the molecular scaffold, in which the peptide ligand comprises an amino acid sequence of formula (I):

-C_i-X₁-U/O₂-X₃-X₄-G₅-C_{ii}-E₆-D₇-F₈-Y₉-X₁₀-X₁₁-C_{iii}- (SEQ ID NO: 1)

(I)

or a pharmaceutically acceptable salt thereof;

in which:

C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively;

X represents any amino acid residue;

U represents a polar, uncharged amino acid residue selected from N, C, Q, M, S and T; and

O represents a non-polar aliphatic amino acid residue selected from G, A, I, L, P and V;

optionally in which the peptide ligand includes one or more modifications selected from:

(i) an N-terminal modification using suitable amino-reactive chemistry, and/or C-terminal modification using suitable carboxy-reactive chemistry;

(ii) an N-terminal modification which comprises the addition of a molecular spacer group which facilitates the conjugation of effector groups and retention of potency of the peptide ligand to its target, such as an Ala, G-Sar10-A group or bAla-Sar10-A group;

(iii) an N-terminal and/or C-terminal modification which comprises addition of a cytotoxic agent;

- (iv) replacement of the amino acid residue at position 4 with a non-natural amino acid residue selected from: 1-naphthylalanine; 2-naphthylalanine; 3,4-dichlorophenylalanine; and homophenylalanine, such as 1-naphthylalanine; 2-naphthylalanine; and 3,4-dichlorophenylalanine, in particular 1-naphthylalanine;
- 5 (v) replacement of the amino acid residue at position 9 and/or 11 with a non-natural amino acid residue selected from: 4-bromophenylalanine or pentafluoro-phenylalanine for position 9 and/or tert-butylglycine for position 11;
- (vi) replacement of the amino acid residue at position 9 with 4-bromophenylalanine;
- (vii) replacement of the amino acid residue at position 11 with tert-butylglycine;
- 10 (viii) 2, 3, 4 or 5 of the following modifications, in particular all of the following 5 modifications: D-alanine at position 1 and/or 5, a 1-naphthylalanine at position 4, a 4-bromophenylalanine at position 9 and a tert-butylglycine at position 11;
- (ix) in which the amino acid residue at position 1 is substituted for a D-amino acid, such as D-alanine; or
- 15 (x) in which the amino acid residue at position 5 is substituted for a D-amino acid, such as D-alanine or D-arginine.
- 2. A peptide ligand as defined in Claim 1, in which:
 - (i) X_1 is selected from any of the following amino acids: Y, M, F or V, such as Y, M or F, in particular, Y or M, more particularly Y; and/or
 - 20 (ii) U/O_2 is selected from a U, such as an N, or an O, such as a G; and/or
 - (iii) X_3 is selected from U or Z, in which U represents a polar, uncharged amino acid residue selected from N, C, Q, M, S and T and Z represents a polar, negatively charged amino acid residue selected from D or E, in particular the U at position 3 is selected from Q or the Z at position 3 is selected from E; and/or

(iv) X_4 is selected from J, in which J represents a non-polar aromatic amino acid residue selected from F, W and Y; and/or

(v) X_{10} is selected from Z, in which Z represents a polar, negatively charged amino acid residue selected from D or E, such as D; and/or

5 (vi) X_{11} is selected from O, in which O represents a non-polar aliphatic amino acid residue selected from G, A, I, L, P and V, such as I.

3. A peptide ligand as defined in Claim 1 or 2, in which the compound of formula (I) is a compound of formula (Ia):

$-C_i-Y/M/F/V-U/O-U/Z-J-G-C_{ii}-E-D-F-Y-Z-O-C_{iii}-$ (SEQ ID NO: 6)

10 (Ia)

in which U, O, J and Z are as defined hereinbefore; or

a compound of formula (Ib):

$-C_i-Y/M/F/V-N/G-E/Q-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}-$ (SEQ ID NO: 7)

(Ib); or

15 a compound of formula (Ic):

$-C_i-Y/M/F-N/G-E/Q-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}-$ (SEQ ID NO: 8)

(Ic); or

a compound of formula (Id):

$-C_i-Y/M-N-E/Q-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}-$ (SEQ ID NO: 9)

20 (Id); or

a compound of formula (Ie):

$-C_i-Y-N-E-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}-$ (17-69-07) (SEQ ID NO: 2)

(Ie).

4. A peptide ligand as defined in Claim 1, 2 or 3, in which the peptide of formula (I) comprises a sequence selected from:

-C_i-Y-N-E-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}- (17-69-07) (SEQ ID NO: 2);

-C_i-M-N-Q-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}- (17-69-12) (SEQ ID NO: 10);

5 -C_i-F-G-E-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}- (17-69-02) (SEQ ID NO: 11);

-C_i-V-N-E-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}- (17-69-03) (SEQ ID NO: 12);

-C_i-F-N-E-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}- (17-69-04) (SEQ ID NO: 13);

-C_i-Y-N-E-Y-G-C_{ii}-E-D-F-Y-D-I-C_{iii}- (17-69-07-N057) (SEQ ID NO: 14); and

-C_i-Y-N-E-W-G-C_{ii}-E-D-F-Y-D-I-C_{iii}- (17-69-44-N002) (SEQ ID NO: 15),

10 such as:

-C_i-Y-N-E-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}- (17-69-07) (SEQ ID NO: 2); and

-C_i-M-N-Q-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}- (17-69-12) (SEQ ID NO: 10),

in particular:

-C_i-Y-N-E-F-G-C_{ii}-E-D-F-Y-D-I-C_{iii}- (17-69-07) (SEQ ID NO: 2).

15 5. A peptide ligand as defined in any preceding claim, which includes one or more modifications selected from:

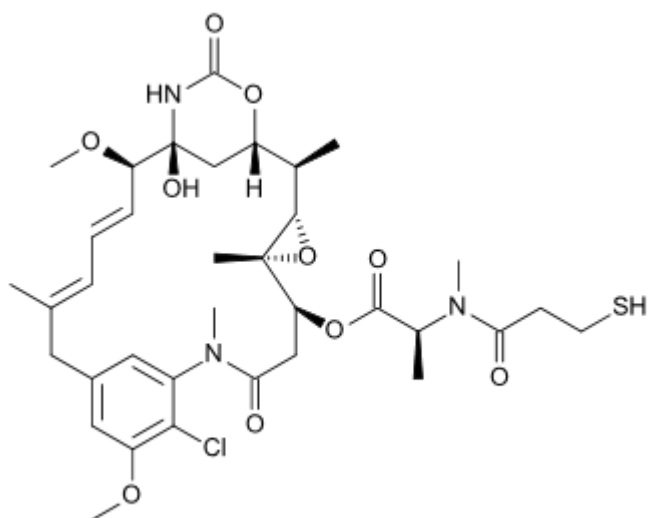
(i) an N-terminal modification using suitable amino-reactive chemistry, and/or C-terminal modification using suitable carboxy-reactive chemistry;

20 (ii) an N-terminal modification which comprises the addition of a molecular spacer group which facilitates the conjugation of effector groups and retention of potency of the peptide ligand to its target, such as an Ala, G-Sar10-A group or bAla-Sar10-A group;

(iii) an N-terminal and/or C-terminal modification which comprises addition of a cytotoxic agent;

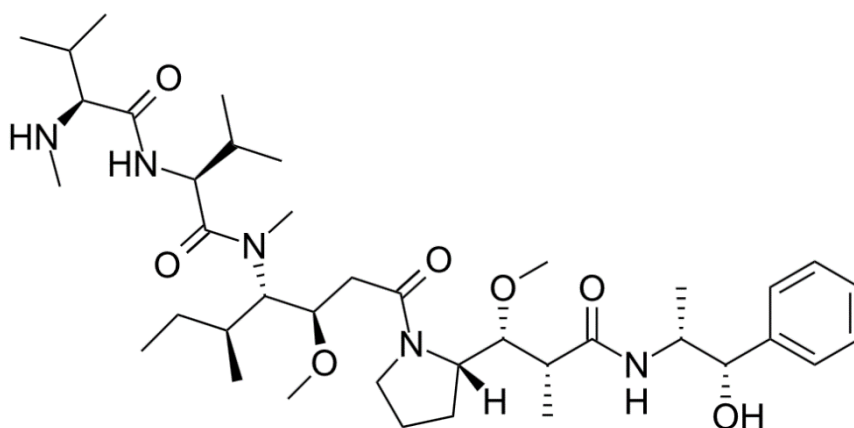
- (iv) replacement of the amino acid residue at position 4 with a non-natural amino acid residue selected from: 1-naphthylalanine; 2-naphthylalanine; 3,4-dichlorophenylalanine; and homophenylalanine, such as 1-naphthylalanine; 2-naphthylalanine; and 3,4-dichlorophenylalanine, in particular 1-naphthylalanine;
- 5 (v) replacement of the amino acid residue at position 9 and/or 11 with a non-natural amino acid residue selected from: 4-bromophenylalanine or pentafluoro-phenylalanine for position 9 and/or tert-butylglycine for position 11;
- (vi) replacement of the amino acid residue at position 9 with 4-bromophenylalanine;
- (vii) replacement of the amino acid residue at position 11 with tert-butylglycine;
- 10 (viii) 2, 3, 4 or 5 of the following modifications, in particular all of the following 5 modifications: D-alanine at position 1 and/or 5, a 1-naphthylalanine at position 4, a 4-bromophenylalanine at position 9 and a tert-butylglycine at position 11;
- (ix) in which the amino acid residue at position 1 is substituted for a D-amino acid, such as D-alanine; or
- 15 (x) in which the amino acid residue at position 5 is substituted for a D-amino acid, such as D-alanine or D-arginine.
6. A peptide ligand as defined in Claim 5, which is:
- (β -Ala)-Sar10-AC(D-Ala)NE(1Nal)(D-Ala)CEDFYD(tBuGly)C (SEQ ID NO: 5), or a pharmaceutically acceptable salt thereof.
- 20 7. A peptide ligand as defined in any preceding claim, in which the molecular scaffold is TBMB which is 1,3,5-tris(bromomethyl)benzene.
8. A drug conjugate comprising a peptide ligand as defined in any preceding claim, conjugated to one or more effector and/or functional groups, such as a cytotoxic agent or a metal chelator.

9. A drug conjugate as defined in Claim 8, in which the cytotoxic agent is linked to the peptide ligand by a cleavable bond, such as a disulphide bond or a protease sensitive bond.
10. A drug conjugate as defined in Claim 8 or 9, in which the cytotoxic agent is selected from DM1 which has the following structure:

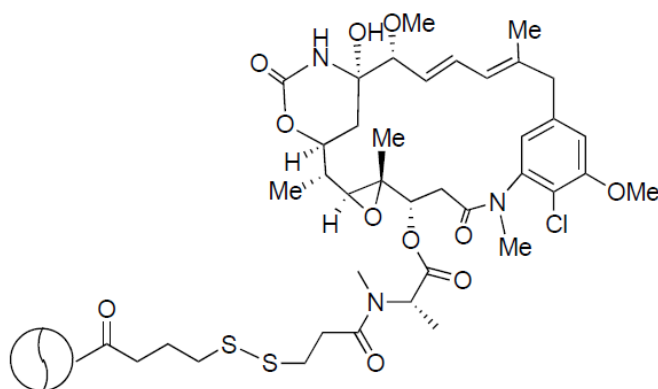


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or MMAE which has the following structure:

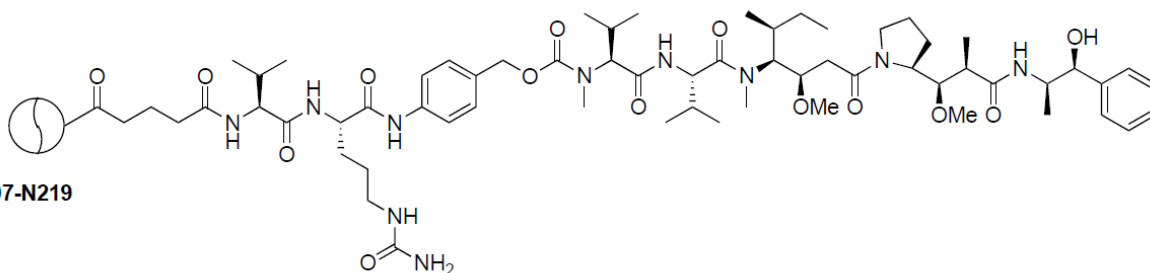


11. A drug conjugate as defined in Claim 8, 9 or 10, which is a compound that has the following structure:



17-69-07-N219

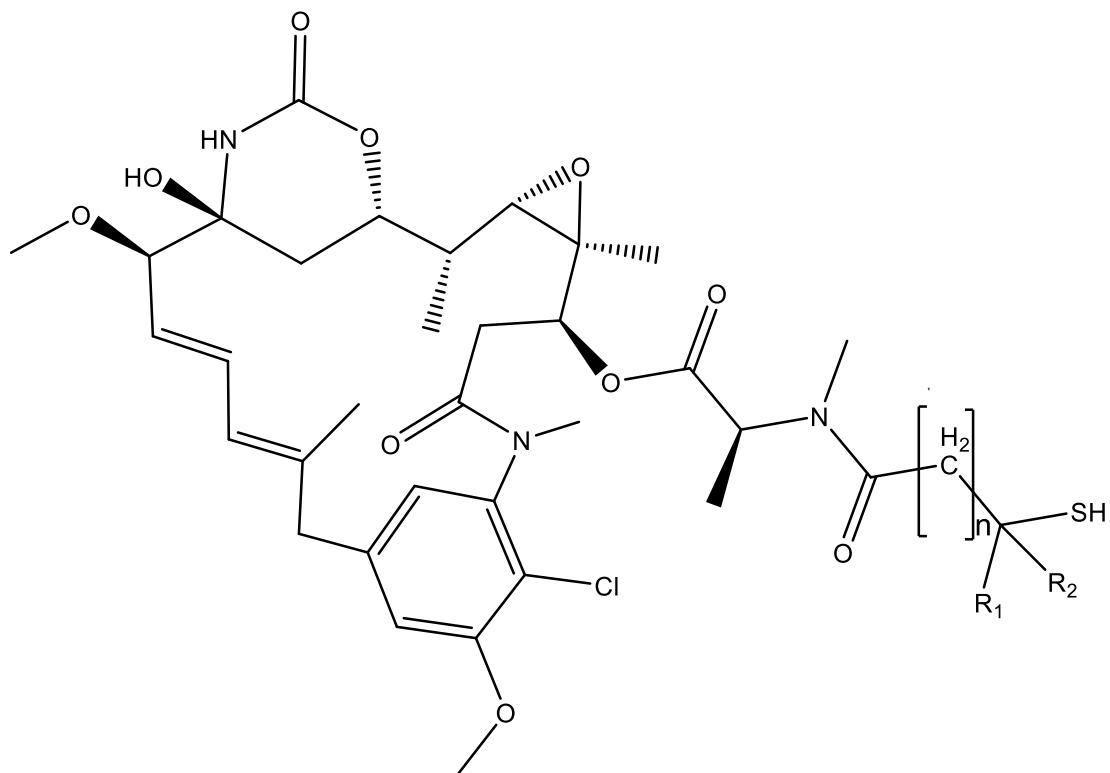
; or



17-69-07-N219

5 in which 17-69-07-N219 represents G-Sar10-ACYNEFGCEDFYDIC (SEQ ID NO: 20).

12. A drug conjugate as defined in Claim 8 or 9, in which the cytotoxic agent is a maytansinoid and selected from a compound of formula (II):



(II)

in which n represents an integer selected from 1 to 10; and

R_1 and R_2 independently represent hydrogen, C_{1-6} alkyl or a carbocyclyl or heterocyclyl group, such as hydrogen or methyl.

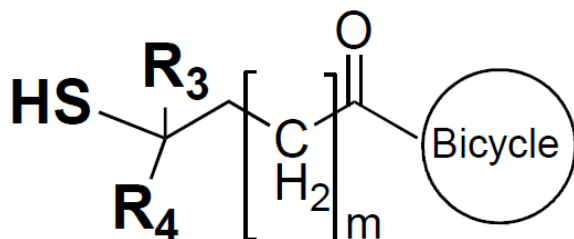
13. A drug conjugate as defined in Claim 12, in which:

n represents 1 and R_1 and R_2 both represent hydrogen (i.e. the maytansine derivative DM1); or

n represents 2, R_1 represents hydrogen and R_2 represents a methyl group (i.e. the maytansine derivative DM3); or

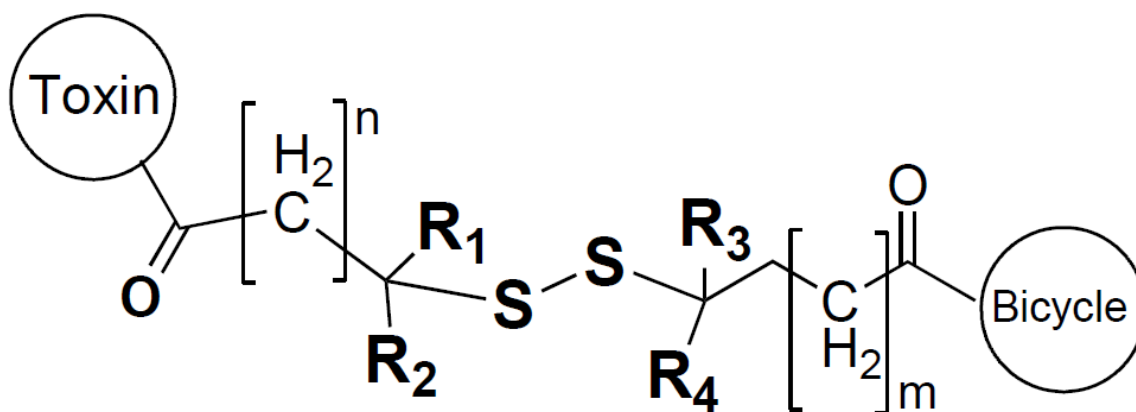
n represents 2 and R_1 and R_2 both represent methyl groups (i.e. the maytansine derivative DM4).

14. A drug conjugate as defined in any of Claims 8 to 13, in which the peptide ligand component of the conjugate has the structure shown in formula (III):



(III)

- 5 in which m represents an integer selected from 0 to 10, and
 R₃ and R₄ independently represent hydrogen, C₁₋₆ alkyl or a carbocyclyl or heterocyclyl group, such as hydrogen or methyl.
15. A drug conjugate as defined in any of Claims 8 to 14, in which the cytotoxic agent is linked to the peptide ligand by a linker defined in formula (IV):



(IV)

in which R₁, R₂, R₃ and R₄ represent hydrogen, C₁₋₆ alkyl or a carbocyclyl or heterocyclyl group, such as hydrogen or methyl;

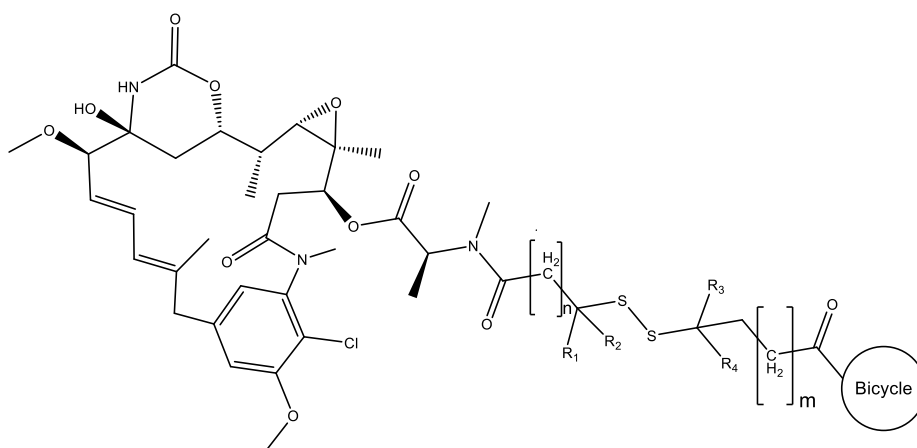
Toxin refers to any suitable cytotoxic agent;

Bicycle represents a peptide ligand as defined in any of Claims 1 to 7;

n represents an integer selected from 1 to 10; and

m represents an integer selected from 0 to 10.

16. A drug conjugate as defined in Claim 15, in which the toxin of compound (IV) is a
5 maytansine and the conjugate comprises a compound of formula (V):



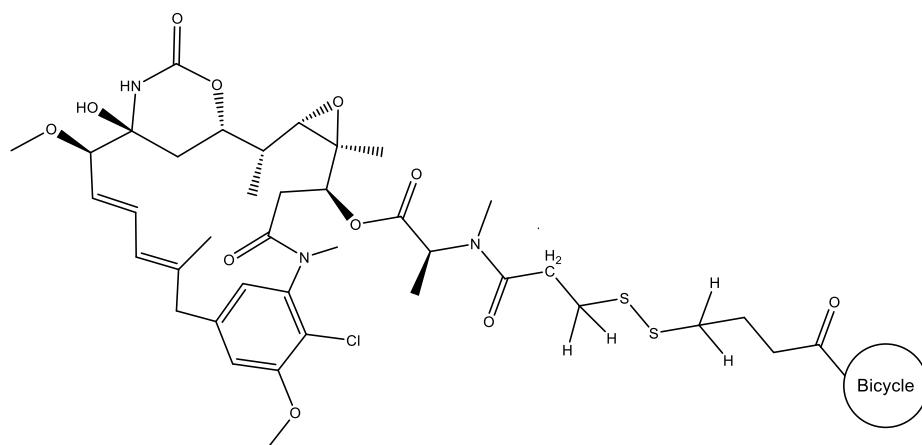
(V)

in which R₁, R₂, R₃ and R₄ represent hydrogen, C₁₋₆ alkyl or a carbocyclyl or heterocyclyl group;

- 10 Bicycle represents a peptide ligand as defined in any of Claims 1 to 7;
n represents an integer selected from 1 to 10; and
m represents an integer selected from 0 to 10.

17. A drug conjugate as defined in Claim 16, in which:

n represents 1 and R₁, R₂, R₃ and R₄ each represent hydrogen, i.e. a compound of

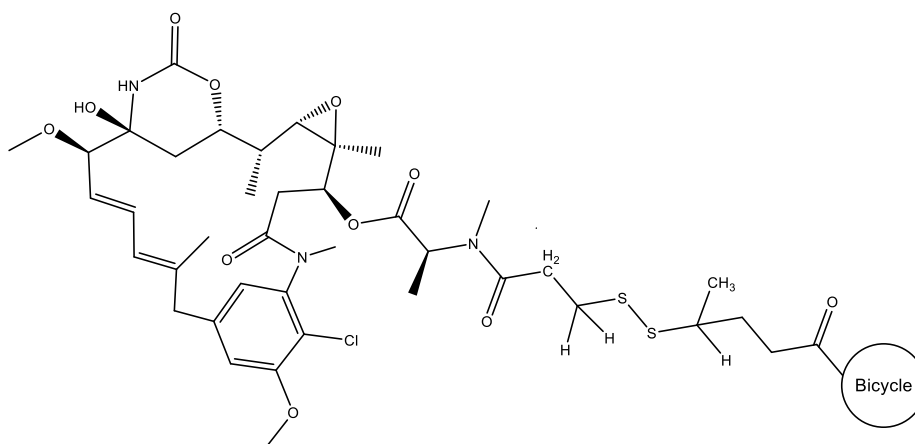


formula (V)^a:

(V)^a; or

n represents 1, R₁ represents methyl and R₂, R₃ and R₄ each represent hydrogen, i.e. a compound of formula (V)^b:

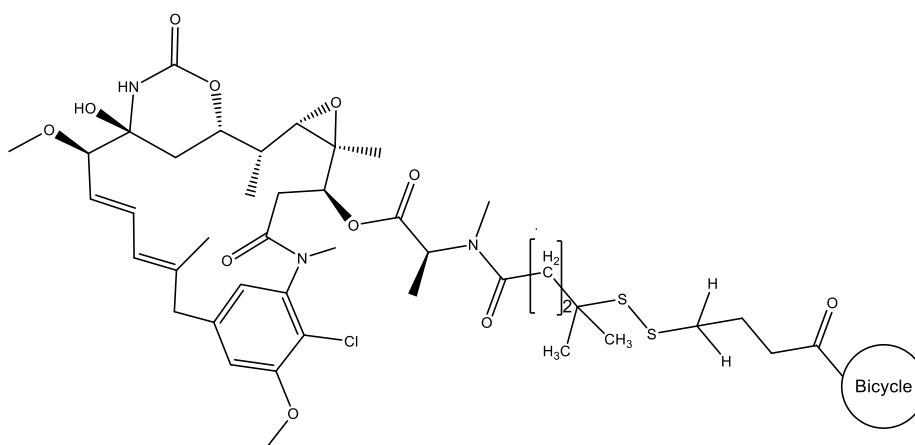
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(V)^b; or

n represents 2, R₁ and R₂ both represent hydrogen and R₃ and R₄ both represent methyl, i.e. a compound of formula (V)^c:

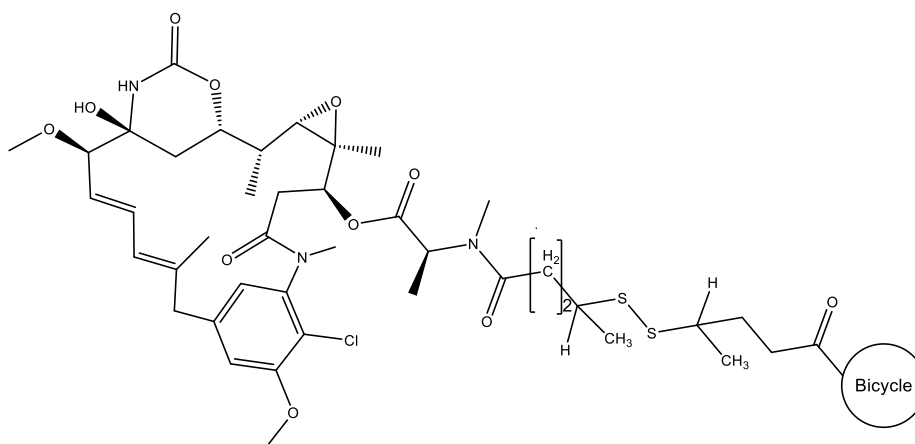
10



(V)^c; or

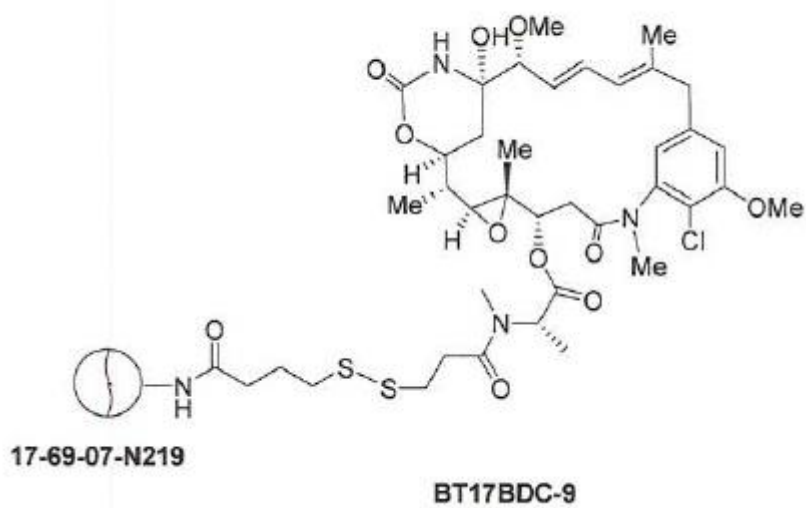
n represents 2, R₁ and R₃ both represent methyl and R₂ and R₄ both represent hydrogen, i.e. a compound of formula (V)^d:

5

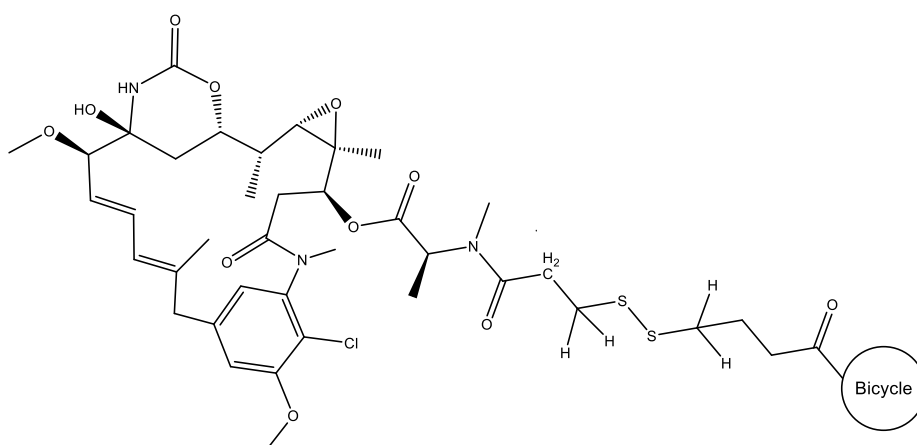


(V)^d.

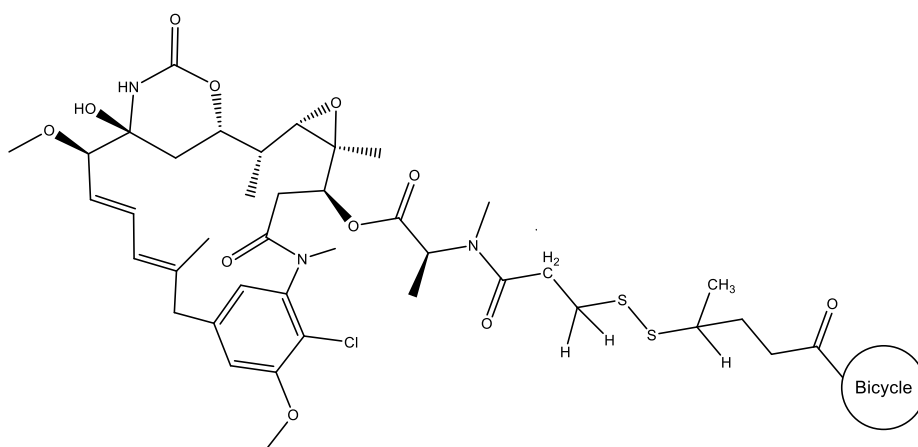
18. A drug conjugate as defined in Claim 8, which is selected from: BT17BDC-9:



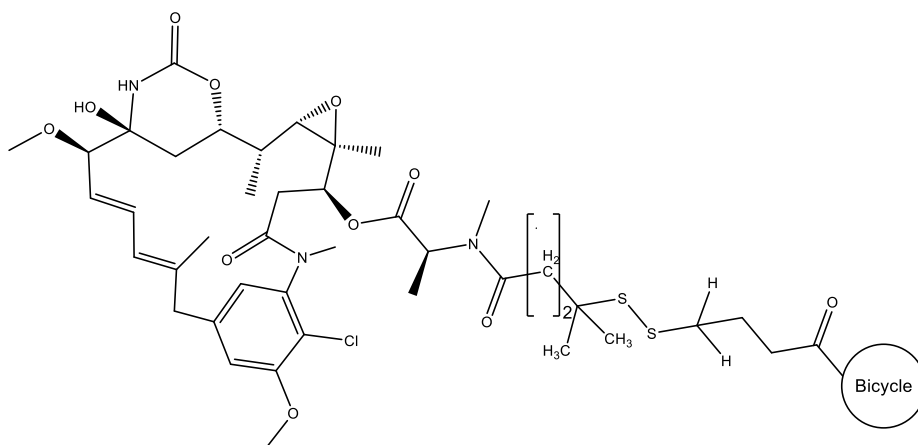
BT17BDC-17:



BT17BDC-18:

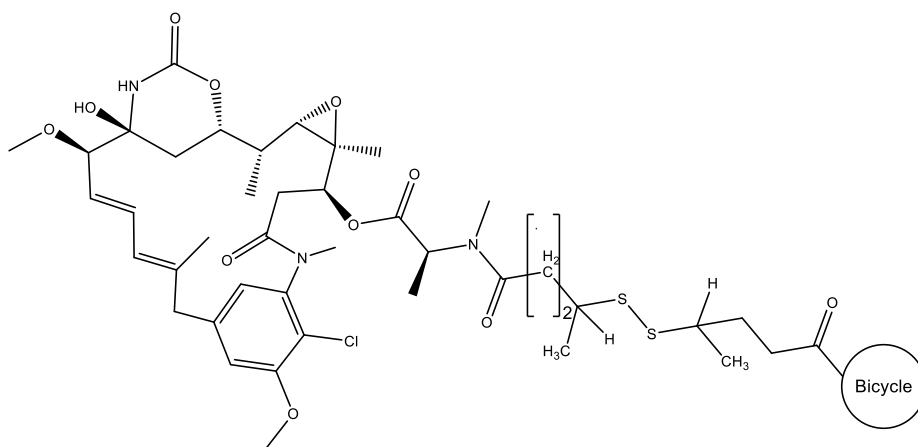


BT17BDC-19:

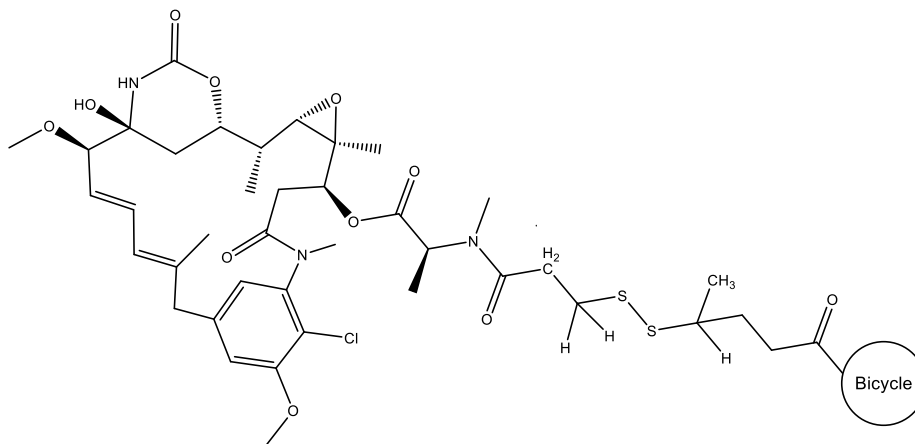


and

BT17BDC-20:



19. A drug conjugate as defined in Claim 18, which is BT17BDC-18:



20. A drug conjugate as defined in Claim 8, in which the effector and/or functional groups comprise a metal chelator.

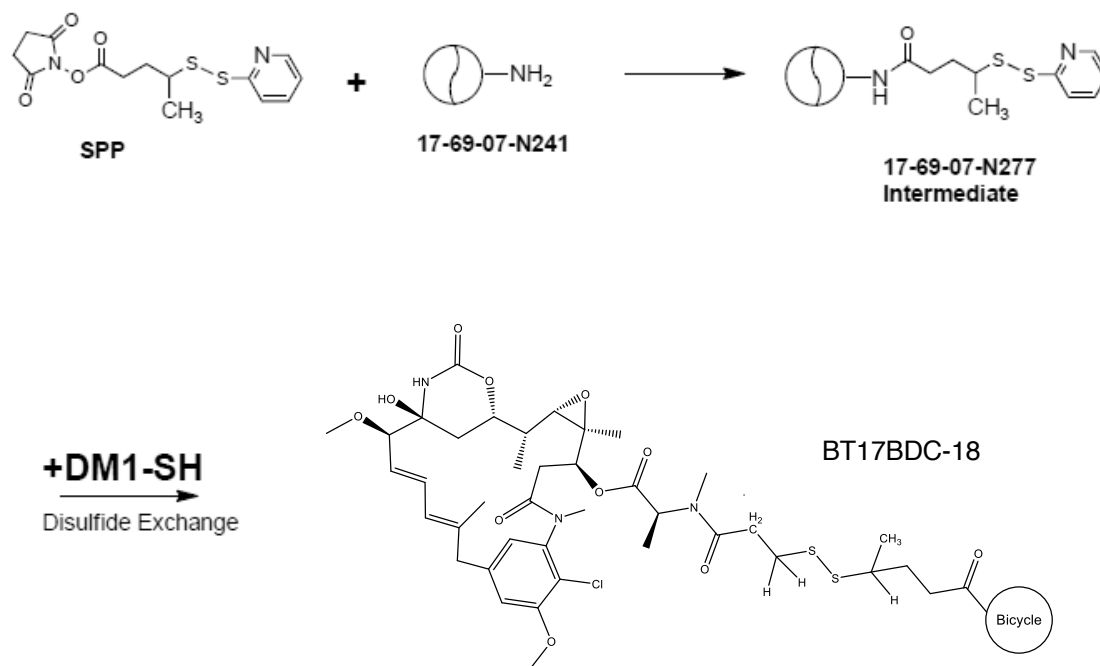
5 21. A drug conjugate as defined in Claim 20, in which the metal chelator is suitable for complexing a metal radioisotope of medicinal relevance.

22. A drug conjugate as defined in Claim 20 or 21, in which the metal chelator is complexed to a metal radioisotope.

23. A drug conjugate as defined in Claim 21 or 22, in which the metal radioisotope is
10 selected from ^{64}Cu , ^{67}Ga , ^{68}Ga , ^{177}Lu , ^{90}Y , and ^{213}Bi .

24. A drug conjugate as defined in any of Claims 20 to 23, in which the metal chelator is selected from DOTA, NOTA, EDTA, DTPA, HEHA and SarAr.

25. A process for preparing a drug conjugate as defined in Claim 19, which comprises the synthetic route described in Scheme III:



Scheme III.

26. A pharmaceutical composition which comprises a peptide ligand as defined in any of Claims 1 to 7 or a drug conjugate as defined in any of Claims 8 to 24, in combination with one or more pharmaceutically acceptable excipients.
27. A drug conjugate as defined in any of Claims 8 to 24, for use in preventing, suppressing or treating cancer, in particular solid tumours such as non-small cell lung carcinomas.
28. A method of diagnosing or imaging cancer in a patient, in which a drug conjugate as defined in any of Claims 20 to 24 is to be administered to the patient.