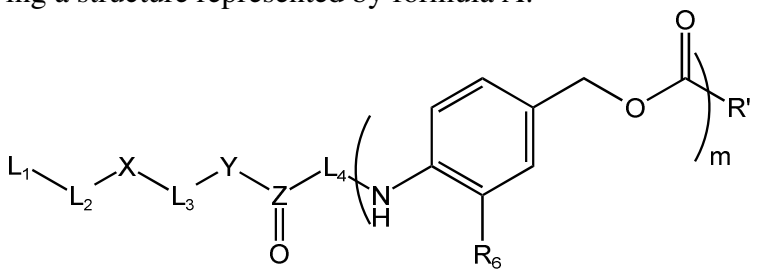
CLAIMS

1. A linker having a structure represented by formula A:



(A)

wherein:

L_1 is a functional group capable of reacting with mercapto;

L_2 and Y are each independently selected from $-(CH_2)_p-$, $-(OCH_2CH_2)_p-$, and $-(CH_2CH_2O)_p-$;

L_3 is a hydrophilic group;

L_4 is an amino acid group;

R' is -OR or -NR"-C_1-C_6 alkylene-NR"R'";

R" and R'" are each independently H and C_1-C_6 alkyl;

R is selected from H and phenyl optionally substituted with one or more nitro groups;

R_6 is selected from H, C_1-C_6 alkoxy, $-(OCH_2CH_2)_pO-C_1-C_6$ alkyl, and $-(CH_2CH_2O)_p-C_1-C_6$ alkyl;

X is selected from -NH-, $-NH(CH_2)_nC(=O)-$, $-C(=O)(CH_2)_nNH-$, and $-(CH_2)_nC(=O)-$;

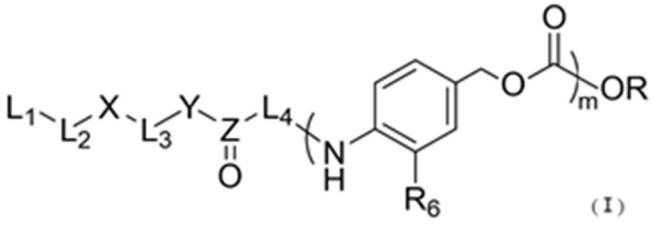
Z is selected from C and S;

m is selected from 0 and 1;

n is selected from 0, 1, and 2;

p is selected from an integer from 1 to 10.

2. The linker according to claim 1, having a structure represented by formula I:



(I)

wherein:

L_1 is a functional group capable of reacting with mercapto;

L_2 and Y are each independently selected from $-(CH_2)_p-$, $-(OCH_2CH_2)_p-$, and $-(CH_2CH_2O)_p-$;

L_3 is a hydrophilic group;

L_4 is an amino acid group;

R is selected from H and phenyl optionally substituted with one or more nitro groups;

R_6 is selected from H, C_1-C_6 alkoxy, $-(OCH_2CH_2)_pO-C_1-C_6$ alkyl, and $-(CH_2CH_2O)_p-C_1-C_6$

alkyl;

X is selected from -NH-, -NH$(CH_2)_n$C(=O)-, -C(=O)$(CH_2)_n$NH-, and -$(CH_2)_n$C(=O)-;

Z is selected from C and S;

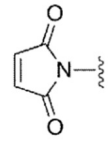
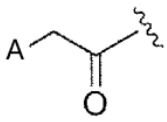
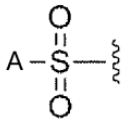
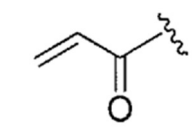
m is selected from 0 and 1;

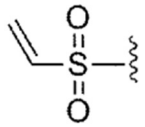
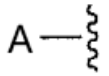
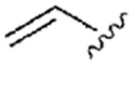
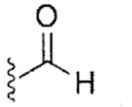
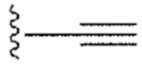
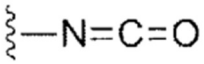
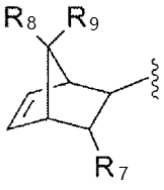
n is selected from 0, 1, and 2;

p is selected from an integer from 1 to 10.

3. The linker according to claim 1 or 2, wherein:

(1) L_1 is selected from maleimide, halogen, halogen-substituted functional groups (e.g., halogen-substituted aldehyde groups or halogen-substituted -S$(O)_2$-), aldehyde groups, alkenyl, alkynyl, alkanones, sulfonyl, silane, isocyanate groups, and norbornenyl; preferably, L_1 is selected from:


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, and

, and derivatives thereof;

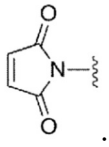
wherein:

R_7, R_8, and R_9 are each independently selected from H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, heteroaryl, C_3-C_9 cycloalkyl, C_3-C_9 heterocyclyl, -$(OCH_2CH_2)_pOCH_3$, -NO_2, -CN, -SCN, -OR_{10}, -SR_{10}, -$N(R_{10})_2$, -C(=O)R_{10}, -C(=O)OR_{10}, -C(=O)$N(R_{10})_2$, -C(=S)OR_{10}, -C(=S)$N(R_{10})_2$, -C(=S)SR_{10}, -NR_{10}(C=O)R_{10}, -NR_{10}(C=S)$N(R_{10})_2$, -O(C=O)$N(R_{10})_2$, -S(=O)$_2R_{10}$, and -S(=O)$_2OR_{10}$, wherein each R_{10} is independently selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl; p is an integer from 1 to 6;

A is halogen;

the wavy line indicates a position where L_1 is connected to L_2;

preferably, L_1 is:


; and/or

(2) L_2 is -$(CH_2)_p$-, and p is an integer from 1 to 4; preferably, L_2 is -CH_2CH_2- or -$CH_2CH_2CH_2$-; and/or

(3) X is -NH- or -NH$(CH_2)_n$C(=O)-; preferably, X is -NH- or -NHC(=O)-; and/or

(4) Y is -$(CH_2)_p$-, and p is 1, 2, or 3; preferably, Y is methylene; and/or

(5) Z is C.

4. The linker according to any one of claims 1-3, wherein L_3 is selected from divalent hydrophilic groups with two monovalent radical centers that result from removal of two hydrogen atoms from a monosaccharide, a disaccharide, and a five- or six-membered saturated heterocycle containing 1-2 nitrogen atoms and a derivative thereof;

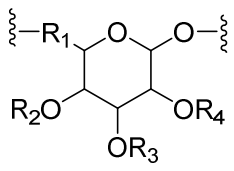
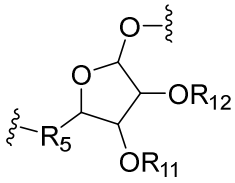
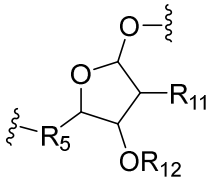
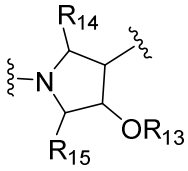
preferably, the monosaccharide is selected from a triose, a tetrose, a pentose, a hexose, and a heptose;

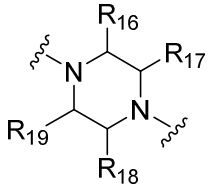
preferably, the disaccharide is selected from maltose, sucrose, and lactose;

preferably, the five- or six-membered saturated heterocycle containing 1-2 nitrogen atoms or the derivative thereof is selected from piperazinyl, piperidinyl, and pyrrolidinyl;

preferably, L_3 is selected from divalent hydrophilic groups with two monovalent radical centers that result from removal of two hydrogen atoms from glucose, galactose, mannose, glucuronic acid, galactonic acid, mannuronic acid, N-acetylglucosamine, N-acetylgalactosamine, N-acetylmannosamine, and N-acetylmuramic acid;

more preferably, L_3 is selected from:





and



wherein in the formulas,

R_1 is selected from $-O(CH_2)_p-$ and -C(=O)-, and p is an integer from 1 to 6, preferably 1, 2, 3, or 4;

R_5 is C_1-C_3 alkylene unsubstituted or substituted with one or more substituents selected from $-OR_{20}$ and $-C(=O)OR_{20}-$;

R_2, R_3, R_4, R_{11}, R_{12}, and R_{13} are independently selected from H, C_1-C_6 alkyl, $-(CH_2CH_2O)_t-C_1$-C_6 alkyl, a sulfonic acid group, and a phosphoric acid group;

R_{14} and R_{15} are independently selected from H, $-OR_{20}$, and $-CH_2R_{20}$;

R_{16}, R_{17}, R_{18}, and R_{19} are independently selected from H and $-OR_{20}$;

R_{20} is selected from H, C_1-C_6 alkyl, $-(CH_2CH_2O)_t-C_1$-C_6 alkyl, a sulfonic acid group, and a phosphoric acid group;

t is an integer from 1 to 20;

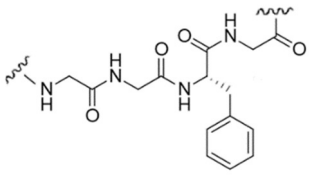
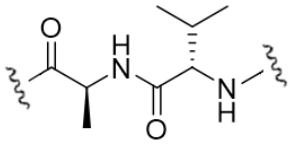
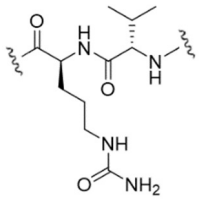
the wavy lines indicate positions where L_3 is connected to X and Y.

5. The linker according to any one of claims 1-4, wherein

L_4 is selected from the following amino acid residues: valine, citrulline, alanine, glycine, phenylalanine, asparagine, glutamic acid, lysine, serine, threonine, cysteine, and tyrosine; the amino acid groups are optionally substituted with one or more $-OR_{20}$, wherein R_{20} is selected from H, C_1-C_6 alkyl, $-(CH_2CH_2O)_t$-C_1-C_6 alkyl, a sulfonic acid group, and a phosphoric acid group, wherein t is an integer from 1 to 20; or

L_4 is selected from the following peptide fragments: valine-citrulline (VC), valine-alanine (VA), glycine-glycine-phenylalanine-glycine (GGFG), glycine-glycine-phenylalanine-glycine-glycine, glycine-glycine-phenylalanine-glycine-glycine-glycine, citrulline-valine, alanine-valine, alanine-alanine, citrulline-alanine, asparagine-citrulline, citrulline-asparagine, citrulline-citrulline, phenylalanine-lysine, and lysine-phenylalanine, preferably from the following peptide fragments: valine-citrulline (VC), valine-alanine (VA), and glycine-glycine-phenylalanine-glycine (GGFG); each of the peptide fragments is optionally substituted with one or more substituents selected from $-OR_{20}$ and $-(OCH_2CH_2)_pO$-C_1-C_6 alkyl, wherein R_{20} is selected from H, C_1-C_6 alkyl, $-(CH_2CH_2O)_t$-C_1-C_6 alkyl, a sulfonic acid group, and a phosphoric acid group, t is an integer from 1 to 20, and p is an integer from 1 to 6;

preferably, L_4 is selected from:


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, and

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6. The linker according to any one of claims 1-5, wherein:

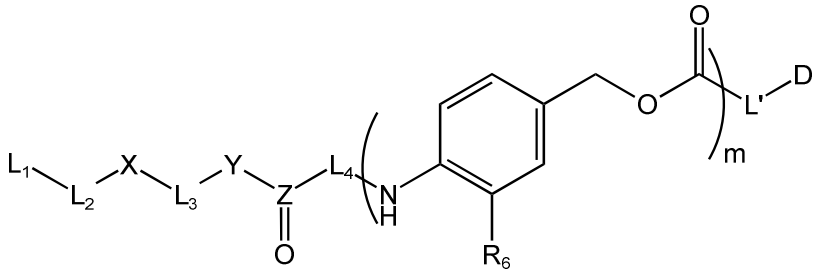
R_6 is H, C_1-C_3 alkoxy, or $-(OCH_2CH_2)_pO$-C_1-C_3 alkyl, wherein p is an integer from 1 to 6; preferably, R_6 is H, methoxy, or $-(OCH_2CH_2)_pOCH_3$, wherein p is an integer from 1 to 6 or from 1 to 4; and/or

R is selected from H and phenyl optionally substituted with 1-3 nitro groups and is preferably H or 4-nitrophenyl.

7. The linker according to any one of claims 1-6, wherein the linker is selected from linkers represented by formulas II to XIV, in each of the formulas, R", R'", R, L_2, X, L_3, R_2-R_4, R_6, R_{11}-R_{13}, and R_{15} are as described in any one of claims 1-6;

preferably, the linker is selected from linkers represented by formulas 1 to 46.

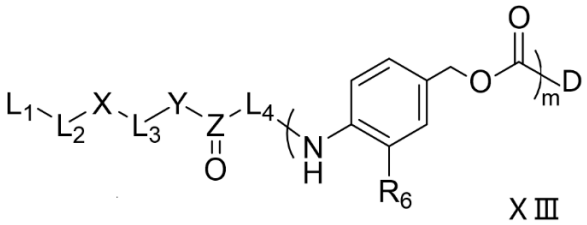
8. A linker-drug conjugate, having a structural formula represented by formula XIII':



(formula XIII')

wherein in the formula, L_1, L_2, L_3, L_4, X, Y, Z, R_6, and m are as described in any one of claims 1-6; L' is a bond, -NR"-C_1-C_6 alkylene-NR"-CO-*, or -NH-CH_2-O-; D is a drug moiety; each R" is independently H and C_1-C_6 alkyl; * indicates a position where L' is connected to D; preferably, the structure other than moiety D in formula XIII' is as shown in claim 7;

preferably, the linker-drug conjugate has a structure represented by formula XIII:



XIII

wherein L_1, L_2, L_3, L_4, X, Y, Z, R_6, and m are as described in any one of claims 1-6; D is a drug moiety; preferably, the structure other than moiety D in formula XIII is as defined in claim 7;

preferably, the drug moiety D is selected from drug moieties represented by formulas D-1 to D-9; in each of the formulas, the wavy line indicates a position where D is connected to the remainder of the linker-drug conjugate;

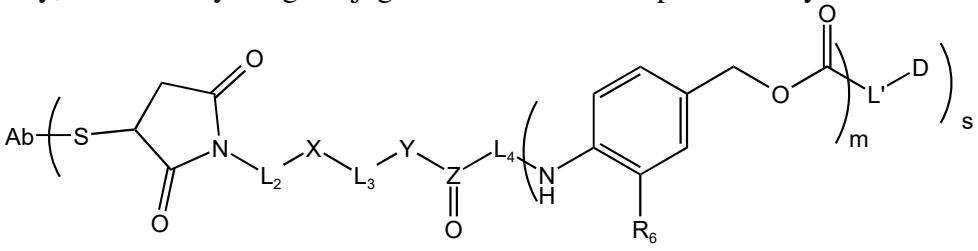
more preferably, the linker-drug conjugate is selected from CPD1, CPD2, CPD3, CPD4, CPD5, CPD6, CPT004, CPT005, CPT006, CPT008, CPT009, CPT010, MMAE Derivate, MMAE Derivate (o-OMe-PAB), Comp.5, Comp6, Comp7, Comp8, and Comp9.

9. An antibody-drug conjugate or a pharmaceutical composition thereof, wherein the antibody-drug conjugate has a structure represented by formula XIV:

$$Ab\text{-}(L\text{-}D)_s \qquad \text{(formula XIV)}$$

wherein L is the linker according to any one of claims 1-7; D is a drug; s represents an average number of L-D units conjugated to Ab, and s ranges from 1 to 8; preferably, s is 2-6; Ab is a targeting moiety; preferably, L-D is the linker-drug conjugate according to claim 8

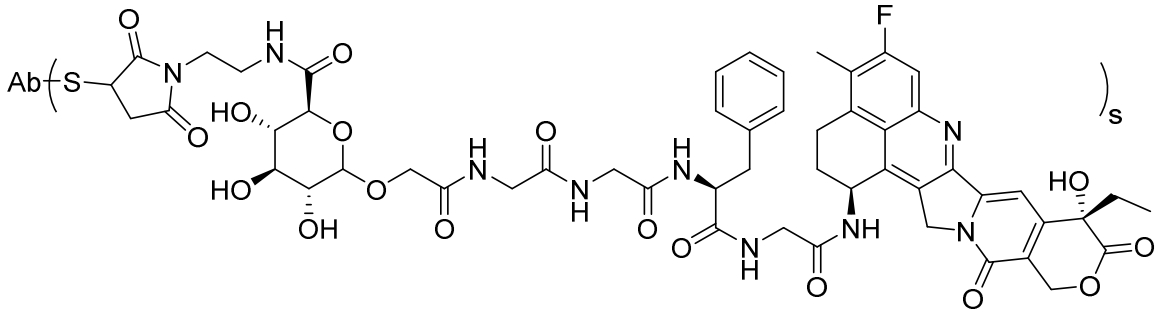
preferably, the antibody-drug conjugate has a structure represented by the following formula:



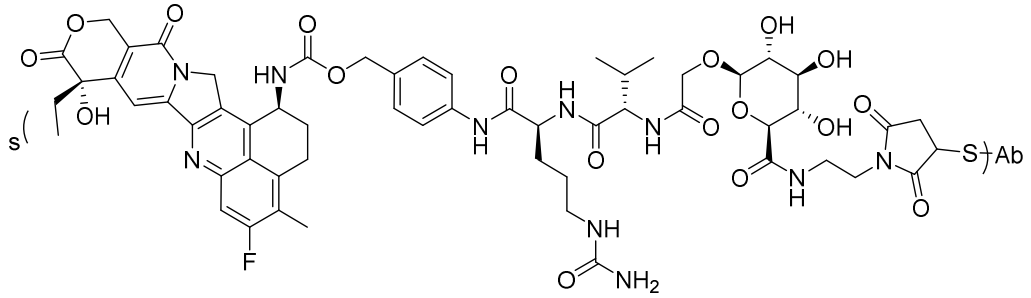
wherein L_2, X, L_3, Y, Z, L_4, R_6, and m are as described in any one of claims 1-6; L' is as described

in claim 8; s represents an average number of L-D units conjugated to Ab, and s ranges from 1 to 8; preferably, s is 2-6; Ab is a targeting moiety; S represents a sulfur atom in a cysteine residue in the antibody;

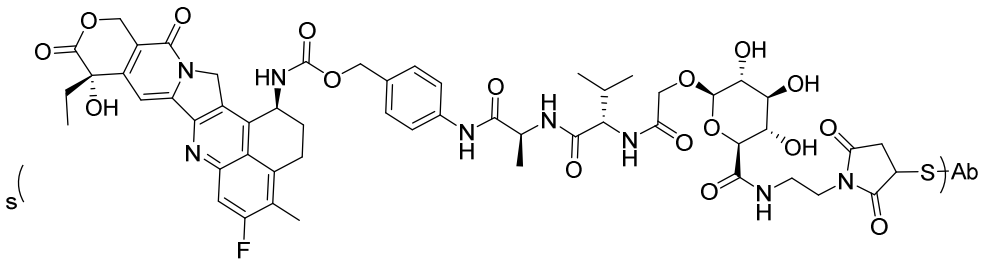
more preferably, the antibody-drug conjugate has a structure of:



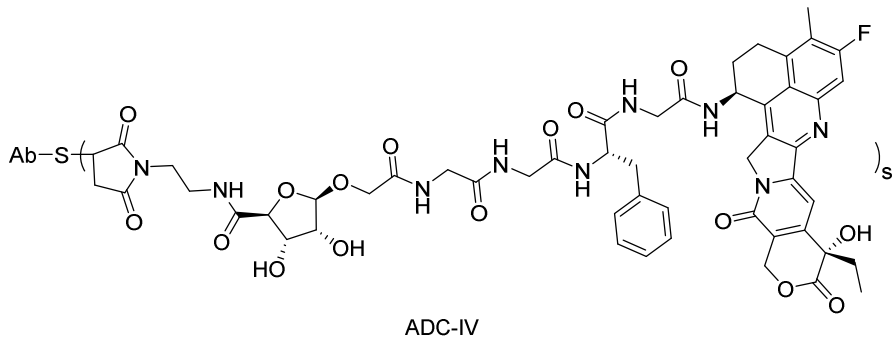
ADC-I



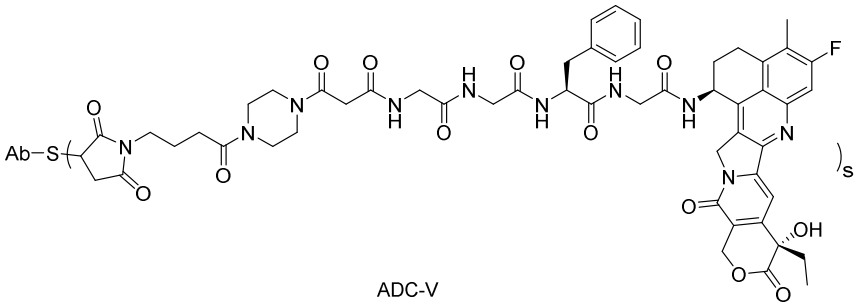
ADC-II



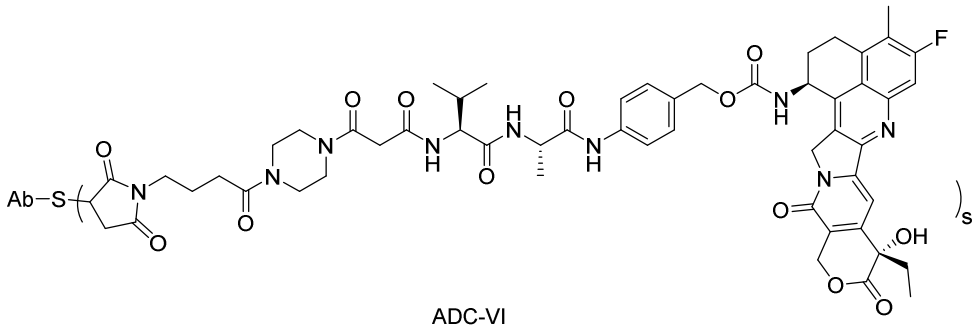
ADC-III



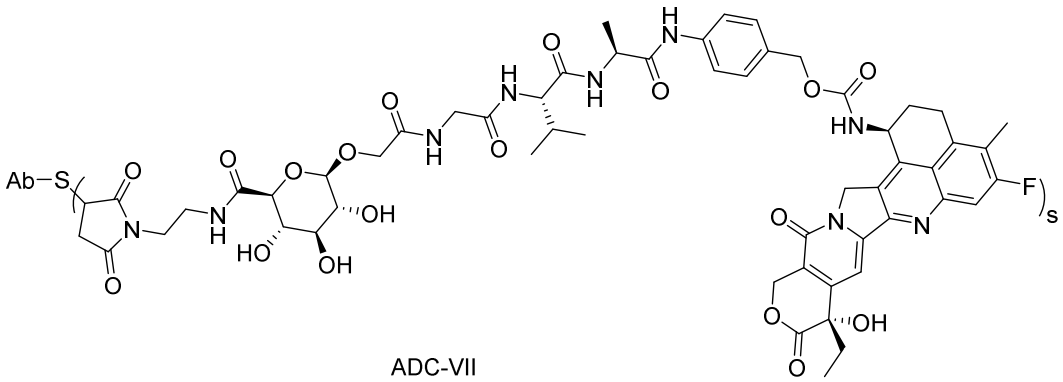
ADC-IV



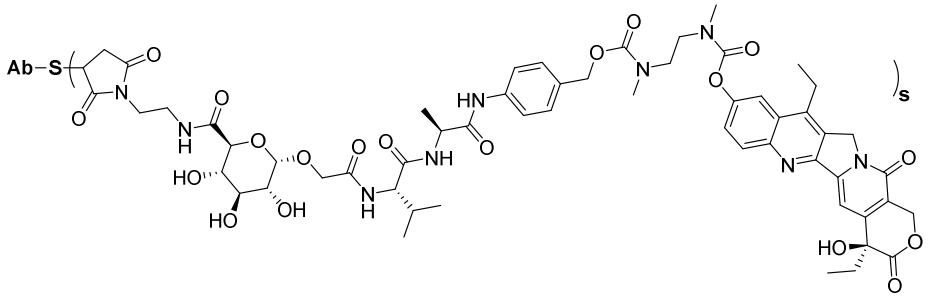
ADC-V



ADC-VI



ADC-VII



ADC VIII

wherein in the formulas, s is 1-8.

10. A connector having a structure represented by the following formula, wherein the connector is used for connecting a drug to a targeting moiety to form a targeting moiety-drug conjugate:

$$-L_1-L_2-X-L_3-Y-Z(=O)-L_4-(L_5)_m-L_6-$$

wherein in the formula,

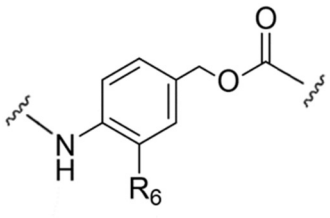
L_1 is selected from -(maleimido-3-yl-N)-, -C(=O)-, $-(CH_2)_nC(=O)-$, -S(=O)-, $-(CH_2)_nS(=O)-$, $-CH_2-(CH_2)_n-$, and -CH=CH-;

L_2 and Y are each independently selected from $-(CH_2)_p-$, $-(OCH_2CH_2)_p-$, and $-(CH_2CH_2O)_p-$;

L_3 is a hydrophilic group;

L_4 is an amino acid group;

L_5 is:



;

R_6 is selected from H, C_1-C_6 alkoxy, -$(OCH_2CH_2)_pO$-C_1-C_6 alkyl, and -$(CH_2CH_2O)_p$-C_1-C_6 alkyl;

L_6 is a bond, -NR"-C_1-C_6 alkylene-NR"-, or -NR"-C_1-C_6 alkylene-NR"-CO-;

each R" is independently H or C_1-C_6 alkyl; preferably, each R" is independently H, methyl, or ethyl; more preferably, each R" is methyl;

X is selected from -NH-, -$NH(CH_2)_nC(=O)$-, -$C(=O)(CH_2)_nNH$-, and -$(CH_2)_nC(=O)$-;

Z is selected from C and S;

n is selected from 0, 1, and 2;

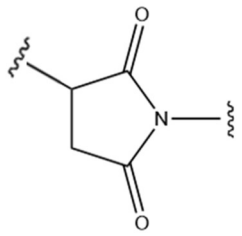
p is selected from an integer from 1 to 10;

m is selected from 0 and 1;

wherein the L_1 is used for connecting to the targeting moiety, and the other end of the connector is used for connecting to the drug;

wherein when m is 0, the drug is connected to the carbonyl end (C(=O)) of L_4; when m is 1, the drug is connected to the carbonyl end (C(=O)) of L_5, and L_4 is connected to the amino end (NH) of L_5;

wherein the -(maleimido-3-yl-N)- is a structure represented by the following formula and is connected to the targeting moiety via locant 3,



;

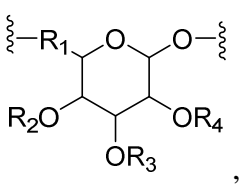
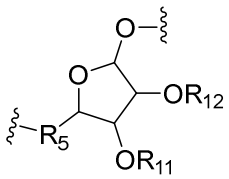
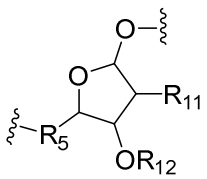
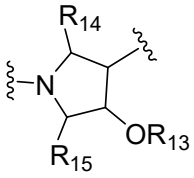
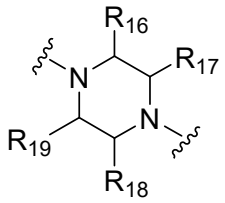
preferably, L_1 is -(maleimido-3-yl-N)-; and/or L_2 is -$(CH_2)_p$-, and p is an integer from 1 to 4; preferably, L_2 is -CH_2CH_2- or -$CH_2CH_2CH_2$-; and/or X is -NH- or -$NH(CH_2)_nC(=O)$-; preferably, X is -NH- or -NHC(=O)-; and/or Y is -$(CH_2)_p$-, and p is 1, 2, or 3; preferably, Y is methylene; and/or Z is C.

11. The connector according to claim 10, wherein L_3 is selected from divalent hydrophilic groups with two monovalent radical centers that result from removal of two hydrogen atoms from a monosaccharide, a disaccharide, and a five- or six-membered saturated heterocycle containing 1-2 nitrogen atoms and a derivative thereof; preferably, the monosaccharide is selected from at least

one of a triose, a tetrose, a pentose, a hexose, and a heptose; the disaccharide is selected from at least one of maltose, sucrose, and lactose; the five- or six-membered saturated heterocycle containing 1-2 nitrogen atoms is selected from piperazinyl, piperidinyl, and pyrrolidinyl;

preferably, L_3 is selected from divalent hydrophilic groups with two monovalent radical centers that result from removal of two hydrogen atoms from glucose, galactose, mannose, glucuronic acid, galactonic acid, mannuronic acid, N-acetylglucosamine, N-acetylgalactosamine, N-acetylmannosamine, and N-acetylmuramic acid;

more preferably, L_3 is selected from:


,

,

,

, and

,

wherein in the formulas,

R_1 is selected from $-O(CH_2)_p-$ and -C(=O)-, and p is an integer from 1 to 6, preferably 1, 2, 3, or 4;

R_5 is C_1-C_3 alkylene unsubstituted or substituted with one or more substituents selected from $-OR_{20}$ and $-C(=O)OR_{20}-$;

R_2, R_3, R_4, R_{11}, R_{12}, and R_{13} are independently selected from H, C_1-C_6 alkyl, $-(CH_2CH_2O)_t-C_1$-C_6 alkyl, a sulfonic acid group, and a phosphoric acid group;

R_{14} and R_{15} are independently selected from H, $-OR_{20}$, and $-CH_2R_{20}$;

R_{16}, R_{17}, R_{18}, and R_{19} are independently selected from H and $-OR_{20}$;

R_{20} is selected from H, C_1-C_6 alkyl, $-(CH_2CH_2O)_t-C_1$-C_6 alkyl, a sulfonic acid group, and a phosphoric acid group;

t is an integer from 1 to 20;

the wavy lines indicate positions where L_3 is connected to X and Y.

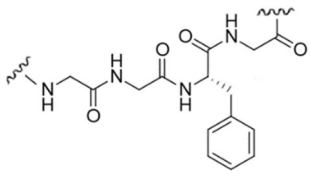
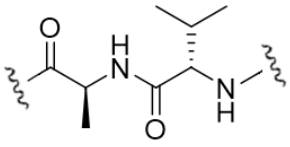
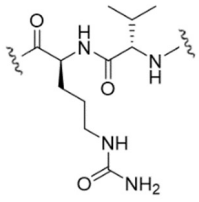
12. The connector according to any one of claims 10-11, wherein

L_4 is selected from the following amino acid residues: valine, citrulline, alanine, glycine, phenylalanine, asparagine, glutamic acid, lysine, serine, threonine, cysteine, and tyrosine; the amino acid groups are optionally substituted with one or more $-OR_{20}$, wherein R_{20} is selected from H, C_1-C_6 alkyl, $-(CH_2CH_2O)_t-C_1$-C_6 alkyl, a sulfonic acid group, and a phosphoric acid group, wherein t is an integer from 1 to 20; or

L_4 is selected from the following peptide fragments: valine-citrulline (VC), valine-alanine

(VA), glycine-glycine-phenylalanine-glycine (GGFG), glycine-glycine-phenylalanine-glycine-glycine, glycine-glycine-phenylalanine-glycine-glycine-glycine, citrulline-valine, alanine-valine, alanine-alanine, citrulline-alanine, asparagine-citrulline, citrulline-asparagine, citrulline-citrulline, phenylalanine-lysine, and lysine-phenylalanine, preferably from the following peptide fragments: valine-citrulline (VC), valine-alanine (VA), and glycine-glycine-phenylalanine-glycine (GGFG); each of the peptide fragments is optionally substituted with one or more substituents selected from $-OR_{20}$ and $-(OCH_2CH_2)_pO-C_1-C_6$ alkyl, wherein R_{20} is selected from H, C_1-C_6 alkyl, $-(CH_2CH_2O)_t-C_1-C_6$ alkyl, a sulfonic acid group, and a phosphoric acid group, t is an integer from 1 to 20, and p is an integer from 1 to 6;

preferably, L_4 is selected from:


,

, and

.

13. The connector according to any one of claims 10-12, wherein

R_6 is H, C_1-C_3 alkoxy, or $-(OCH_2CH_2)_pO-C_1-C_3$ alkyl, wherein p is an integer from 1 to 6; preferably, R_6 is H, methoxy, or $-(OCH_2CH_2)_pOCH_3$, wherein p is an integer from 1 to 6 or from 1 to 4.

14. The connector according to any one of claims 10-13, wherein the connector is selected from connectors represented by formulas II-1 to XIV-1; in each of the formulas, R, L_2, X, L_3, R_2-R_4, $R_{11}-R_{13}$, and R_{15} are as described in any one of claims 1-6;

preferably, the connector is selected from connectors represented by formulas 1-1 to 46-1.

15. The linker according to any one of claims 1-7 for use in the preparation of a linker-drug conjugate or an antibody-drug conjugate, wherein preferably, the linker-drug conjugate is the linker-drug conjugate according to claim 8, and the antibody-drug conjugate is the antibody-drug conjugate according to claim 9; or

the antibody-drug conjugate or the pharmaceutical composition thereof according to claim 9 for use in treating or preventing a disease; preferably, the disease is selected from a cancer, an autoimmune disease, an inflammatory disease, and an infectious disease.