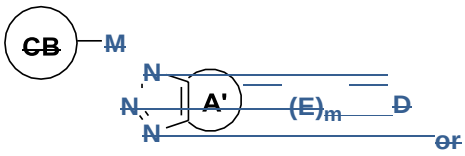
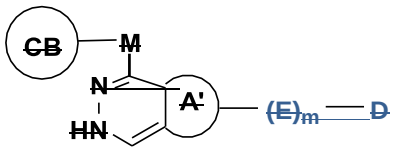
WHAT IS CLAIMED IS

1. An isolated conjugate of Formula III or Formula III'



Formula III

or



Formula III'

wherein:

CB is a cell-binding agent;

M is a non-natural amino acid;

A' is a carbocyclyl or heterocyclyl

D is a payload;

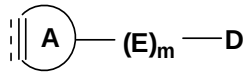
Each E is independently selected from the group consisting of -CO-, -CR^1R^2-, -NR^3-, -S-S-, -S-, -SO-, -SO_2-, -O-, -CR^3=N-NR^3-, -CR^3=N-O-, -CR^3=N-NR^3-CO-, -N=N-CO-, alkyl, C3-C8 carbocyclyl, -O-$(CR^1R^2)_a$-, aryl, -$(CR^1R^2)_a$-aryl, heteroaryl, -$(CR^1R^2)_a$-heteroaryl, -$(CR^1R^2)_a$-C3-C8 carbocyclyl, heterocyclyl, -$(CR^1R^2)_a$-heterocyclyl, -$(CH_2CH_2O)_a$-, -$(CH_2CH_2O)_a$-$(CH_2)_b$, -$(CH_2)_a$C(O)-, amino acid, and peptide;

R^1 and R^2 are each independently selected from the group consisting of H, F, Cl, Br, I, OH, -$N(R^3)_2$, -$N(R^3)_3^+$, C1-C8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, -SO_2R^3, -$S(=O)R^3$, -SR^3, -$SO_2N(R^3)_2$, -$C(=O)R^3$, -CO_2R^3, -$C(=O)N(R^3)_2$, -CN, -N_3, -NO_2, C1-C8 alkoxy, polyethyleneoxy, phosphonate, phosphate, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, aryl, heteroaryl, C3-C8 carbocyclyl, and C1-C20 heterocyclyl; or, when taken together, R^1 and R^2 form a carbonyl (=O), or spiro carbocyclic ring of 3 to 7 carbon atoms; and,

R^3 is selected from the group consisting of H, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C6-C20 aryl, C6-C20 heteroaryl, C3-C8 carbocyclyl, and C1-C20 heterocyclyl;

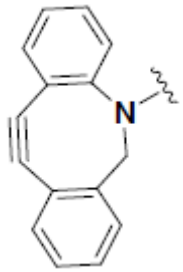
alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl are optionally independently substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, -$N(R^3)_2$, -$N(R^3)_3^+$, C1-C8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, C1-C8 alkylsulfonate, C1-C8 alkylamino, 4-dialkylaminopyridinium, C1-C8 alkylhydroxyl, C1-C8 alkylthiol, -SO_2R, -$S(=O)R^3$, -SR^3, -$SO_2N(R^3)_2$, -$C(=O)R^3$, -CO_2R^3, -$C(=O)N(R^3)_2$, -CN, -N_3, -NO_2, C1-C8 alkoxy, C1-C8 trifluoroalkyl, C1-C8 alkyl, C3-C12 carbocycle, C6-C20 aryl, C6-C20 heteroaryl, C3-C8 carbocyclyl, C2-C20 heterocyclyl, polyethyleneoxy, phosphonate, and phosphate;

~~m is an integer from 1 to 100; and,~~
~~a and b are each an integer from 1 to 100.~~ A compound of Formula I



Formula I

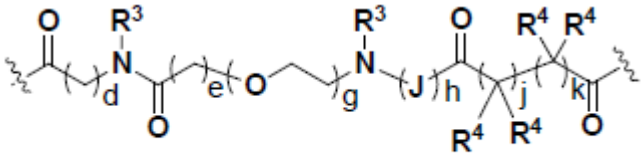
wherein

A is selected from the group consisting of dibenzocyclooctynyl, cyclooct-4-ynoxyl, (1R,8S,9S)-bicyclo[6.1.0]non-4-yn-9-ylmethyloxy, and 

;

D is a maytansinoid;

E is



E4

,

wherein:

J is an amino acid or a peptide;

d, e, g, j, and k are each independently an integer from 1 to 30;

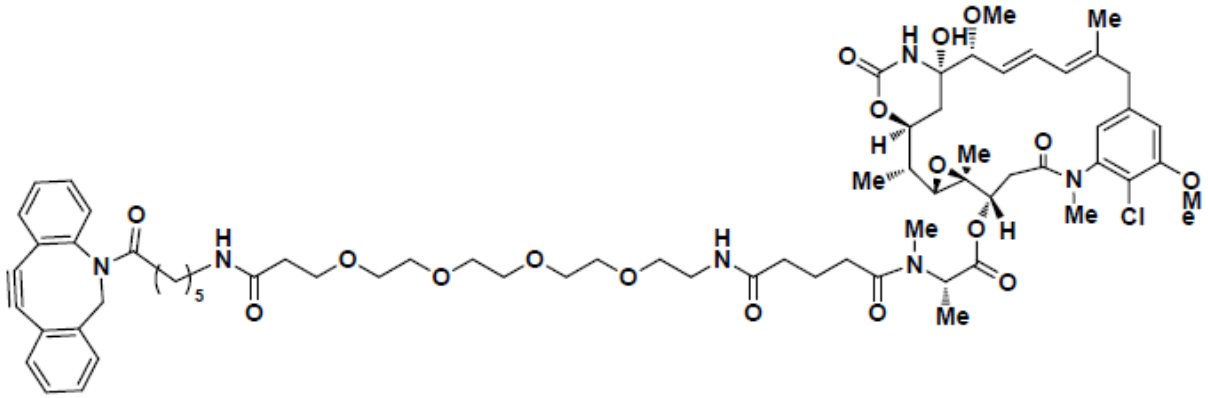
h is an integer from 0 to 30;

Each R^4 is independently selected from the group consisting of H, alkyl, $-N(R^3)_2$, $-SR^3$, C1-C8 alkoxy, and aryl;

Each R^3 is selected from the group consisting of H, and C1-C8 alkyl; and

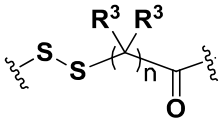
m is 1;

provided that the compound of Formula I is not



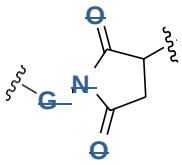
I1.

2. ~~An isolated conjugate according to claim 1, wherein each E is independently selected from the group consisting of -$(CH_2CH_2O)_a$-, -$(CH_2)_aC(O)NR^3$-, -$(CH_2)_aNR^3C(O)$-, -$(CH_2)_aC(O)NR^3(CH_2)_b$-, -$(CH_2)_aC(O)NR^3(CH_2CH_2O)_b$-, -$(CH_2)_aC(O)NR^3(CH_2CH_2O)_b(CH_2)_c$-, -$(CH_2CH_2O)_aC(O)NR^3(CH_2CH_2O)_b$-, -$(CH_2CH_2O)_aC(O)NR^3(CH_2CH_2O)_b$-, -$(CH_2CH_2O)_aC(O)NR^3(CH_2)_b$-, -$(CH_2CH_2O)_a(CH_2)_b$-, -$(CH_2)_aC(O)$-, -$CR^3$=N-$NR^3$-, -$CR^3$=N-O-, -$CR^3$=N-$NR^3$-CO-, -N=N-CO-, -S-, -SO-, -SO_2-, dipeptide, tripeptide;~~



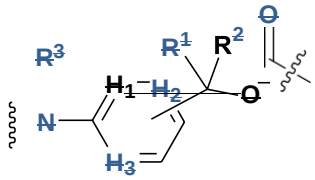
~~; and,~~

~~E1~~



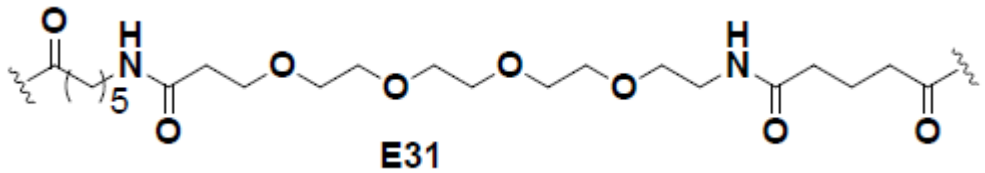
~~E2~~

~~wherein G is selected from the group consisting of alkyl, aryl, carbocyclyl, and heterocyclyl; and,~~

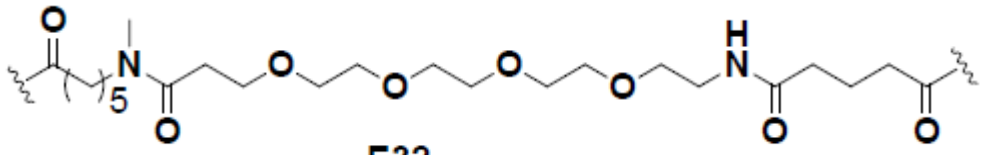


~~G1~~

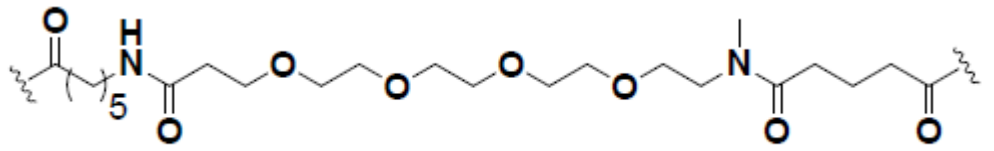
~~wherein H_1, H_2, and H_3 are each independently selected from N or CR^1.~~ A compound of Formula I according to claim 1, wherein E is selected from the group consisting of



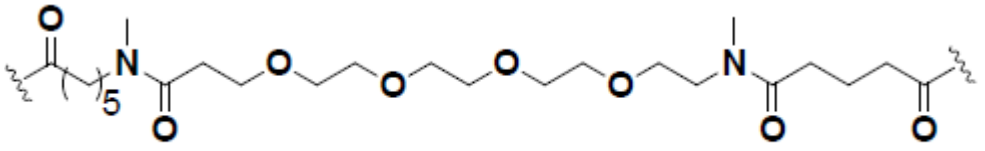
E31 ;



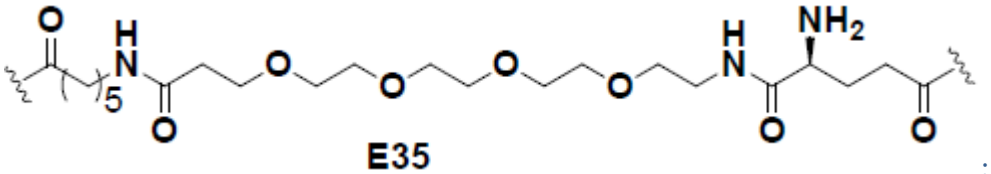
E32 ;



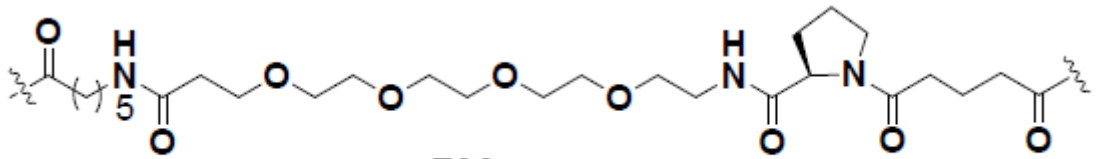
E33 ;



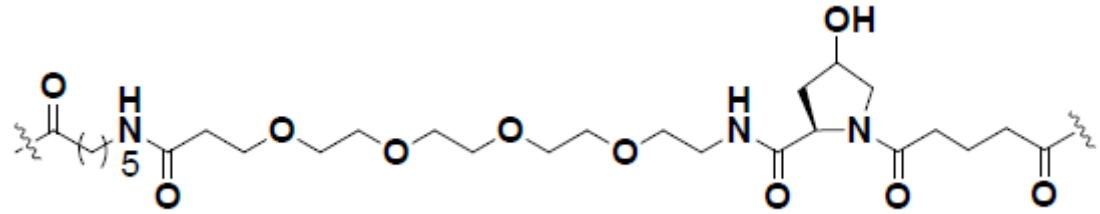
E34 ;



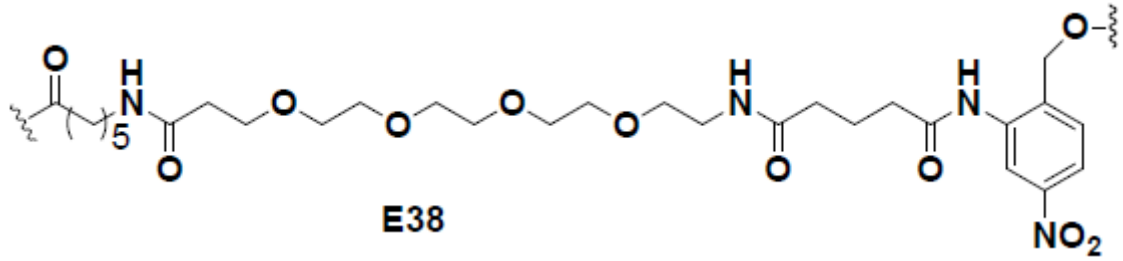
E35 ;



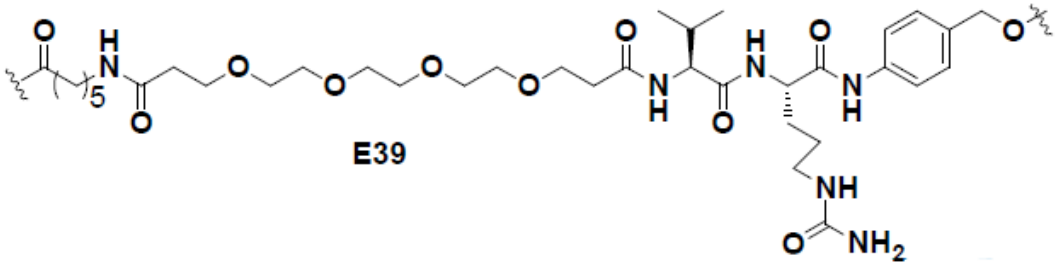
E36 ;



E37 ;



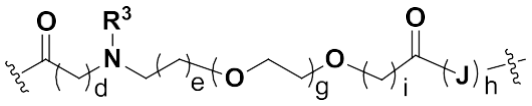
E38 ; and



E39

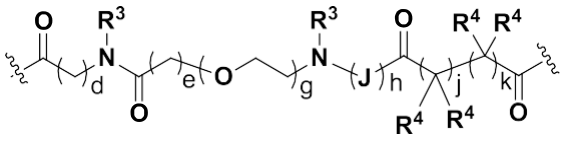
.

3. ~~An isolated conjugate according to claim 1 wherein each E is independently selected from the group consisting of~~



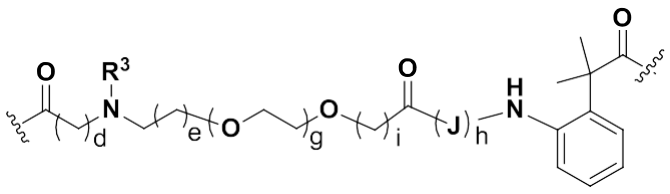
,

~~E3~~



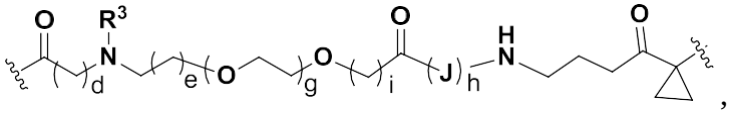
,

~~E4~~



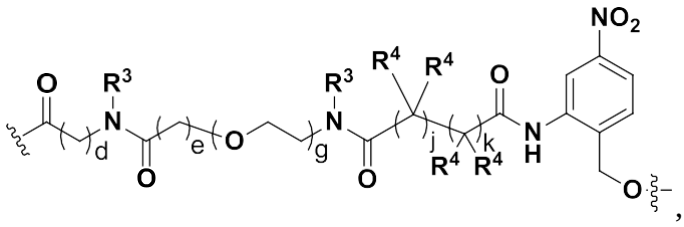
,

~~E5~~



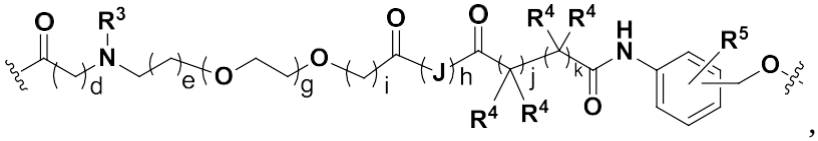
,

~~E6~~



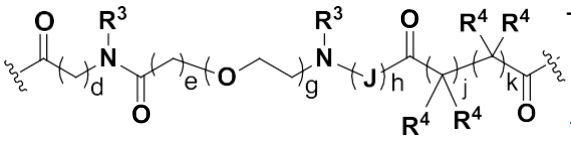
,

~~E7~~



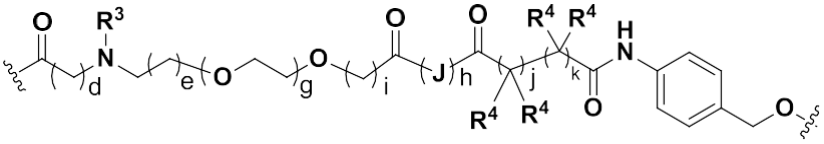
,

~~E8~~



~~; and,~~

~~E9~~



~~E10~~

~~wherein:~~

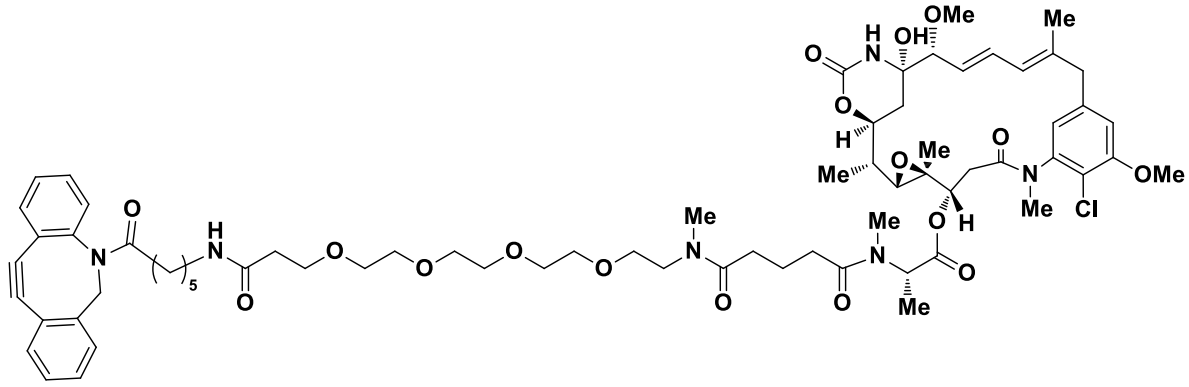
~~J is an amino acid or peptide;~~

~~d, e, g, i, j, and k are each independently an integer from 1 to 30;~~

~~h is an integer from 0 to 30;~~

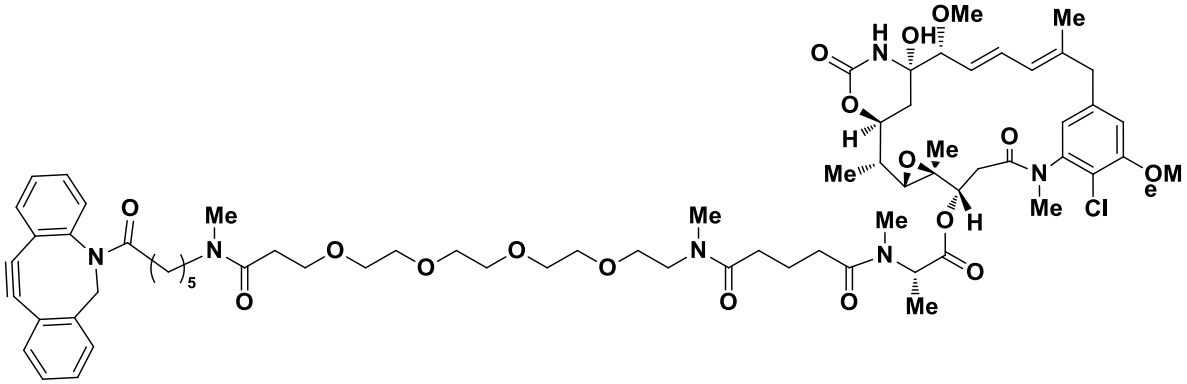
~~Each R^4 is independently selected from the group consisting of H, alkyl, $-N(R^3)_2$, $-SR^3$, and C1-C8 alkoxy, aryl; and,~~

~~R^5 is selected from the group consisting of H, $-N(R^3)_2$, $-SR^3$, C1-C8 alkoxy, aryl, and NO_2.~~ A compound of Formula I according to claim 1 selected from the group consisting of



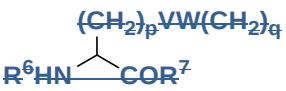
I3

and



I4.

4. ~~An isolated conjugate according to claim 1, wherein M exhibits the structure~~



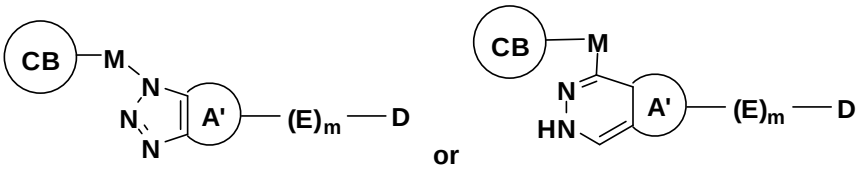
~~Formula IV~~

~~wherein p and q are each an integer from 0-10;~~

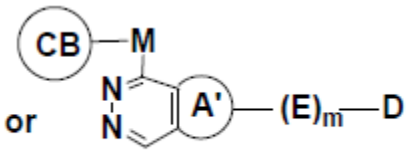
~~R^6 is is H, amino acid, polypeptide, or a bond;~~

~~R^7 is OH, amino acid, polypeptide, or a bond;~~

~~V is an alkyl, aryl, carbocycle, heterocycle, or absent; and, W is O, N, S, or absent.~~A conjugate of Formula III or Formula III' or Formula III''



Formula III Formula III'



Formula III"

wherein:

CB is a cell-binding agent;

M is a non-natural amino acid;

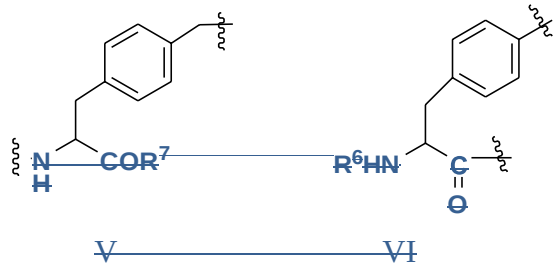
A' is defined as A in any one of claims 1 to 3;

D is a maytansinoid;

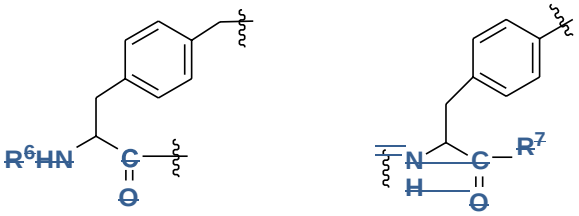
E is defined as in any one of claims 1 to 3; and

m is 1.

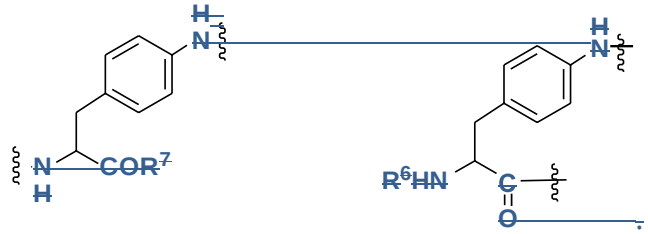
5. ~~An isolated conjugate according to claim 4, wherein M is selected from the group consisting essentially of~~



~~V~~ ~~VI~~

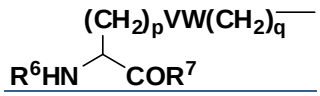


~~VII~~ ~~VIII~~



~~IX X~~

A conjugate according to claim 4, wherein M exhibits the structure



Formula IV

wherein p and q are each an integer from 0-10;

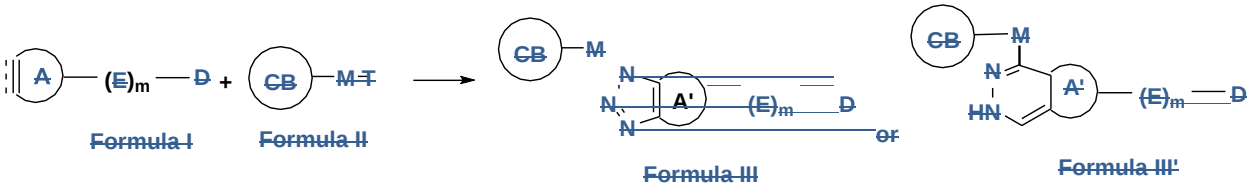
R^6 is H, amino acid, polypeptide, or a bond;

R^7 is OH, amino acid, polypeptide, or a bond;

V is an alkyl, aryl, carbocycle, heterocycle, or absent; and,

W is O, N, S, or absent.

6. ~~An isolated conjugate of Formula III or Formula III' produced by the process of reacting a compound of Formula I with a compound of Formula II~~



~~Formula I~~ ~~Formula II~~ ~~Formula III~~ ~~Formula III'~~

~~wherein, with reference to Formula I,~~

~~A is a strained alkyne ring or a strained alkene ring wherein the ring is carbocyclyl or heterocyclyl;~~

~~D is a payload;~~

~~Each E is independently selected from the group consisting of -CO-, -CR^1R^2-, -NR^3-, -S-S-, -S-, -SO-, -SO_2-, -O-, -CR^3=N-NR^3-, -CR^3=N-O-, -CR^3=N-NR^3-CO-, -N=N-CO-, alkyl, C3-C8 carbocyclyl, -O-$(CR^1R^2)_a$-, aryl, -$(CR^1R^2)_a$-aryl, heteroaryl, -$(CR^1R^2)_a$-heteroaryl, -$(CR^1R^2)_a$-C3-C8 carbocyclyl, heterocyclyl, -$(CR^1R^2)_a$-heterocyclyl, -$(CH_2CH_2O)_a$-, -$(CH_2CH_2O)_a$-$(CH_2)_b$, $(CH_2)_aC(O)$-, amino acid, and peptide;~~

~~R^1 and R^2 are each independently selected from the group consisting of H, F, Cl, Br, I, OH, $N(R^3)_2$, $N(R^3)_3^+$, C1-C8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, SO_2R^3, $S(=O)R^3$, SR^3, $SO_2N(R^3)_2$, $C(=O)R^3$, CO_2R^3, $C(=O)N(R^3)_2$, CN, N_3, NO_2, C1-C8 alkoxy, polyethyleneoxy, phosphonate, phosphate, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, aryl, heteroaryl, C3-C8 carbocyclyl, and C1-C20 heterocyclyl; or, when taken together, R^1 and R^2 form a carbonyl (=O), or spiro carbocyclic ring of 3 to 7 carbon atoms; and,~~

~~R^3 is selected from the group consisting of H, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C6-C20 aryl, C6-C20 heteroaryl, C3-C8 carbocyclyl, and C1-C20 heterocyclyl;~~

~~alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl are optionally independently substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, $N(R^3)_2$, $N(R^3)_3^+$, C1-C8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, C1-C8 alkylsulfonate, C1-C8 alkylamino, 4-dialkylaminopyridinium, C1-C8 alkylhydroxyl, C1-C8 alkylthiol, $-SO_2R$, $S(=O)R^3$, SR^3, $SO_2N(R^3)_2$, $C(=O)R^3$, CO_2R^3, $C(=O)N(R^3)_2$, CN, N_3, NO_2, C1-C8 alkoxy, C1-C8 trifluoroalkyl, C1-C8 alkyl, C3-C12 carbocycle, C6-C20 aryl, C6-C20 heteroaryl, C3-C8 carbocyclyl, C2-C20 heterocyclyl, polyethyleneoxy, phosphonate, and phosphate;~~

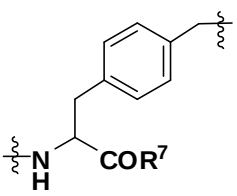
~~m is an integer from 1 to 100;~~

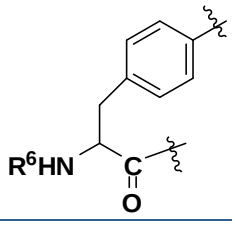
~~a and b are each an integer from 1 to 100; and~~

~~with reference to Formula II,~~

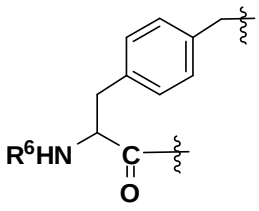
~~CB is a cell-binding agent; M is a non-natural amino acid; T is an azide group or a tetrazine group; and,~~

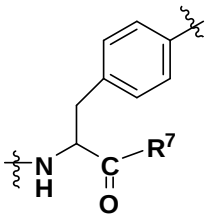
~~with reference to Formula III and Formula III', A' is a carbocyclyl or heterocyclyl.~~ A conjugate according to claim 5, wherein M is selected from the group consisting of



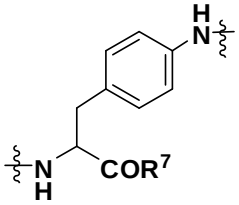


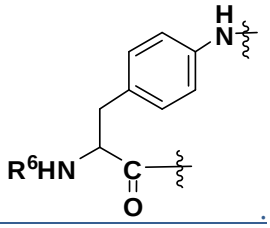
V ; VI ;





VII ; VIII ;

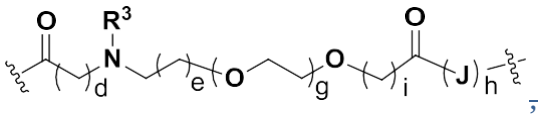




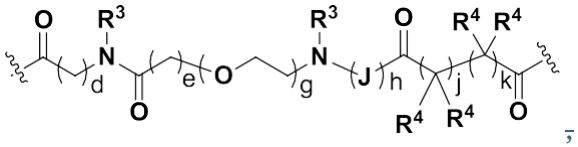
.

IX ; and X

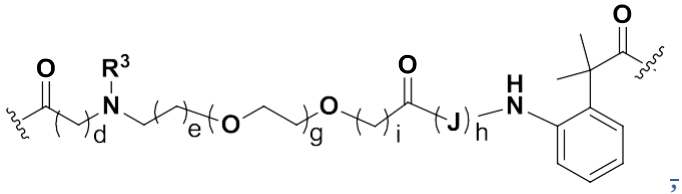
7. ~~An isolated conjugate of Formula III or Formula III' produced by the process according to claim 6 wherein, with reference to Formula I, each E is independently selected from the group consisting of~~



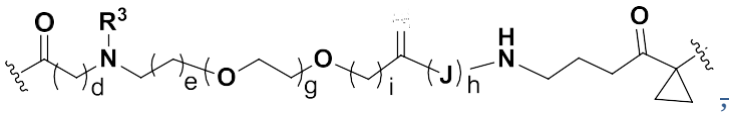
~~E3~~



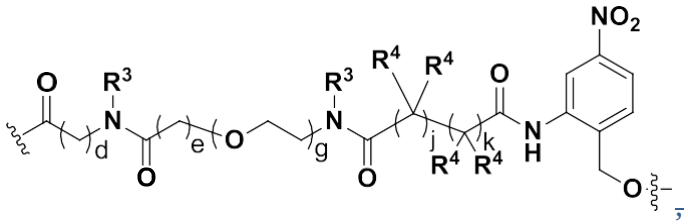
~~E4~~



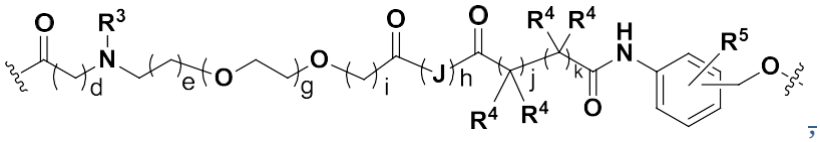
~~E5~~



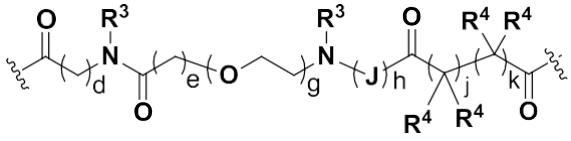
~~E6~~



~~E7~~

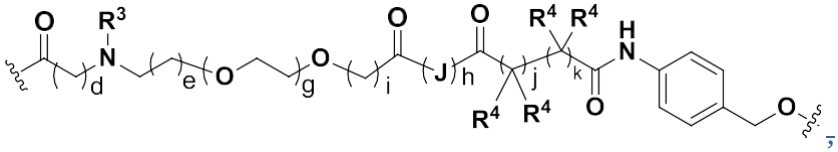


~~E8~~



~~; and,~~

~~E9~~



~~E10~~

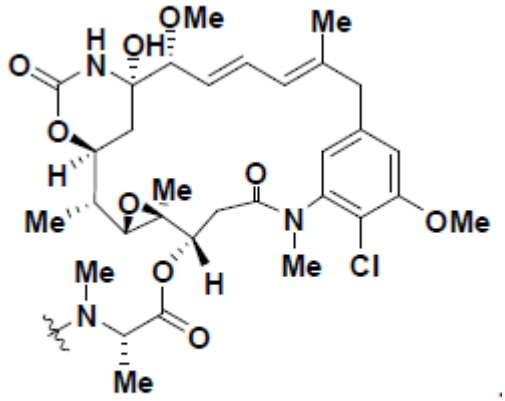
~~wherein J is an amino acid or peptide;~~

~~d, e, g, i, j, and k are each independently an integer from 1 to 30;~~

~~h is an integer from 0 to 30;~~

~~Each R^4 is independently selected from the group consisting of H, alkyl, $-N(R^3)_2$, $-SR^3$, and C1-C8 alkoxy, aryl; and,~~

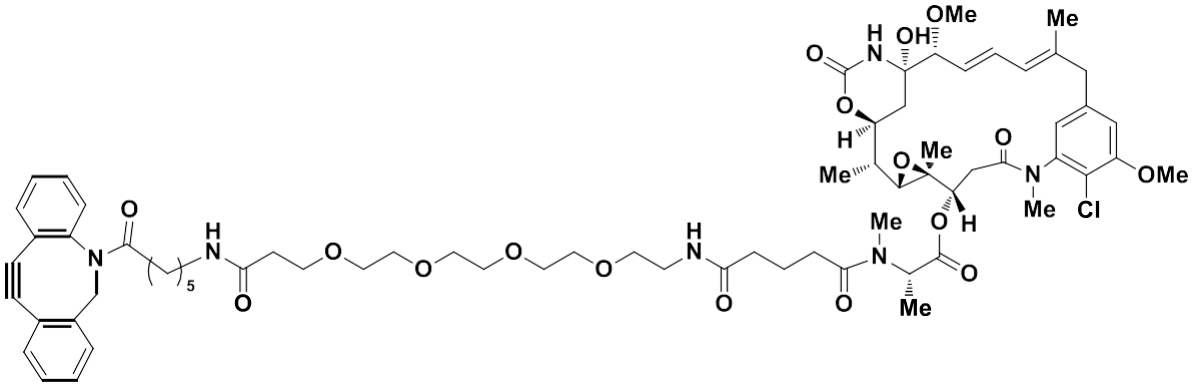
~~R^5 is selected from the group consisting of H, $-N(R^3)_2$, $-SR^3$, C1-C8 alkoxy, aryl, and NO_2.~~ A compound or conjugate according to any one of claims 1 to 6, wherein the maytansinoid is of the structure



C2

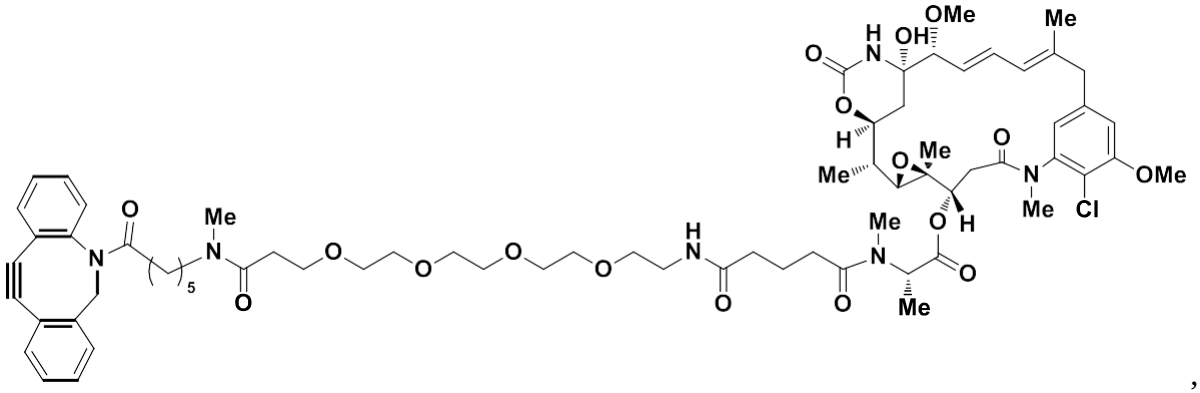
8. ~~An isolated conjugate of Formula III or Formula III' produced by the process according to~~

~~claim 6 wherein each compound of Formula I is independently selected from the group consisting of~~



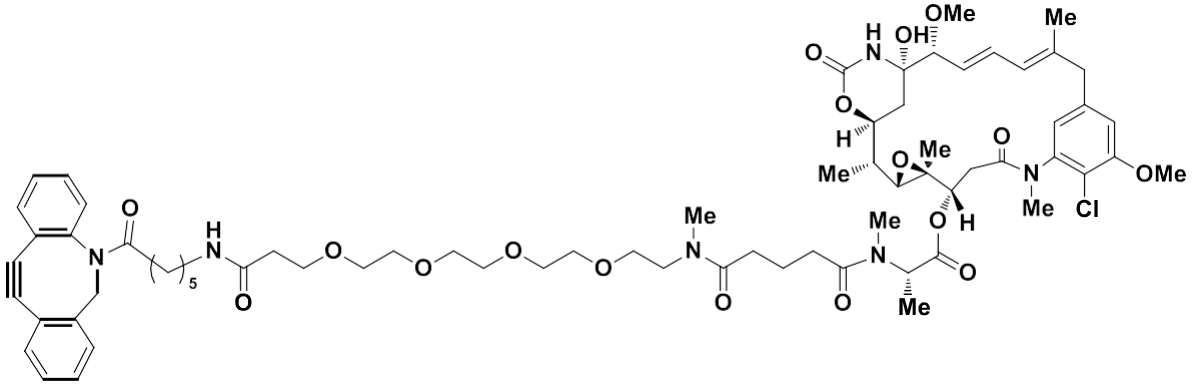
,

~~I1~~



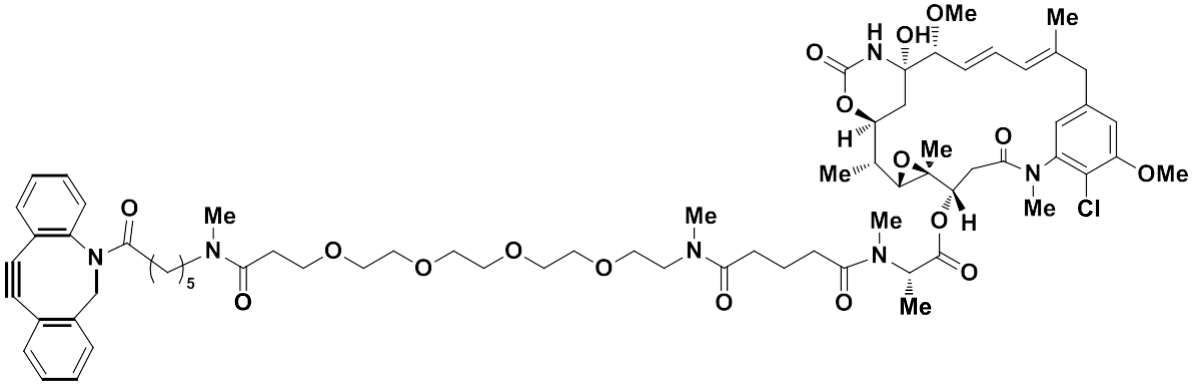
,

~~I2~~



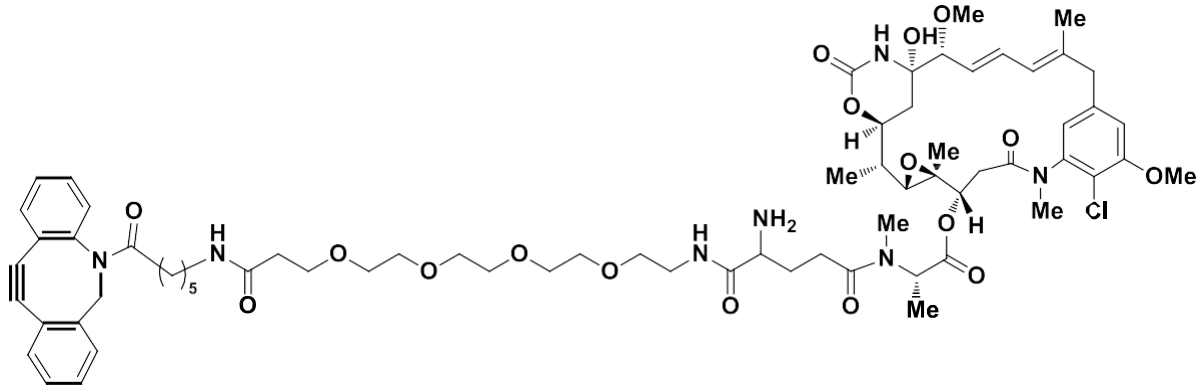
,

~~I3~~



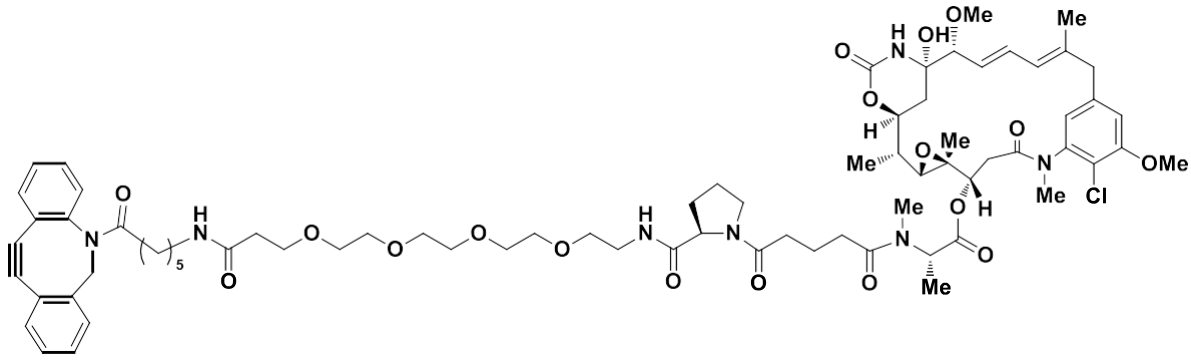
~~,~~

~~I4~~



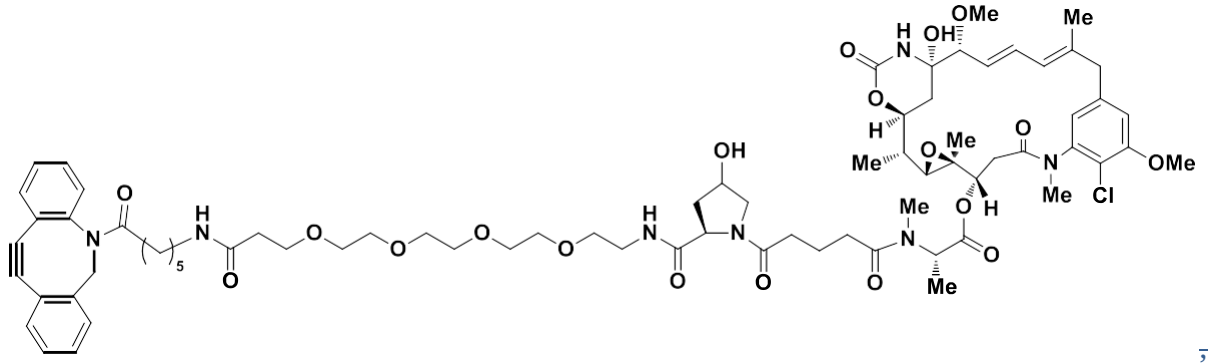
;

~~I5~~



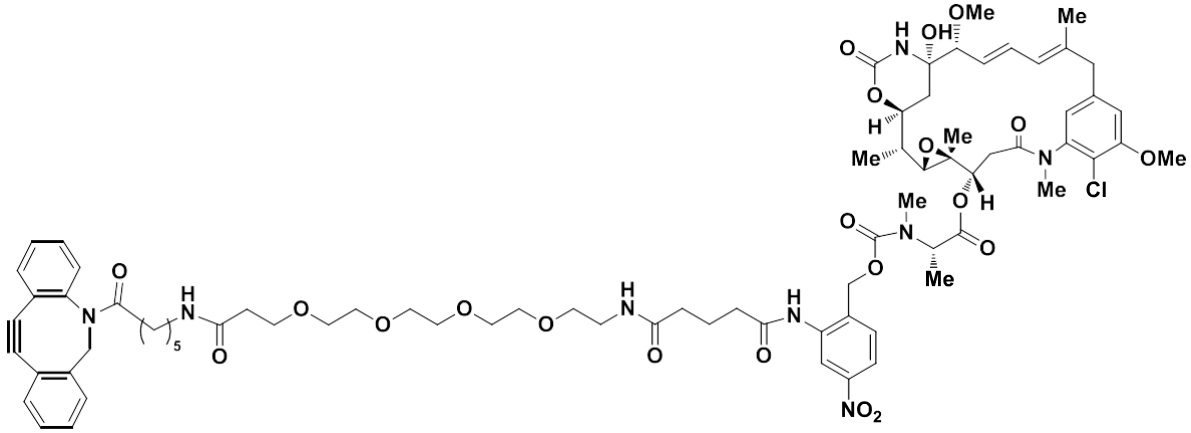
;

~~I6~~



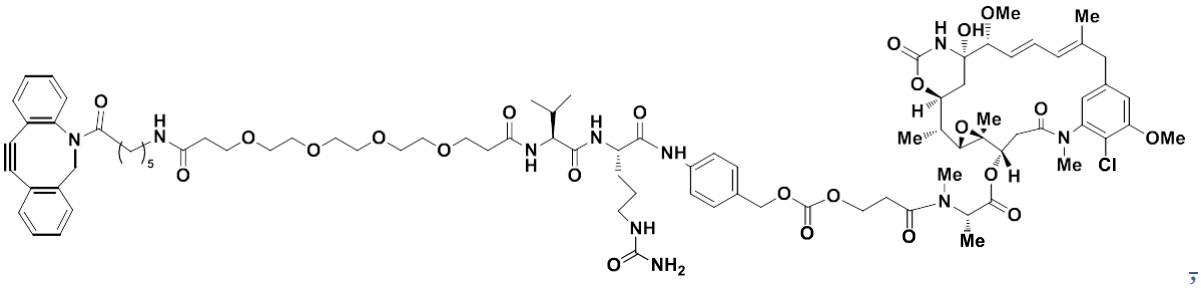
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~~I7~~

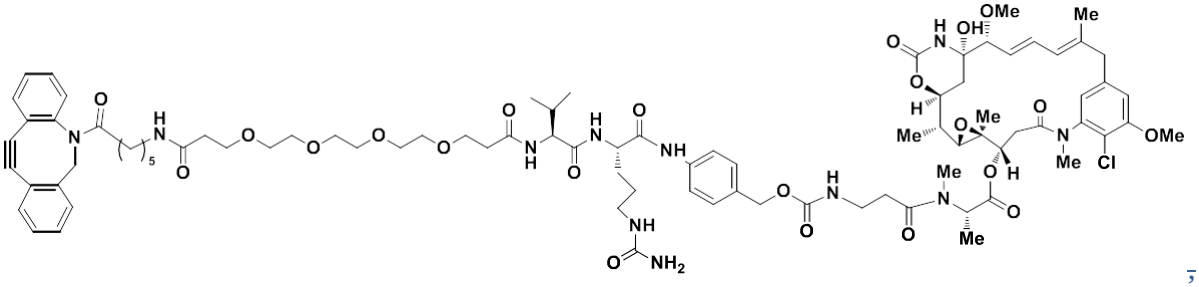


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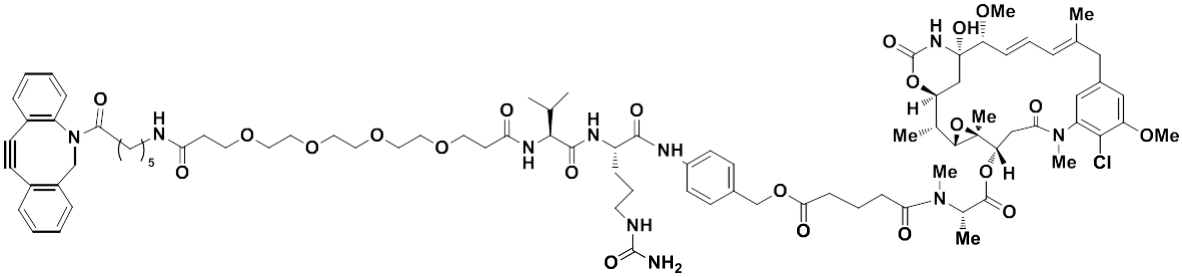
~~I8~~



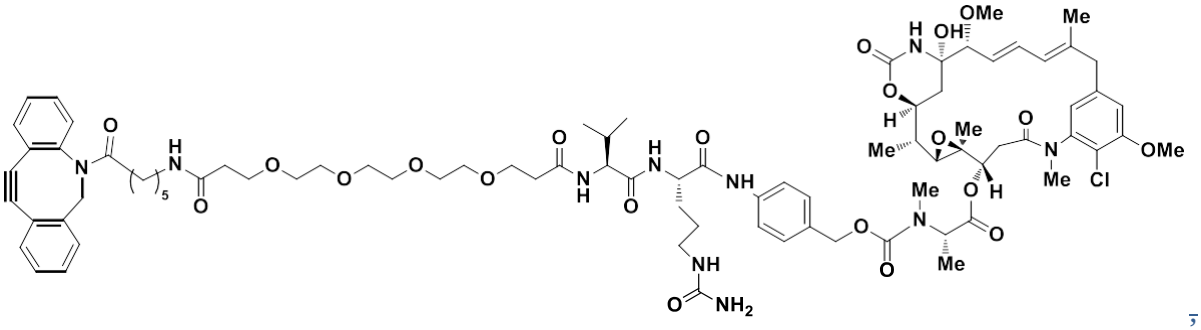
~~I9~~



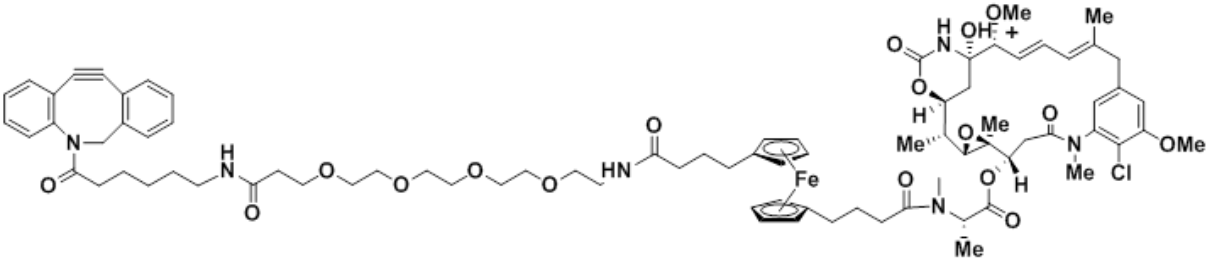
~~I10~~



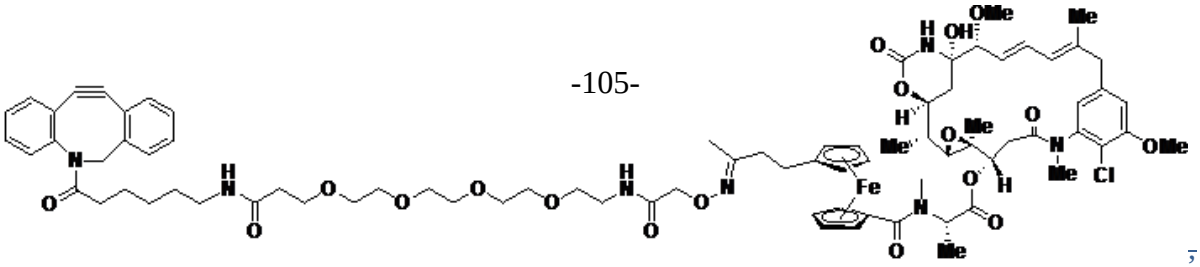
~~I11~~



~~I12~~

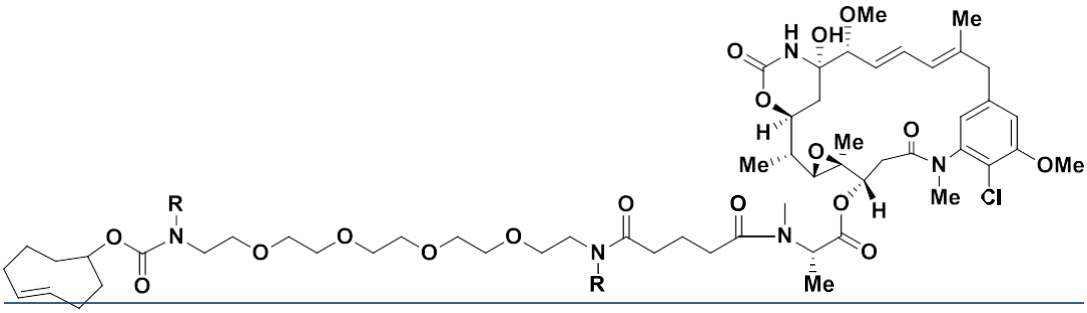


~~I13~~



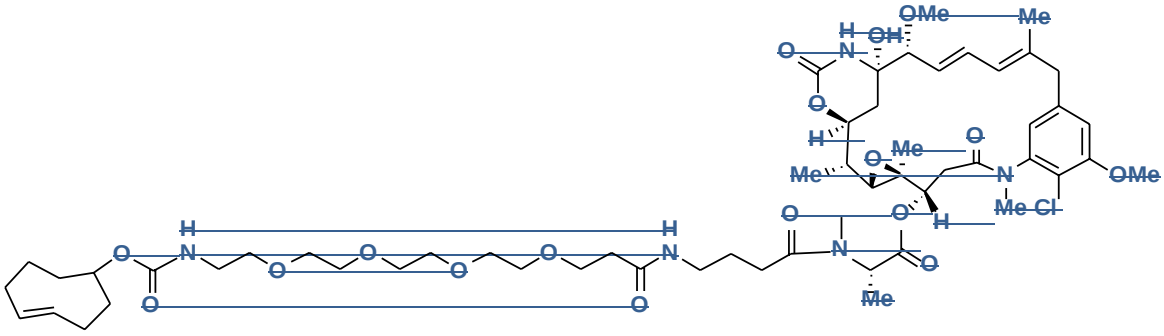
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~~I14~~



~~I15~~

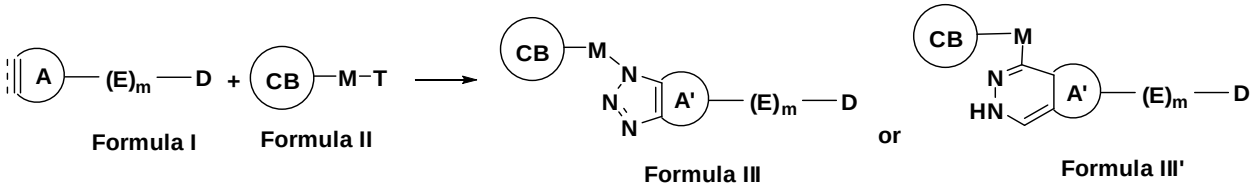
~~R = H or CH3 (methyl); and,~~

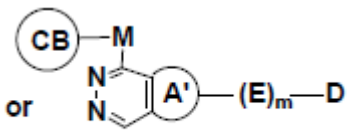


;

~~I16~~

A process for preparing a conjugate of Formula III or Formula III' or Formula III'', the process comprising the step of reacting a compound of Formula I with a compound of Formula II





Formula III"

wherein

Formula I is defined as in any one of claims 1 to 3,

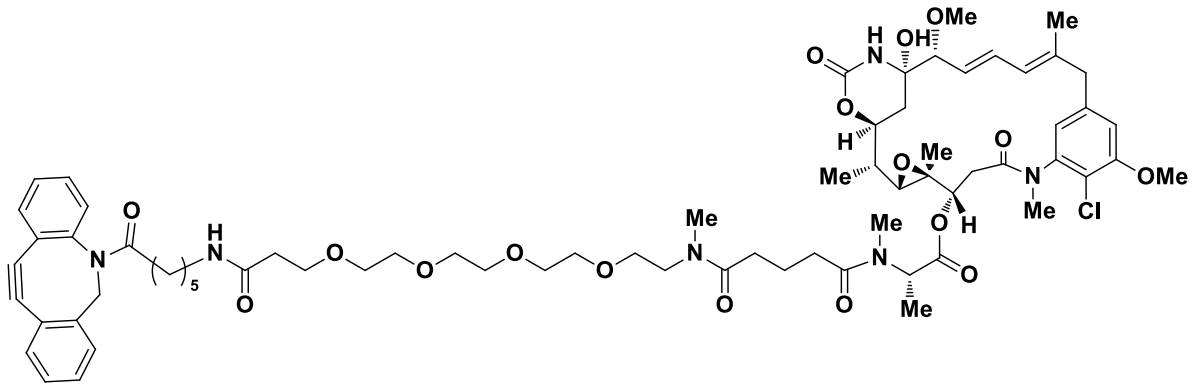
with reference to Formula II,

CB is a cell-binding agent; M is a non-natural amino acid; T is an azide group or a tetrazine group; and,

with reference to Formula III and Formula III', and Formula III'',

A' is defined as A in any one of claims 1 to 3.

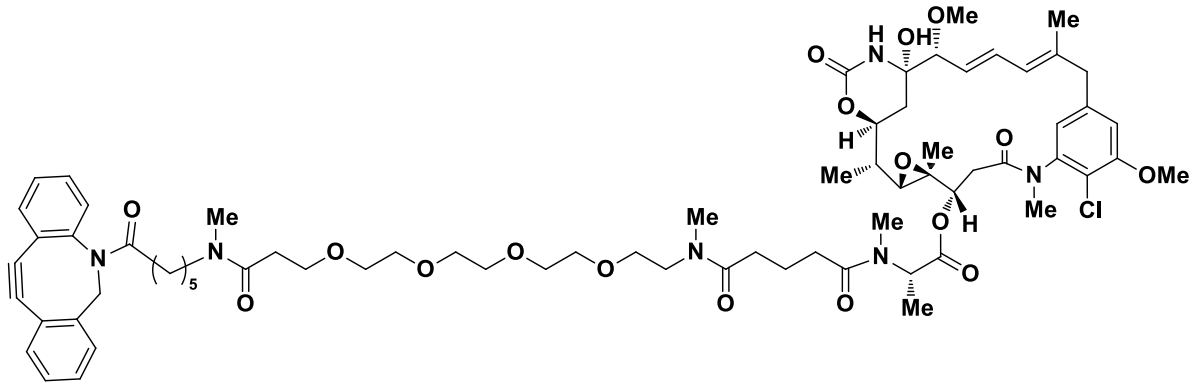
9. ~~An isolated conjugate according to claim 1 wherein D is a maytansinoid.~~ A process according to claim 8 wherein each compound of Formula I is independently selected from the group consisting of



,

I3

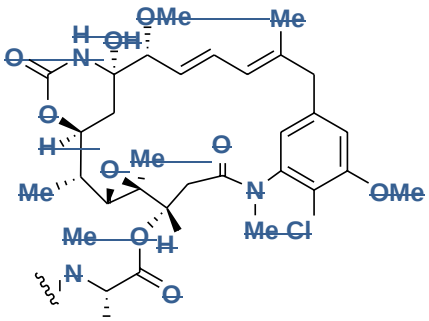
and



,

I4.

10. ~~An isolated conjugate according to claim 9 wherein the maytansinoid is of the structure~~



~~Me~~ .

~~C1~~

A pharmaceutical composition comprising an effective amount of a conjugate according to any one of claims 4 to 7 and at least one pharmaceutically acceptable excipient.

11. ~~A pharmaceutical composition comprising an effective amount of a conjugate according to claim 1 and at least one pharmaceutically acceptable excipient.~~ A conjugate according to any one of claims 4 to 7, or the composition of claim 10, for use in the treatment of a disorder in a mammal.

12. ~~A pharmaceutical composition comprising an effective amount of a conjugate according to claim 9 and at least one pharmaceutically acceptable excipient.~~ The conjugate according to claim 11, wherein the disorder is selected from the group consisting of malignant tumors, autoimmune diseases, graft rejections, graft versus host disease, viral infections, microorganism infections, and parasite infections.

13. ~~A method of treatment of a disorder in a mammal comprising administering an effective amount of a conjugate according to claim 1.~~ Use of the conjugate according to any one of claims 4-7, or the composition of claim 10, for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder in a mammal, wherein the disorder is responsive to suppression of cell growth or induction of cell death.

14. ~~A method of treatment of a disorder in a mammal comprising administering an effective amount of a conjugate according to claim 9.~~ The use according to claim 13, wherein the disorder is selected from the group consisting of malignant tumors, autoimmune diseases, graft rejections, graft versus host disease, viral infections, microorganism infections, and parasite infections.