CLAIMS

1. A compound of Formula (I)

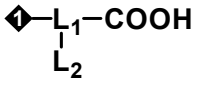


(I),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof, wherein

Q denotes to a junction moiety capable of being coupled to a ligand via a bond selected from the group consisting of carbonyl, thioether, amide, disulfide and hydrazone bond;

L denotes to a linker moiety capable of connecting Q to a therapeutic agent, and having a structure of:



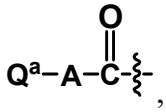
,

where L_1 is a polypeptide residue consisting of three to eight amino acid residues which comprises at least one amino acid residue with a side chain carboxyl group, where "-COOH" denotes carboxyl group of an amino acid residue at C-terminal of the polypeptide residue;

L_2 is absent or a monodentate, bidentate or tridentate hydrophilic group attached to the side chain carboxyl group on the amino acid residue of the polypeptide residue L_1, and L_2 has a structure of $-NHC(R^{L2a})(R^{L2b})(R^{L2c})$, where R^{L2a}, R^{L2b}, and R^{L2c} are each independently selected from the group consisting of H, $-(CH_2O)(CH_2CH_2O)_m(CH_2)_pC(O)OH$, and $-(CH_2O)(CH_2CH_2O)_m(CH_2)_pC(O)NHR^{L2d}$, R^{L2d} is H or C_{1-6} alkyl optionally substituted with 1 to 6 hydroxy groups, each m is independently an integer from 0 to 10, and each p is independent an integer from 1 to 4; and

 denotes to the N-terminal side of the polypeptide residue covalently attached to the junction moiety Q;

the junction moiety Q has a structure of:



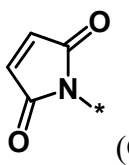
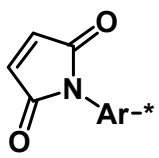
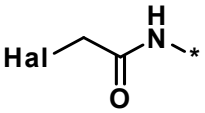
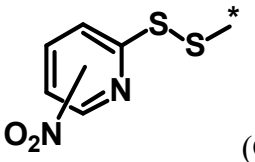
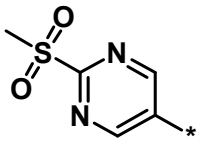
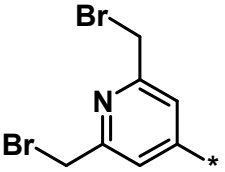
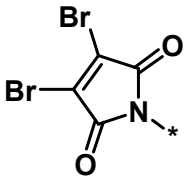
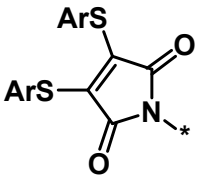
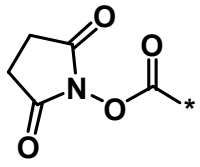
,

wherein Q^a is a function group capable of being coupled to a ligand;

A is selected from optionally substituted C_{3-8} alkylidene, optionally substituted C_{3-8} alkenylidene, optionally substituted C_{3-6} cycloalkenylidene, optionally substituted C_{3-8} cycloalkylidene, optionally substituted diglycol to octaglycol acyl, where alkylidene, alkenylidene, cycloalkenylidene, cycloalkylidene, diglycol to octaglycol acyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, R^{Qa1}, $-OR^{Qa1}$, $-SR^{Qa1}$, and $-N(R^{Qa1})_2$, where each R^{Qa1} is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, 3- to 10-membered heterocyclyl, C_{6-10} aryl, and 5- to 10- membered heteroaryl; and

"" denotes to the site covalently attached to the linker moiety L.

2. The compound or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to claim 1, wherein the function group Q^a is selected from the group consisting of


(Qa-1),

(Qa-2),

(Qa-3),

(Qa-4),

(Qa-5),

(Qa-6),

(Qa-7),

(Qa-8),
and

(Qa-9),

where Hal is a halogen selected from the group consisting of Cl, Br and I;

Ar is selected from the group consisting of optionally substituted C_{5-6} cycloalkenyl, optionally substituted C_6 aryl and optionally substituted 5- to 6- membered heteroaryl, where cycloalkenyl, aryl and heteroaryl optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, R^{Qa2}, -OR^{Qa2}, -SR^{Qa2}, and -$N(R^{Qa2})_2$, where each R^{Qa2} is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, 3- to 10-membered heterocyclyl, C_{6-10} aryl, and 5- to 10- membered heteroaryl; and

"*" denotes to the site covalently attached to A;

or, the polypeptide residue L_1 has a sequence as shown below:

$$^{NH}\text{-}AA^1AA^2AA^3\ldots AA^p\text{-}^{COOH},$$

wherein each AA^1, AA^2, AA^3, …AA^p is independently optionally substituted amino acid residue, and at least one of AA^1, AA^2, AA^3, …AA^p is an amino acid residue with a side chain carboxyl group, preferably Glu or Asp;

p is an integer from 3 to 8, preferably from 3 to 5;

"NH-" denotes to N-terminal side of the polypeptide residue;

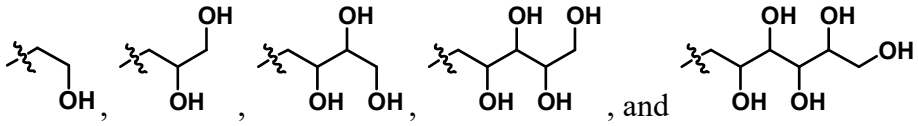
"-COOH" denotes to C-terminal side of the polypeptide residue;

or, each AA1, AA2, AA3, …AAp independently optionally substituted amino acid residue selected from the group consisting of Glu, Asp, Pro, Nva, Leu, Ile, Met, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Arg, Phe, Lys, Val, Ala, Cit, Gly, and N-alkyl amino acids, and at least one of AA1, AA2, AA3, …AAp is Glu or Asp;

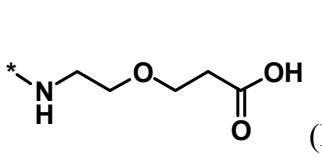
or, AA^1 is an amino acid residue with a side chain carboxyl group, preferably Glu or Asp; each AA^2, AA^3, …AA^p is independently optionally substituted amino acid residue selected from the group consisting of Pro, Nva, Leu, Ile, Met, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Arg, Phe, Lys, Val, Ala, Cit, and Gly;

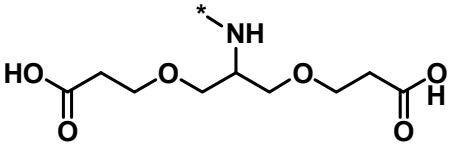
or, the polypeptide residue L_1 is selected from the group consisting of ^{NH}-Glu-Phe-Lys($NR^{Lys1}R^{Lys2}$)-^{COOH}, ^{NH}-Glu-Val-Lys($NR^{Lys1}R^{Lys2}$)-^{COOH}, ^{NH}-Glu-Ala-Ala-Ala-^{COOH}, ^{NH}-Glu-Ala-Ala-^{COOH}, ^{NH}-Glu-Val-Ala-^{COOH}, ^{NH}-Glu-Val-Cit-^{COOH}, ^{NH}-Glu-Gly-Gly-Phe-Gly-^{COOH}, ^{NH}-Asp-Phe-Lys-^{COOH}, ^{NH}-Asp-Ala-Ala-Ala-^{COOH}, ^{NH}-Asp-Val-Ala-^{COOH}, ^{NH}-Asp-Val-Cit-^{COOH}, ^{NH}-Asp-Gly-Gly-Phe-Gly-^{COOH}, and ^{NH}-Asp-Val-Lys($NR^{Lys1}R^{Lys2}$)-^{COOH}, where R^{Lys1} and R^{Lys2} are each independently H or C_{1-6} alkyl;

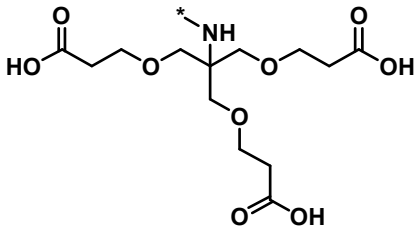
or, the hydrophilic group L_2 has a structure of -NHC(R^{L2a})(R^{L2b})(R^{L2c}), where R^{L2a}, R^{L2b}, and R^{L2c} are each independently selected from the group consisting of H, -$CH_2O(CH_2)_2C(O)OH$, and -$CH_2O(CH_2)_2C(O)NHR^{L2d}$, and at most two of R^{L2a}, R^{L2b}, and R^{L2c} are simultaneously H, R^{L2d} is C_{4-6} alkyl substituted with 3 to 5 hydroxy groups, preferably R^{L2d} is C_{4-6} alkyl substituted with 3 to 5 hydroxy groups, where no more than one hydroxyl group is substituted on each carbon atom, for example, R^{L2d} is selected from the group consisting of:

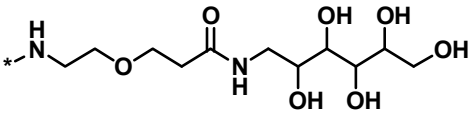

, and ;

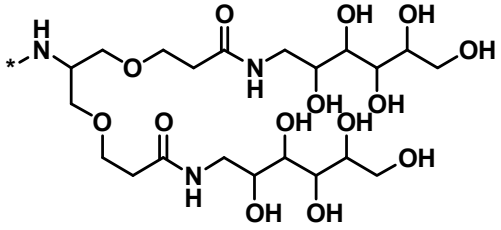
or, the hydrophilic group L_2 is selected from the group consisting of:

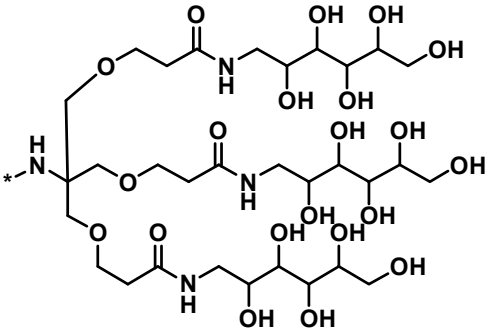

(L_2-1),


(L_2-2),


(L_2-3),

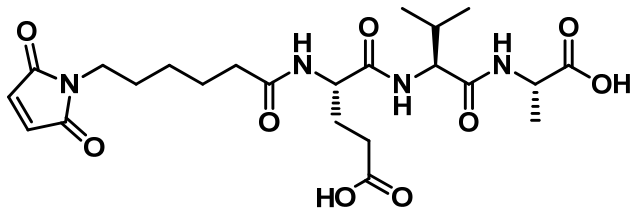

(L_2-4),

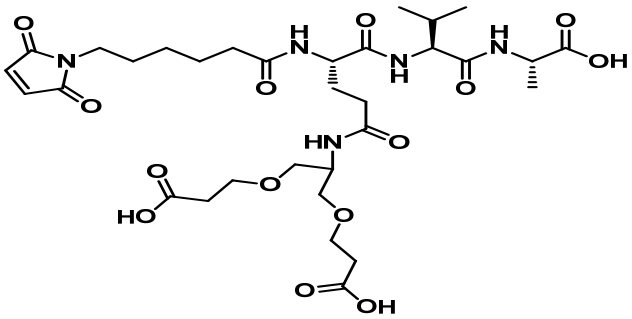

(L_2-5),


(L_2-6),

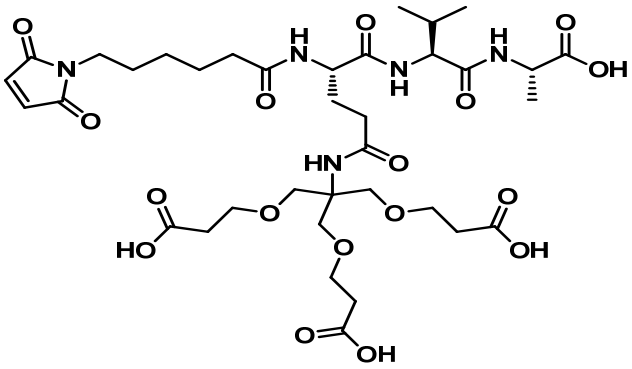
"*" denotes the site covalently attached to polypeptide residue L_1.

3. The compound or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to any of claims 1 to 2, wherein the compound is selected from the group consisting of:

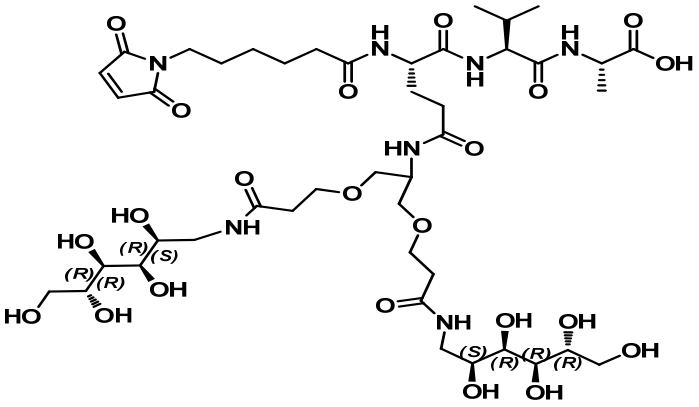

(I)-1



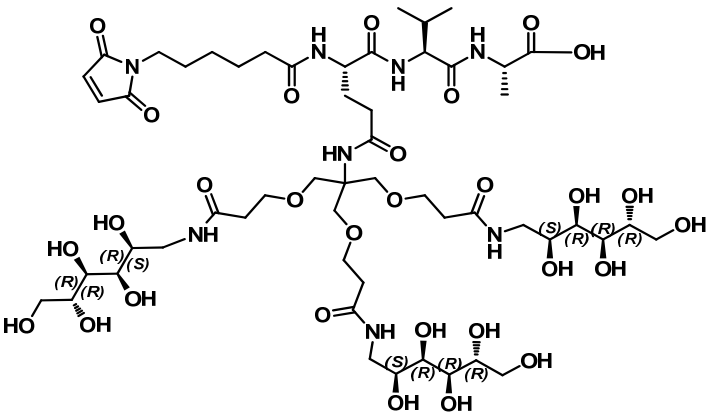
(I)-2



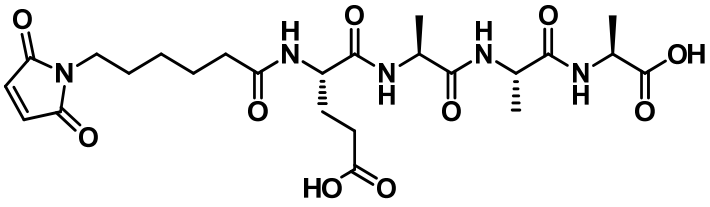
(I)-3



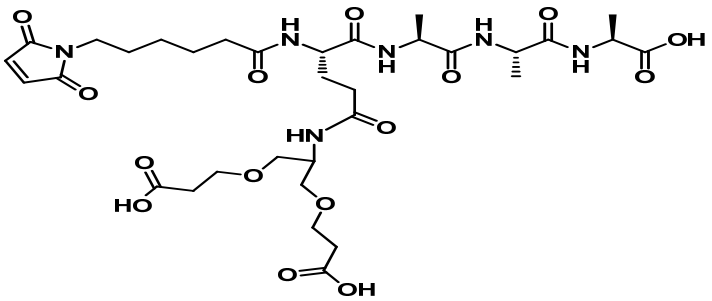
(I)-4



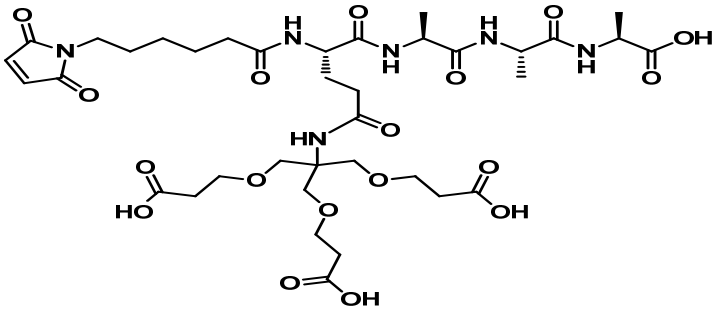
(I)-5



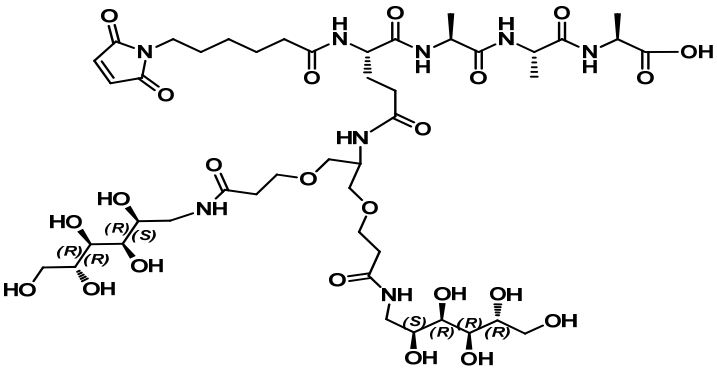
(I)-6



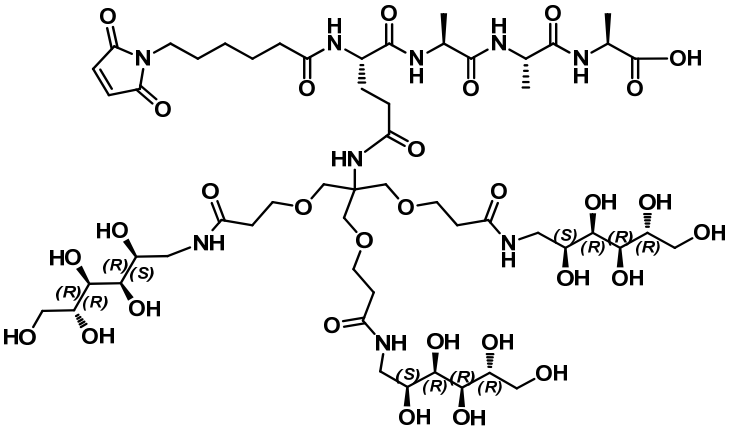
(I)-7



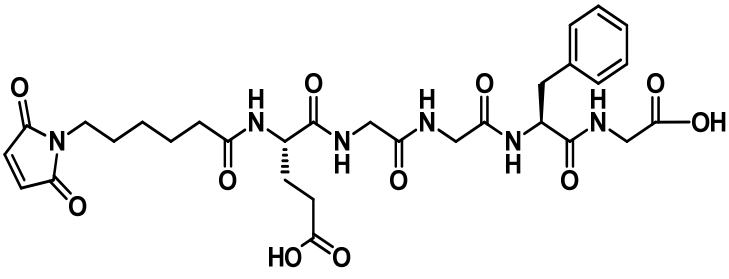
(I)-8



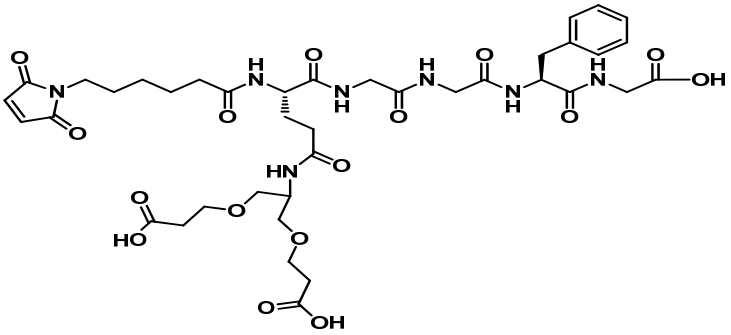
(I)-9



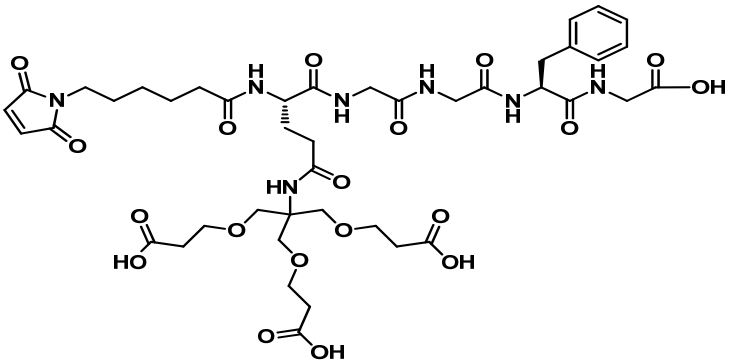
(I)-10



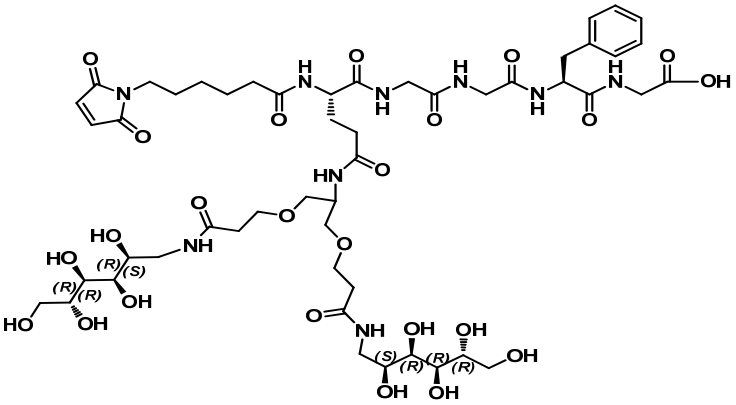
(I)-11



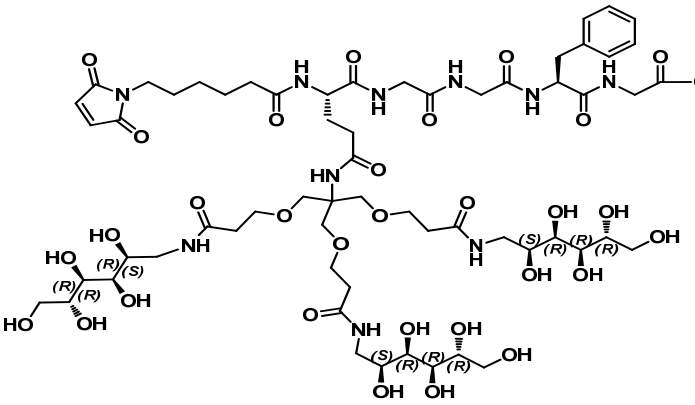
(I)-12



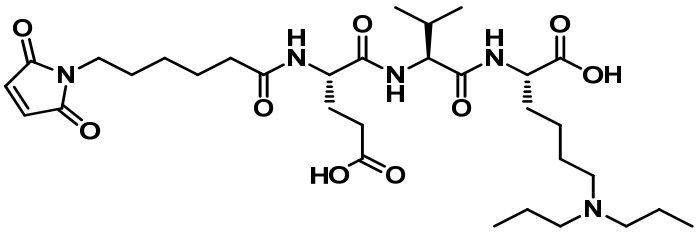
(I)-13



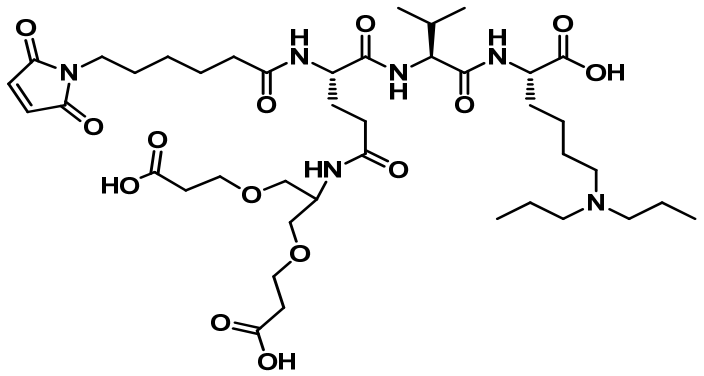
(I)-14



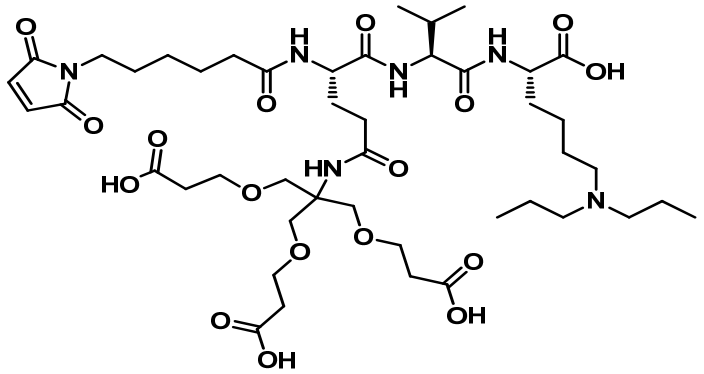
(I)-15



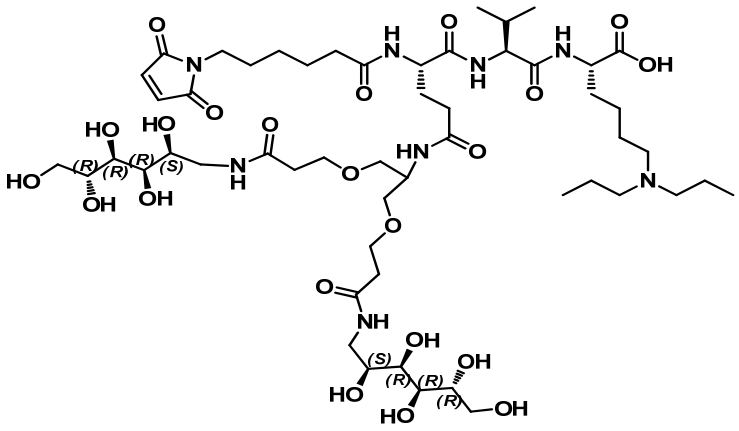
(I)-16



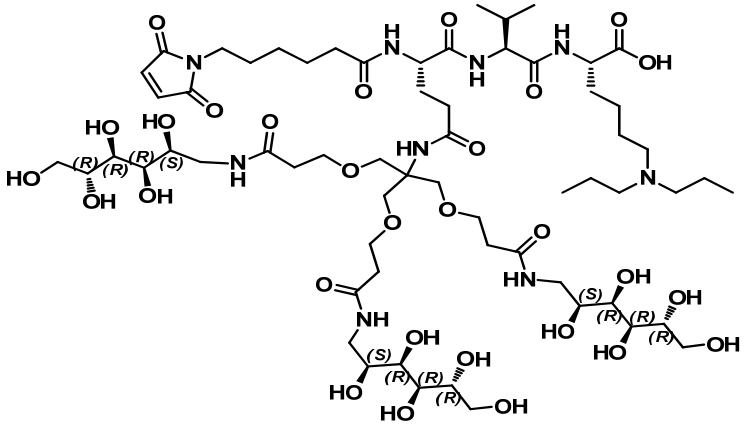
(I)-17



(I)-18

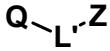


(I)-19



(I)-20.

4. A compound of Formula (II)



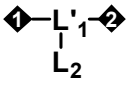
(II)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof, wherein TA denotes to a therapeutic agent;

Z is absent or denotes to an auxiliary moiety connecting L' to the therapeutic agent TA via a bond selected from the group consisting of disulfide, thioether, thioester, hydrazone, ester, ether, carbamate and amide bond;

Q denotes to a junction moiety capable of being coupled to a ligand via a bond selected from the group consisting of carbonyl, thioether, amide, disulfide and hydrazone bond;

L' denotes to a linker moiety connecting Q to the therapeutic agent TA, and having a structure of:



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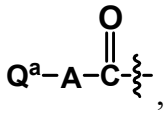
where L'_1 is a polypeptide residue consisting of three to eight amino acid residues which comprises at least one amino acid residue with a side chain carboxyl group;

L_2 is absent or a monodentate, bidentate or tridentate hydrophilic group attached to the side chain carboxyl group on the amino acid residue of the polypeptide residue L_1, and L_2 has a structure of $-NHC(R^{L2a})(R^{L2b})(R^{L2c})$, where R^{L2a}, R^{L2b}, and R^{L2c} are each independently selected from the group consisting of H, $-(CH_2O)(CH_2CH_2O)_m(CH_2)_pC(O)OH$, and $-(CH_2O)(CH_2CH_2O)_m(CH_2)_pC(O)NHR^{L2d}$, R^{L2d} is H or C_{1-6} alkyl optionally substituted with 1 to 6 hydroxy groups, each m is independently an integer from 0 to 10, and each p is independent an integer from 1 to 4;

 denotes to the N-terminal side of the polypeptide residue covalently attached to the junction moiety Q; and

 denotes to the C-terminal side of the polypeptide residue covalently attached to the auxiliary moiety Z or the therapeutic agent TA;

the junction moiety Q has a structure of:



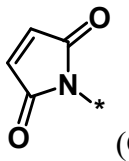
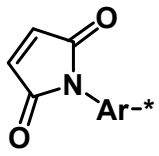
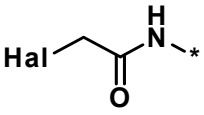
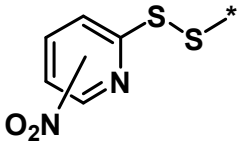
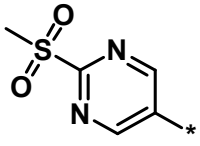
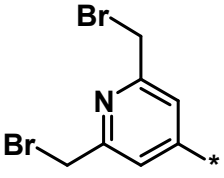
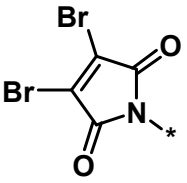
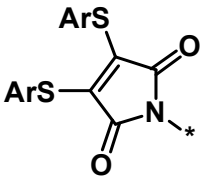
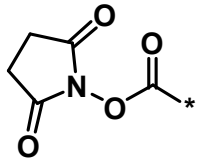
,

wherein Q^a is a function group capable of being coupled to a ligand;

A is selected from optionally substituted C_{3-8} alkylidene, optionally substituted C_{3-8} alkenylidene, optionally substituted C_{3-6} cycloalkenylidene, optionally substituted C_{3-8} cycloalkylidene, optionally substituted diglycol to octaglycol acyl, where alkylidene, alkenylidene, cycloalkenylidene, cycloalkylidene, diglycol to octaglycol acyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, R^{Qa1}, $-OR^{Qa1}$, $-SR^{Qa1}$, and $-N(R^{Qa1})_2$, where each R^{Qa1} is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, 3- to 10-membered heterocyclyl, C_{6-10} aryl, and 5- to 10- membered heteroaryl; and

"〰" denotes to the site covalently attached to the linker moiety L'.

5. The compound or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to claim 4, wherein the function group Q^a is selected from the group consisting of


(Qa-1),

(Qa-2),

(Qa-3),

(Qa-4),

(Qa-5),

(Qa-6),

(Qa-7),

(Qa-8),
and

(Qa-9),

where Hal is a halogen selected from the group consisting of Cl, Br and I;

Ar is selected from the group consisting of optionally substituted C_{5-6} cycloalkenyl, optionally substituted C_{5-6} aryl and optionally substituted 5- to 6- membered heteroaryl, where cycloalkenyl, aryl and heteroaryl optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, R^{Qa2}, $-OR^{Qa2}$, $-SR^{Qa2}$, and $-N(R^{Qa2})_2$, where each R^{Qa2} is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, 3- to 10-membered heterocyclyl, C_{6-10} aryl, and 5- to 10- membered heteroaryl; and

"*" denotes to the site covalently attached to A;

or, the polypeptide residue L'_1 has a sequence as shown below:

$$^{NH}\text{-}AA^1AA^2AA^3\ldots AA^p\text{-}^{C(=O)},$$

wherein each AA^1, AA^2, AA^3, …AA^p is independently optionally substituted amino acid residue, and at least one of AA^1, AA^2, AA^3, …AA^p is an amino acid residue with a side chain carboxyl group, preferably Glu or Asp;

p is an integer from 3 to 8, preferably from 3 to 5;

"NH-" denotes to N-terminal side of the polypeptide residue;

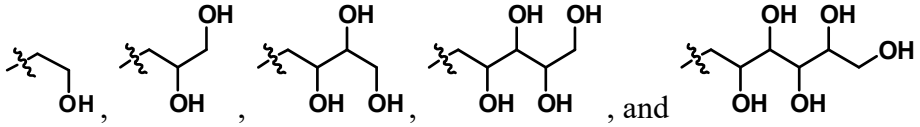
"-C(=O)" denotes to C-terminal side of the polypeptide residue;

or, each AA^1, AA^2, AA^3, …AA^p independently optionally substituted amino acid residue selected from the group consisting of Glu, Asp, Pro, Nva, Leu, Ile, Met, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Arg, Phe, Lys, Val, Ala, Cit, Gly, and N-alkyl amino acids, and at least one of AA^1, AA^2, AA^3, …AA^p is Glu or Asp;

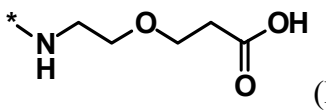
or, AA^1 is an amino acid residue with a side chain carboxyl group, preferably Glu or Asp; each AA^2, AA^3, …AA^p is independently optionally substituted amino acid residue selected from the group consisting of Pro, Nva, Leu, Ile, Met, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Arg, Phe, Lys, Val, Ala, Cit, and Gly;

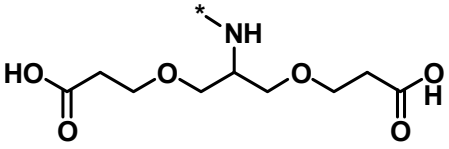
or, the polypeptide residue L'_1 is selected from the group consisting of ^{NH}-Glu-Phe-Lys($NR^{Lys1}R^{Lys2}$)-$^{C(=O)}$, ^{NH}-Glu-Val-Lys($NR^{Lys1}R^{Lys2}$)-$^{C(=O)}$, ^{NH}-Glu-Ala-Ala-Ala-$^{C(=O)}$, ^{NH}-Glu-Ala-Ala-$^{C(=O)}$, ^{NH}-Glu-Val-Ala-$^{C(=O)}$, ^{NH}-Glu-Val-Cit-$^{C(=O)}$, ^{NH}-Glu-Gly-Gly-Phe-Gly-$^{C(=O)}$, ^{NH}-Asp-Phe-Lys-$^{C(=O)}$, ^{NH}-Asp-Ala-Ala-Ala-$^{C(=O)}$, ^{NH}-Asp-Val-Ala-$^{C(=O)}$, ^{NH}-Asp-Val-Cit-$^{C(=O)}$, ^{NH}-Asp-Gly-Gly-Phe-Gly-$^{C(=O)}$, and ^{NH}-Asp-Val-Lys($NR^{Lys1}R^{Lys2}$)-$^{C(=O)}$, where R^{Lys1} and R^{Lys2} are each independently H or C_{1-6} alkyl;

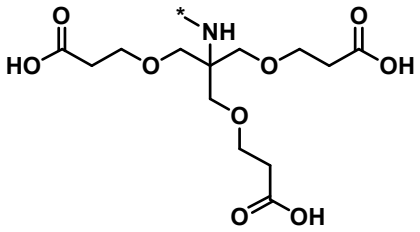
or, the hydrophilic group L_2 has a structure of $-NHC(R^{L2a})(R^{L2b})(R^{L2c})$, where R^{L2a}, R^{L2b}, and R^{L2c} are each independently selected from the group consisting of H, $-CH_2O(CH_2)_2C(O)OH$, and $-CH_2O(CH_2)_2C(O)NHR^{L2d}$, and at most two of R^{L2a}, R^{L2b}, and R^{L2c} are simultaneously H, R^{L2d} is C_{4-6} alkyl substituted with 3 to 5 hydroxy groups, preferably R^{L2d} is C_{4-6} alkyl substituted with 3 to 5 hydroxy groups, where no more than one hydroxyl group is substituted on each carbon atom, for example, R^{L2d} is selected from the group consisting of:

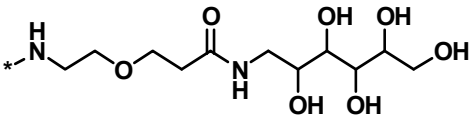

, and ;

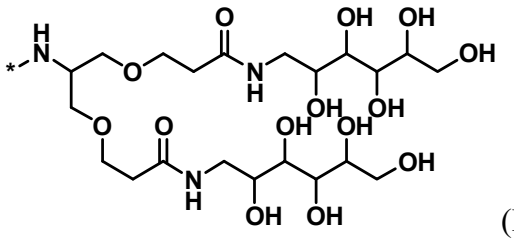
or, the hydrophilic group L_2 is selected from the group consisting of:

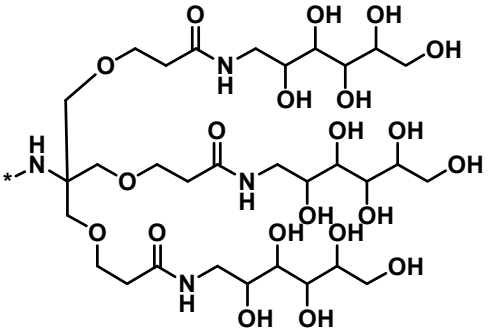

(L_2-1),


(L_2-2),


(L_2-3),


(L_2-4),


(L_2-5),

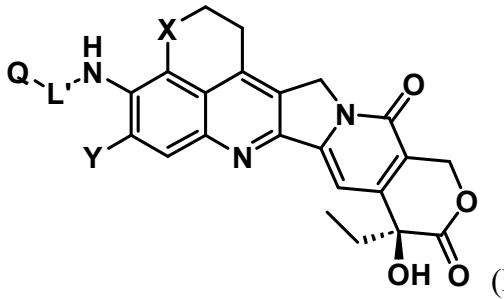

(L_2-6),

"*" denotes to the site covalently attached to polypeptide residue L'_1;

or, the auxiliary moiety Z is selected from the group consisting of mercapto, disulfide, amino, carboxyl, aldehyde, maleimide, haloacetyl, hydrazide and hydroxyl groups;

or, the therapeutic agent is a cytotoxic or cytostatic agent, e.g. a camptothecin compound, an analogue or a derivative thereof;

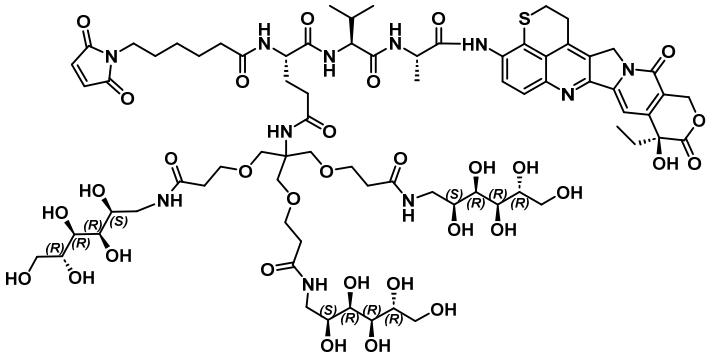
or, the compound is a compound of Formula (II'):


(II'),

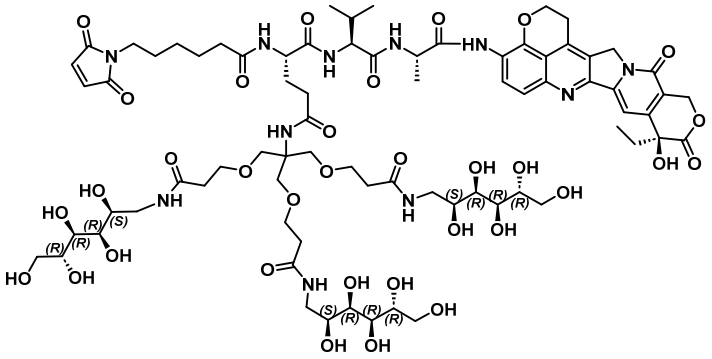
X is selected from the group consisting of $-CH_2-$, O and S; Y is selected from the group consisting of H, D, and F;

Q and L' are as defined in the preceding claims.

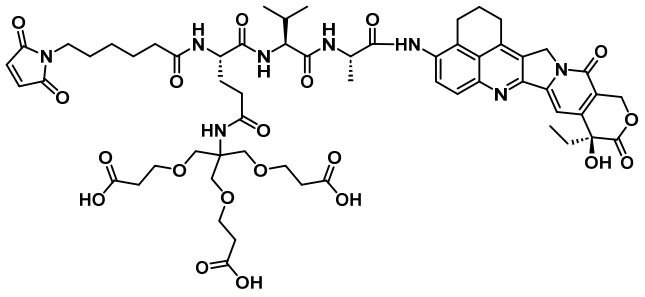
6. The compound or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to any of claims 4 to 5, wherein the compound is selected from the group consisting of:



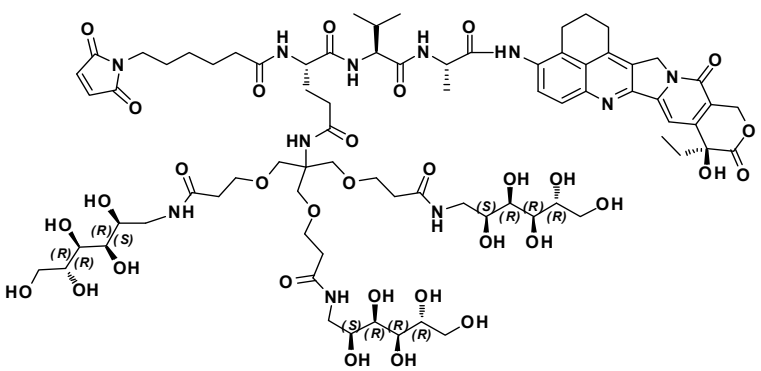
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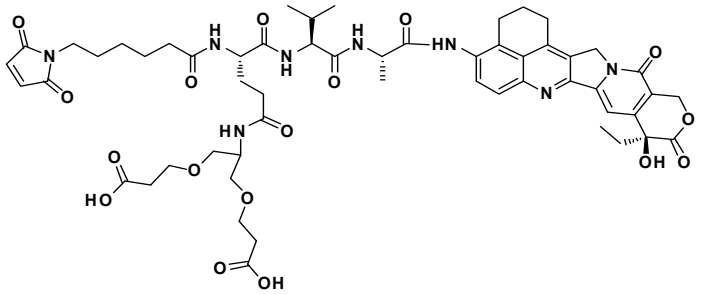
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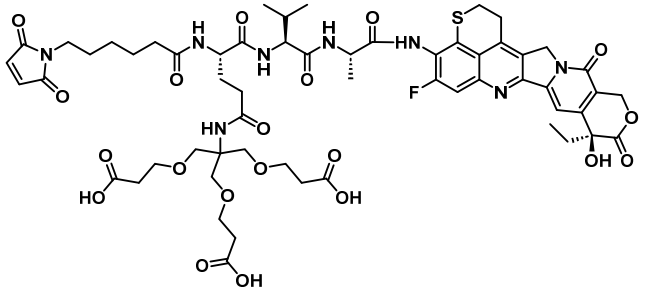
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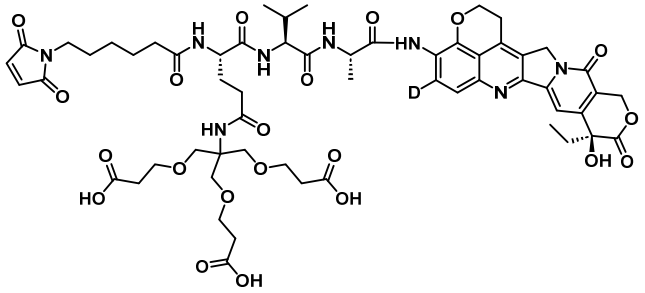
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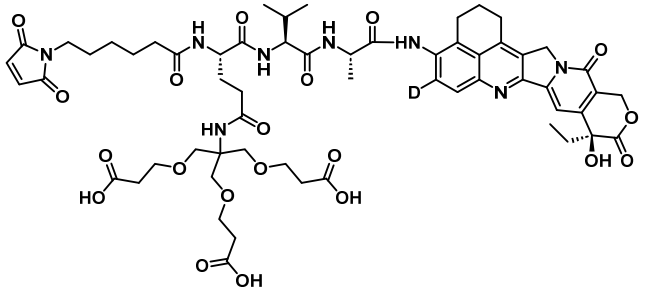
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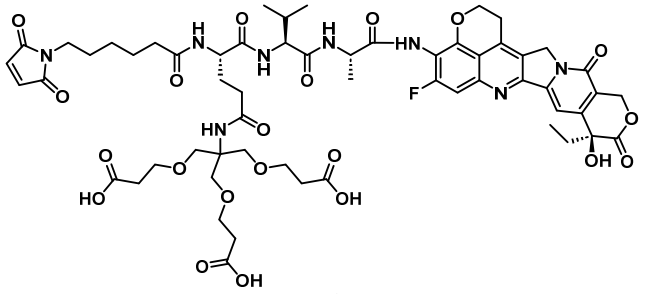
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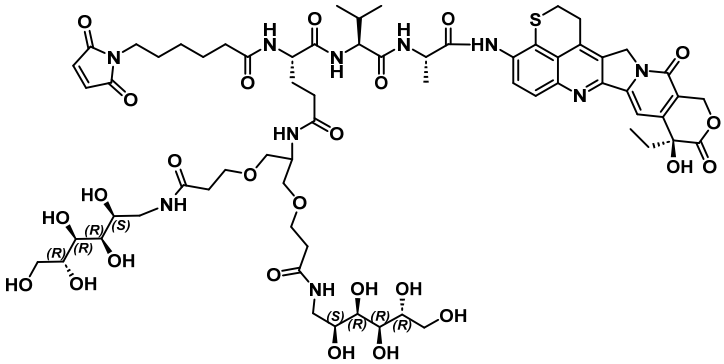
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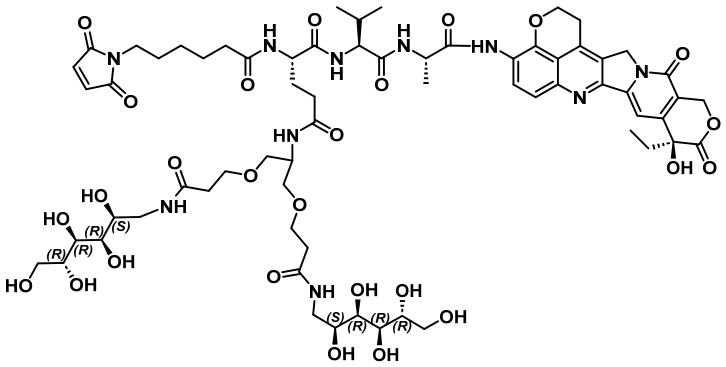
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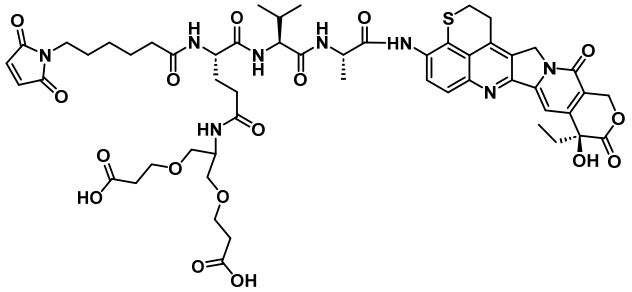
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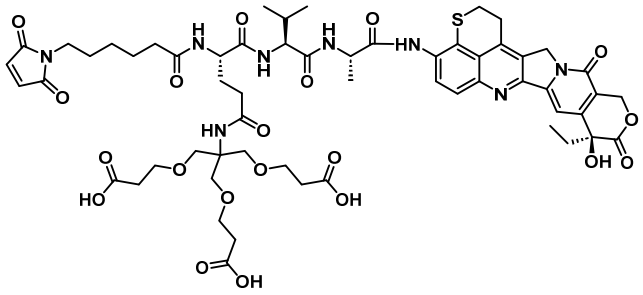
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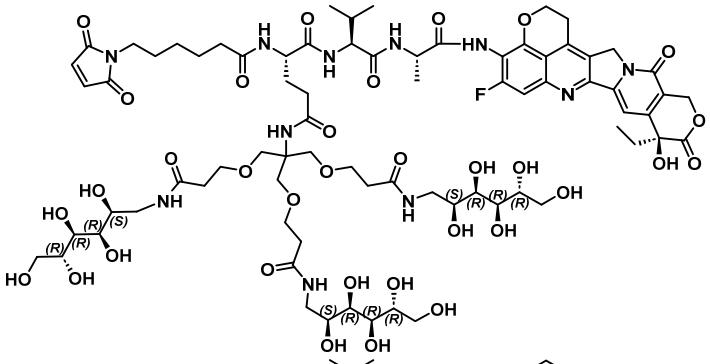
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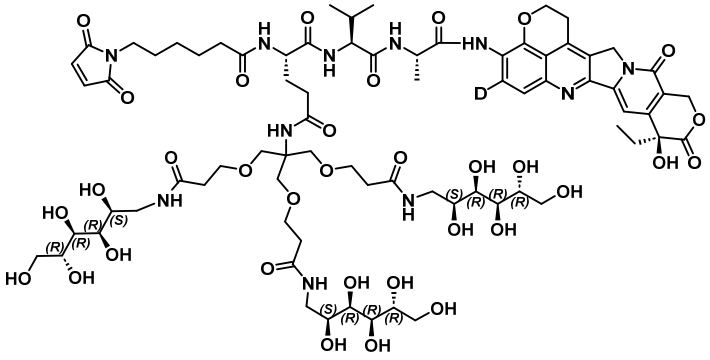
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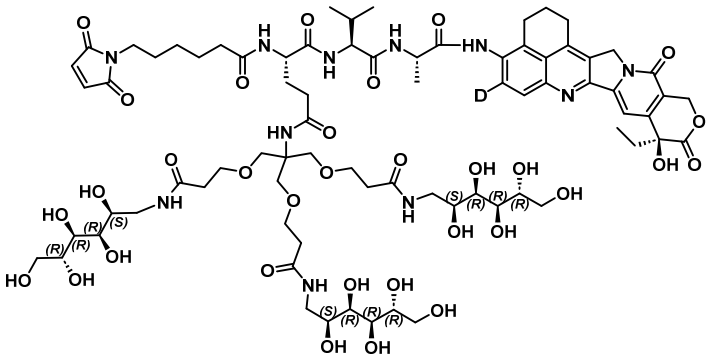
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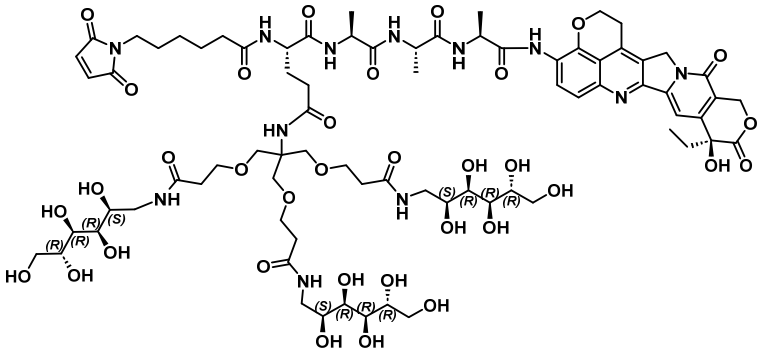
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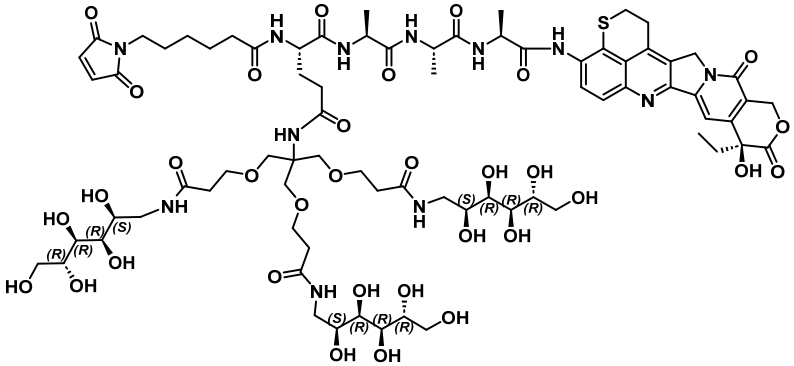
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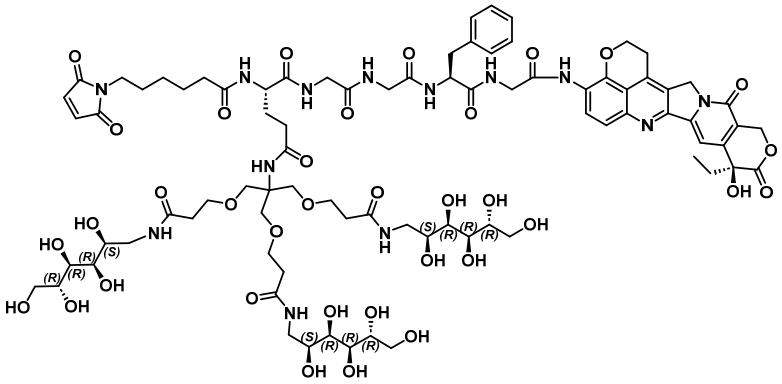
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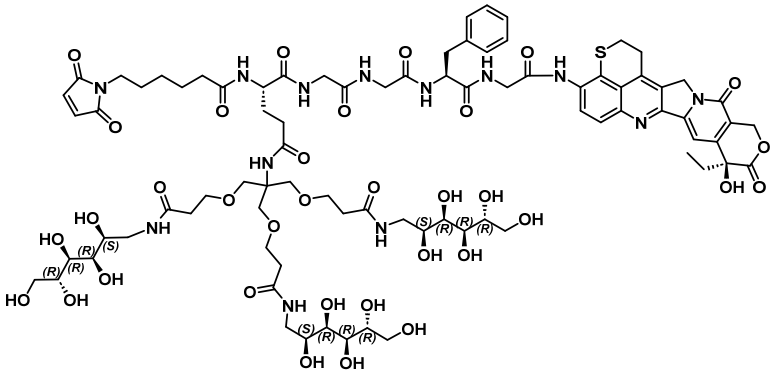
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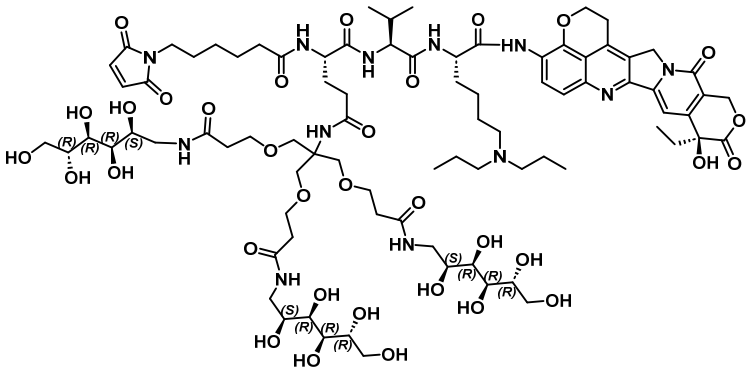
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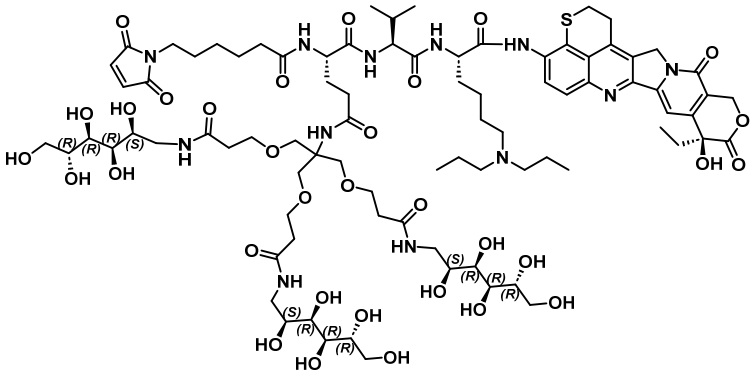
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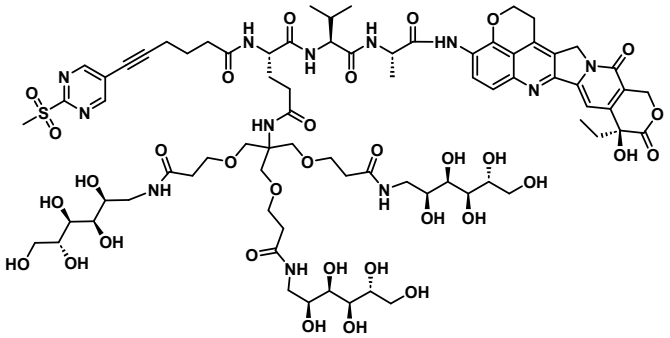
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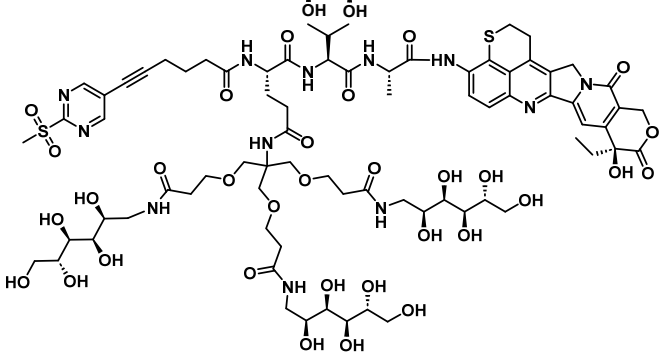
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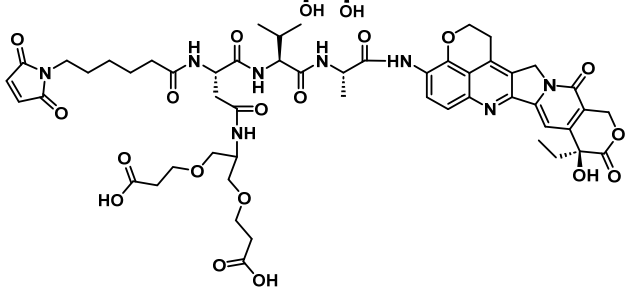
(II')-22



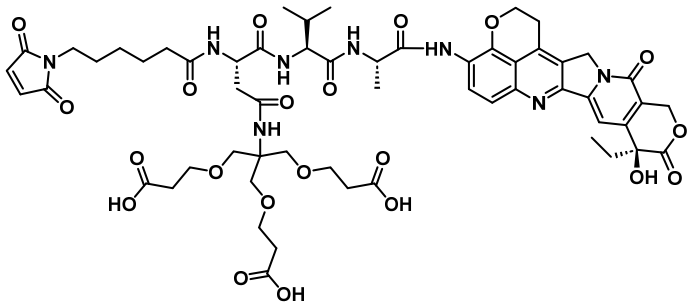
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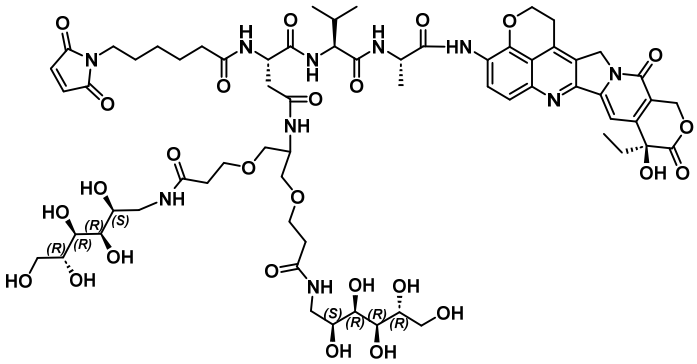
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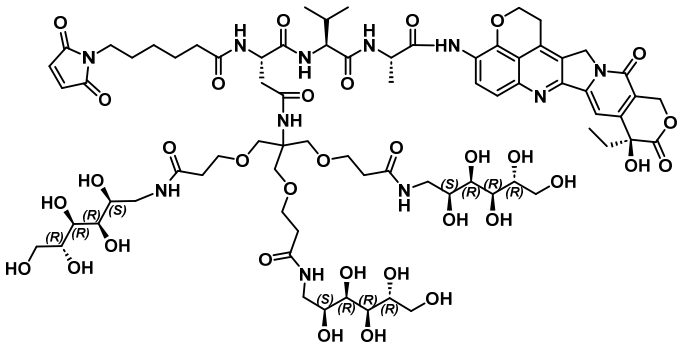
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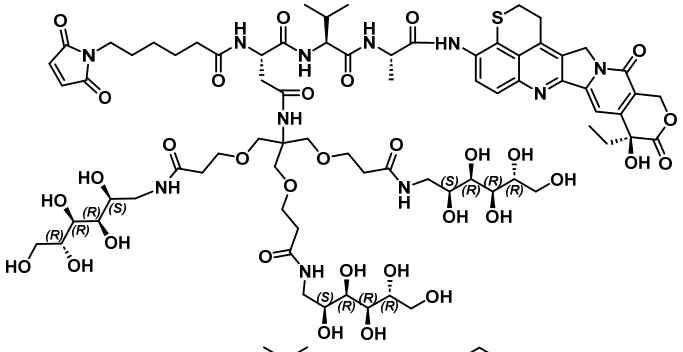
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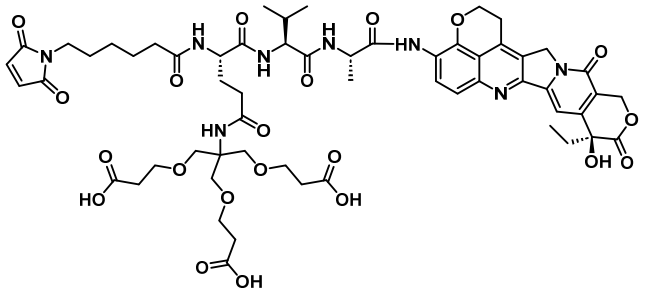
(II')-27



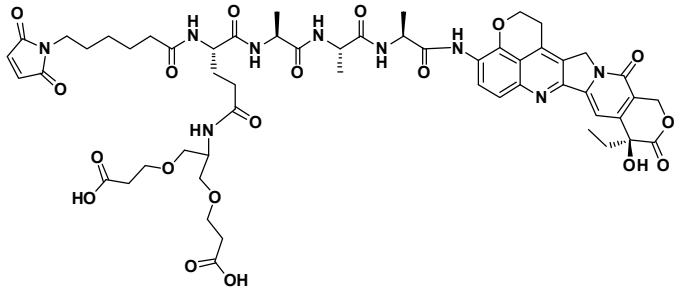
(II')-28



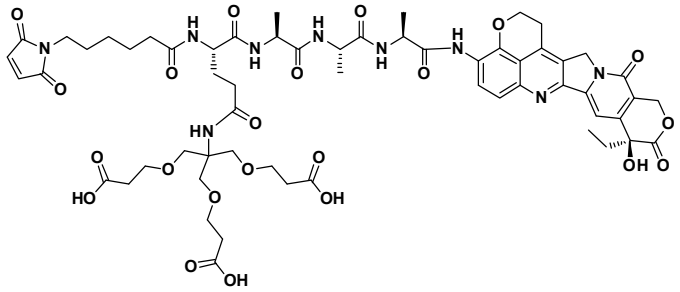
(II')-29



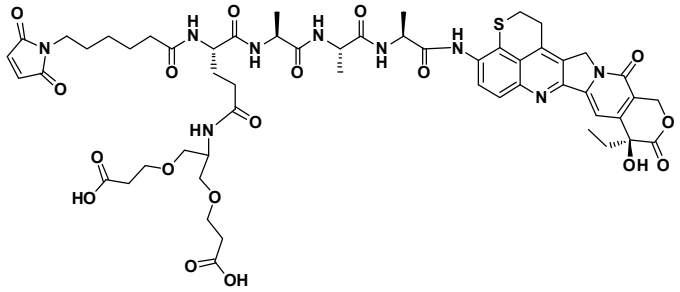
(II')-30



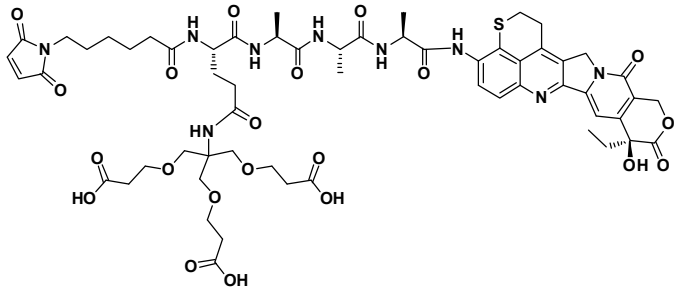
(II')-31



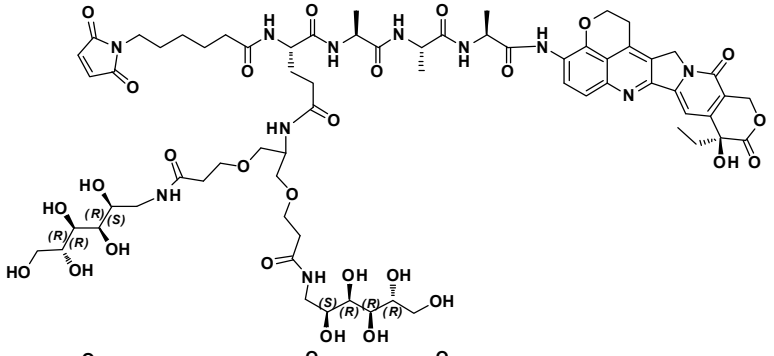
(II')-32



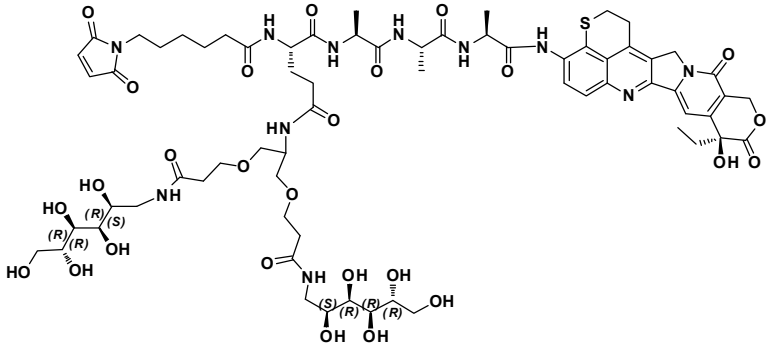
(II')-33



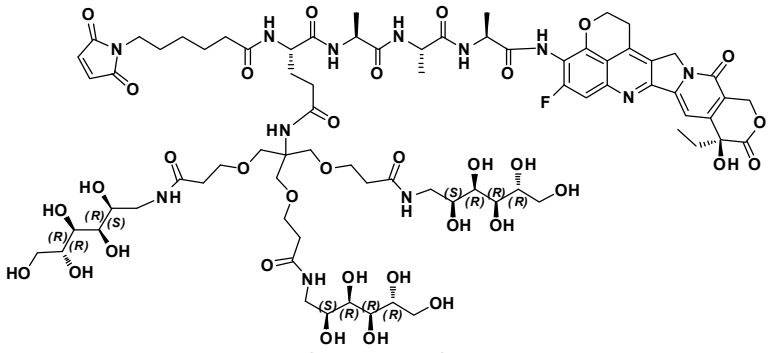
(II')-34



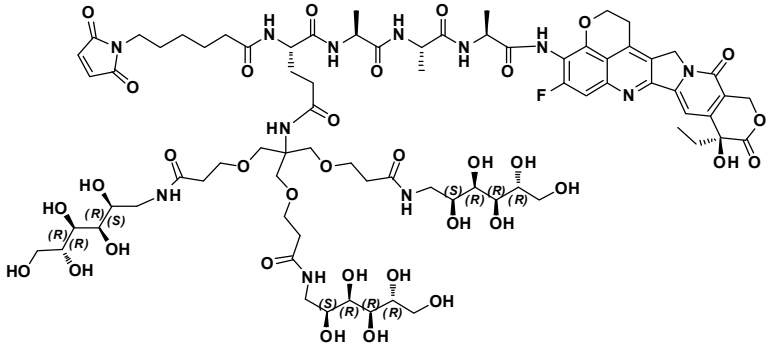
(II')-35



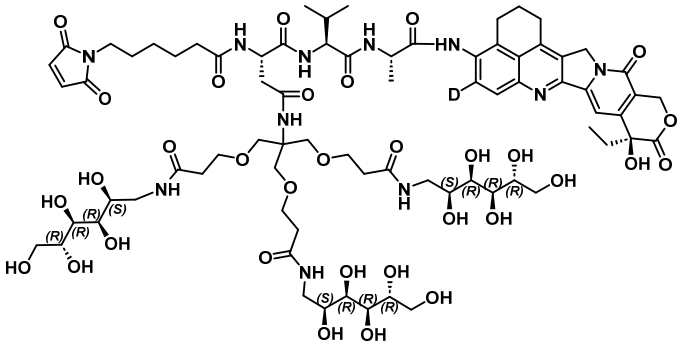
(II')-36



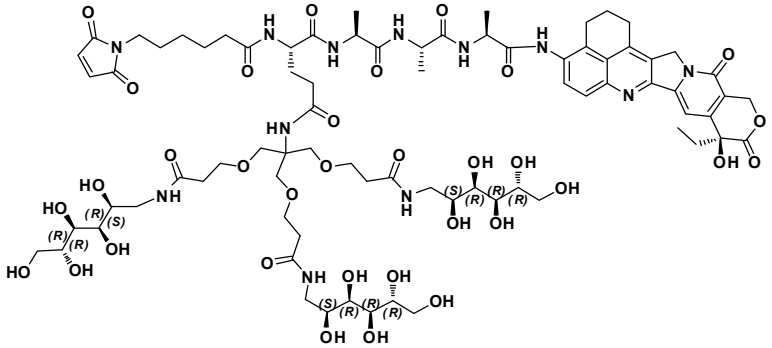
(II')-37



(II')-38

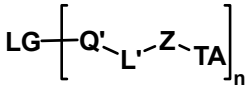


(II')-39



(II')-40.

7. A ligand-drug conjugate of Formula (III):



(III)

or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof, wherein

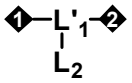
LG denotes to a ligand;

TA denotes to a therapeutic agent;

Z is absent or denotes to an auxiliary moiety connecting L' to the therapeutic agent TA via a bond selected from the group consisting of disulfide, thioether, thioester, hydrazone, ester, ether, carbamate and amide bond;

Q’ denotes to a junction moiety coupled to the ligand LG via a bond selected from the group consisting of carbonyl, thioether, amide, disulfide and hydrazone bond;

L’ denotes to a linker moiety connecting Q to the therapeutic agent TA, and having a structure of:



,

where L'_1 is a polypeptide residue consisting of three to eight amino acid residues which comprises at least one amino acid residue with a side chain carboxyl group;

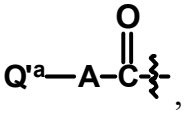
L_2 is absent or a monodentate, bidentate or tridentate hydrophilic group attached to the side chain carboxyl group on the amino acid residue of the polypeptide residue L_1, and L_2 has a structure of $-NHC(R^{L2a})(R^{L2b})(R^{L2c})$, where R^{L2a}, R^{L2b}, and R^{L2c} are each independently selected from the group consisting of H, $-(CH_2O)(CH_2CH_2O)_m(CH_2)_pC(O)OH$, and $-(CH_2O)(CH_2CH_2O)_m(CH_2)_pC(O)NHR^{L2d}$, R^{L2d} is H or C_{1-6} alkyl optionally substituted with 1 to 6 hydroxy groups, each m is independently an integer from 0 to 10, and each p is independent an integer from 1 to 4;

❶ denotes to the N-terminal side of the polypeptide residue covalently attached to the junction moiety Q’;

❷ denotes to the C-terminal side of the polypeptide residue covalently attached to the therapeutic agent TA; and

n is a number in the range from 1 to 8;

the junction moiety Q’ has a structure of:



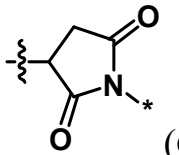
,

wherein Q'^a is a function group capable of being coupled to a ligand;

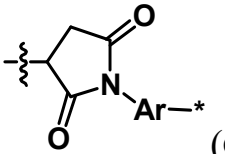
A is selected from optionally substituted C_{3-8} alkylidene, optionally substituted C_{3-8} alkenylidene, optionally substituted C_{3-6} cycloalkenylidene, optionally substituted C_{3-8} cycloalkylidene, optionally substituted diglycol to octaglycol acyl, where alkylidene, alkenylidene, cycloalkenylidene, cycloalkylidene, diglycol to octaglycol acyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, $R^{Q'a1}$, $-OR^{Q'a1}$, $-SR^{Q'a1}$, and $-N(R^{Q'a1})_2$, where each $R^{Q'a1}$ is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, 3- to 10-membered heterocyclyl, C_{6-10} aryl, and 5- to 10-membered heteroaryl; and

“ ” denotes to the site covalently attached to the linker moiety L’.

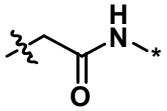
8. The ligand-drug conjugate or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to claim 7, wherein the junction moiety Q'^a is selected from the group consisting of:



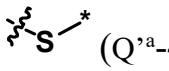
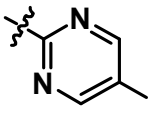
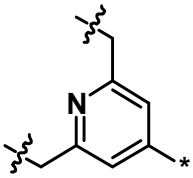
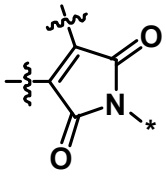
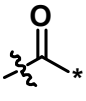
(Q'^a-1),



(Q'^a-2),



(Q'^a-3),


(Q'^{a}-4),

(Q'^{a}-5),

(Q'^{a}-6),

(Q'^{a}-7), and

(Q'^{a}-8),

where, Ar is selected from the group consisting of optionally substituted C_{5-6} cycloalkenyl, optionally substituted C_{5-6} aryl and optionally substituted 5- to 6- membered heteroaryl, where cycloalkenyl, aryl and heteroaryl optionally substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, R^{Qa2}, -OR^{Qa2}, -SR^{Qa2}, and -$N(R^{Qa2})_2$, where each R^{Qa2} is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, 3- to 10-memberedheterocyclyl, C_{6-10} aryl, and 5- to 10- membered heteroaryl;

"*" denotes to the site covalently attached to A;

"〰" denotes to the site covalently attached to the ligand LG;

or, the polypeptide residue L'_1 has a sequence as shown below:

$$^{NH}\text{-}AA^1AA^2AA^3\ldots AA^p\text{-}^{C(=O)},$$

wherein each AA^1, AA^2, AA^3, …AA^p is independently optionally substituted amino acid residue, and at least one of AA^1, AA^2, AA^3, …AA^p is an amino acid residue with a side chain carboxyl group, preferably Glu or Asp;

p is an integer from 3 to 8, preferably from 3 to 5;

"NH-" denotes to N-terminal side of the polypeptide residue;

"-C(=O)" denotes to C-terminal side of the polypeptide residue;

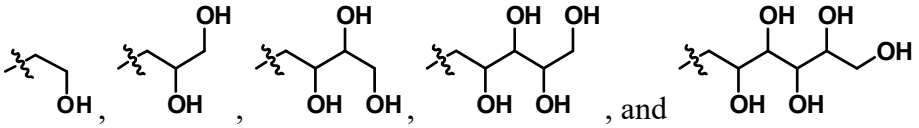
or, each AA^1, AA^2, AA^3, …AA^p independently optionally substituted amino acid residue selected from the group consisting of Glu, Asp, Pro, Nva, Leu, Ile, Met, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Arg, Phe, Lys, Val, Ala, Cit, Gly, and N-alkyl amino acids, and at least one of AA^1, AA^2, AA^3, …AA^p is Glu or Asp;

or, AA^1 is an amino acid residue with a side chain carboxyl group, preferably Glu or Asp; each AA^2, AA^3, …AA^p is independently optionally substituted amino acid residue selected from the group consisting of Pro, Nva, Leu, Ile, Met, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Arg, Phe, Lys, Val, Ala, Cit, and Gly;

or, the polypeptide residue L'_1 is selected from the group consisting of ^{NH}-Glu-Phe-Lys($NR^{Lys1}R^{Lys2}$)-$^{C(=O)}$, ^{NH}-Glu-Val-Lys($NR^{Lys1}R^{Lys2}$)-$^{C(=O)}$, ^{NH}-Glu-Ala-Ala-Ala-$^{C(=O)}$, ^{NH}-Glu-Ala-Ala-$^{C(=O)}$, ^{NH}-Glu-Val-Ala-$^{C(=O)}$, ^{NH}-Glu-Val-Cit-$^{C(=O)}$, ^{NH}-Glu-Gly-Gly-Phe-Gly-$^{C(=O)}$, ^{NH}-Asp-Phe-Lys-$^{C(=O)}$, ^{NH}-Asp-Ala-Ala-Ala-$^{C(=O)}$, ^{NH}-Asp-Val-Ala-$^{C(=O)}$, ^{NH}-Asp-Val-Cit-$^{C(=O)}$, ^{NH}-Asp-Gly-Gly-Phe-Gly-$^{C(=O)}$, and ^{NH}-Asp-Val-Lys($NR^{Lys1}R^{Lys2}$)-$^{C(=O)}$, where R^{Lys1} and R^{Lys2} are each independently H or C_{1-6} alkyl;

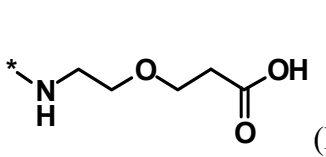
or, the hydrophilic group L_2 has a structure of -$NHC(R^{L2a})(R^{L2b})(R^{L2c})$, where R^{L2a}, R^{L2b}, and R^{L2c} are each independently selected from the group consisting of H, -$CH_2O(CH_2)_2C(O)OH$, and -$CH_2O(CH_2)_2C(O)NHR^{L2d}$, and at most two of R^{L2a}, R^{L2b}, and R^{L2c} are simultaneously H, R^{L2d} is C_{4-6} alkyl substituted with 3 to 5 hydroxy groups, preferably R^{L2d} is C_{4-6} alkyl substituted with 3 to 5 hydroxy groups, where no more than one hydroxyl group is

substituted on each carbon atom, for example, R^{L2d} is selected from the group consisting of:

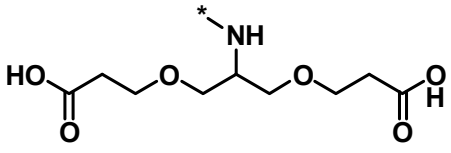


, and ;

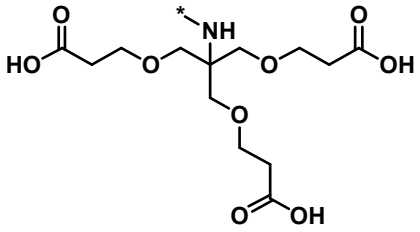
or, the hydrophilic group L_2 is selected from the group consisting of:



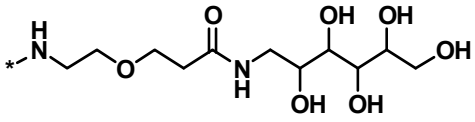
(L_2-1),



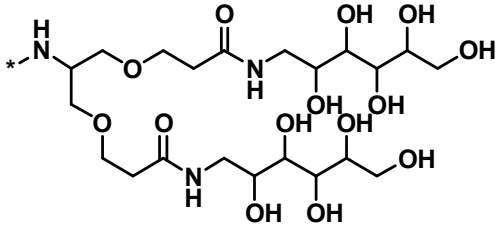
(L_2-2),



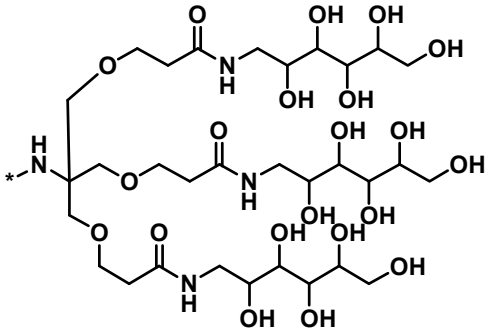
(L_2-3),



(L_2-4),



(L_2-5),



(L_2-6),

"*" denotes to the site covalently attached to polypeptide residue L'1;

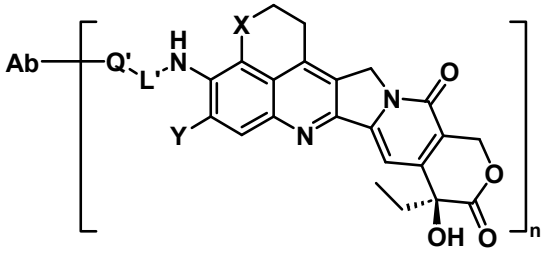
or, the auxiliary moiety Z is selected from the group consisting of mercapto, disulfide, amino, carboxyl, aldehyde, maleimide, haloacetyl, hydrazide and hydroxyl groups;

or, the ligand LG is an antibody or antigen-binding fragment thereof;

or, the therapeutic agent is a cytotoxic or cytostatic agent;

or, the therapeutic agent is a camptothecin compound, an analogue or a derivative thereof;

or, the ligand-drug conjugate is a compound of Formula (III'):



(III')

or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof, wherein

X is selected from the group consisting of -CH_2-, O, and S; Y is selected from the group consisting of H, D, and F;

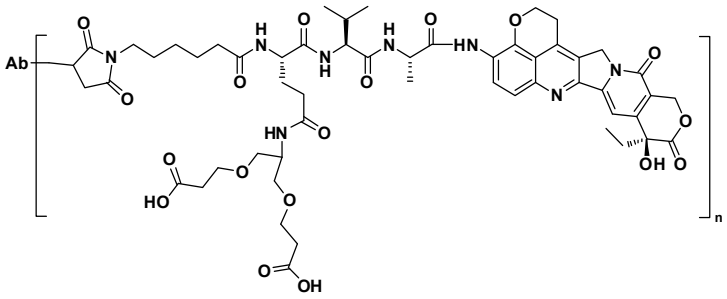
Ab denotes to an antibody;

Q and L' are as defined in the preceding claims; and

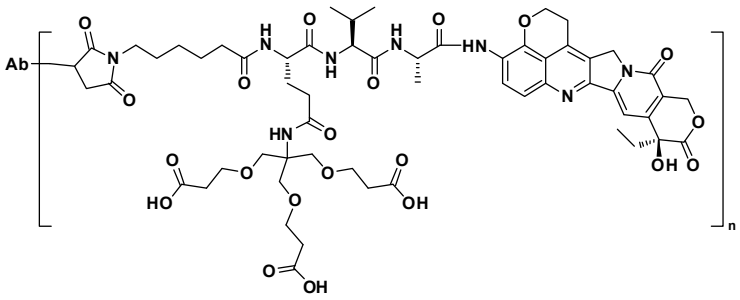
n is a number in the range from 1 to 8.

9. The ligand-drug conjugate or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to any of claims 7 to 8, wherein the ligand-drug conjugate

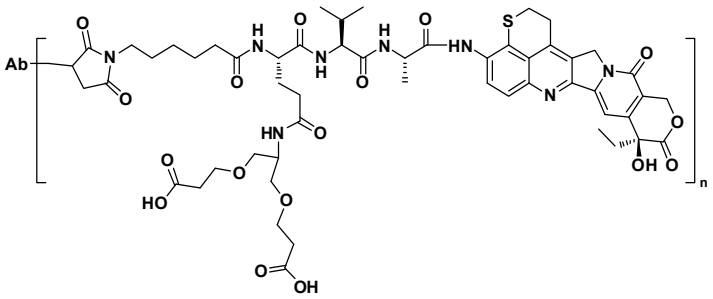
is selected from the group consisting of:



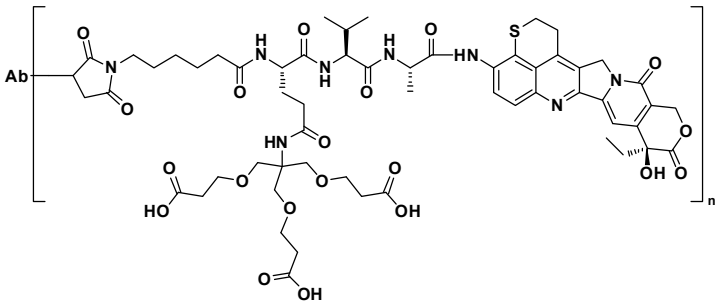
(III')-1



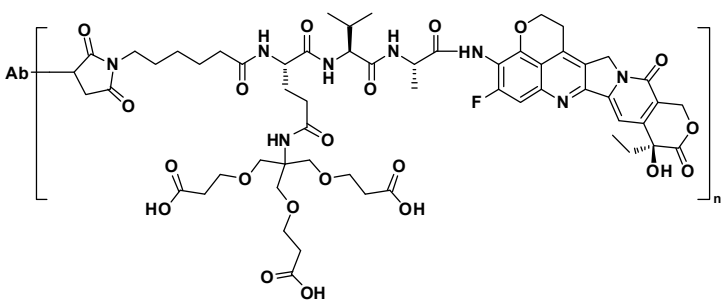
(III')-2



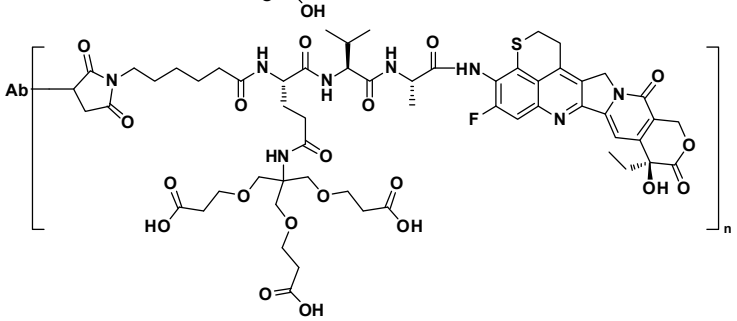
(III')-3



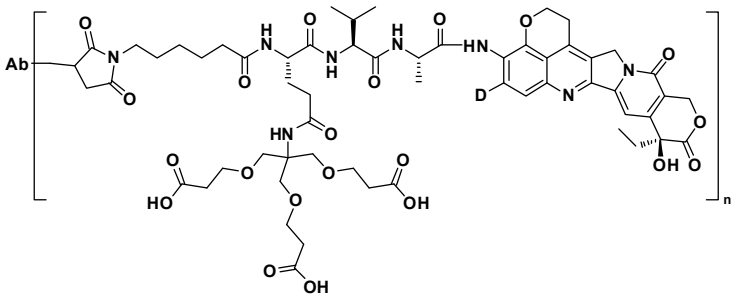
(III')-4



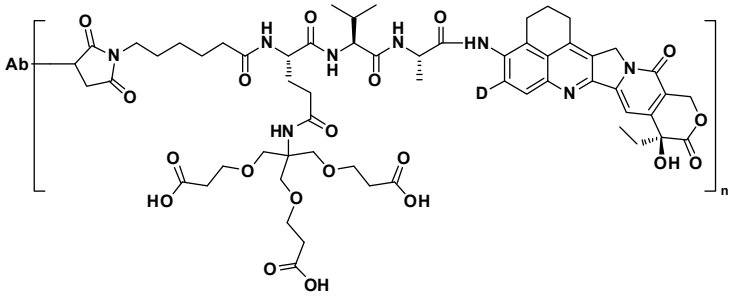
(III')-5



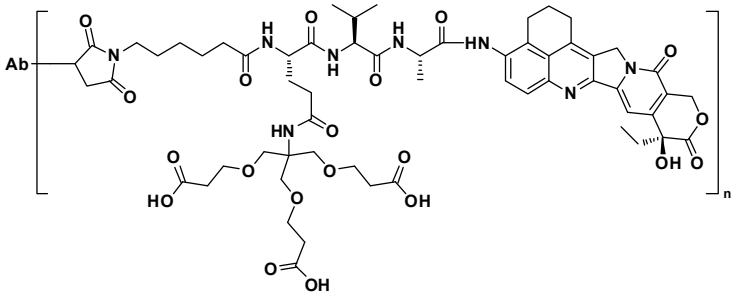
(III')-6



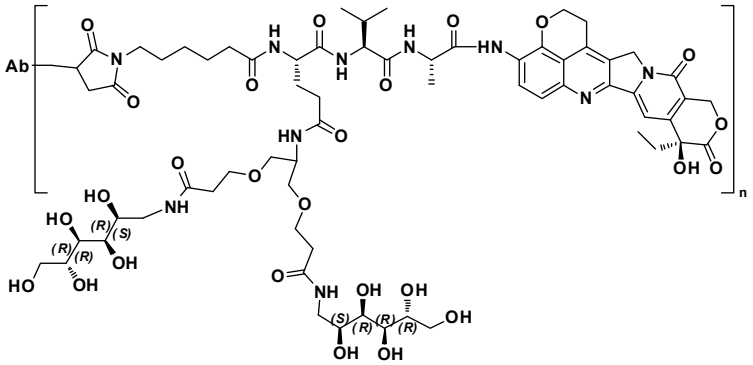
(III')-7



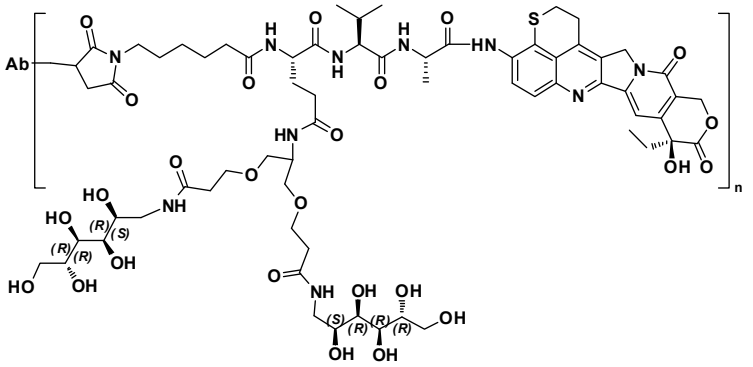
(III')-8



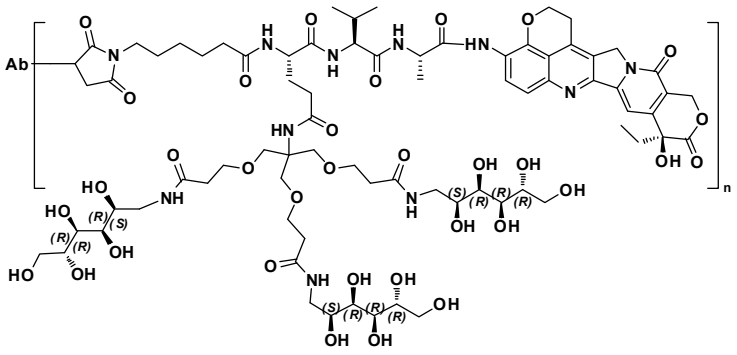
(III')-9



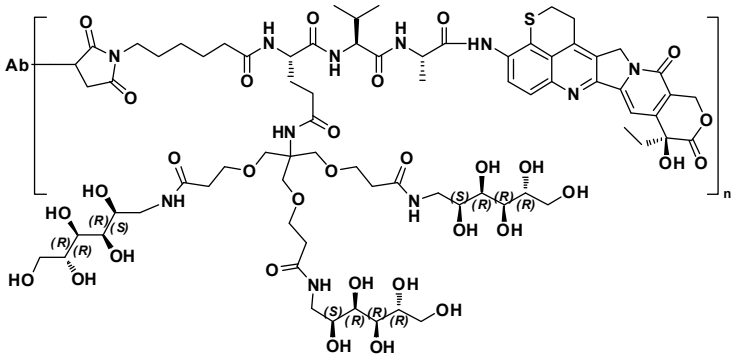
(III')-10



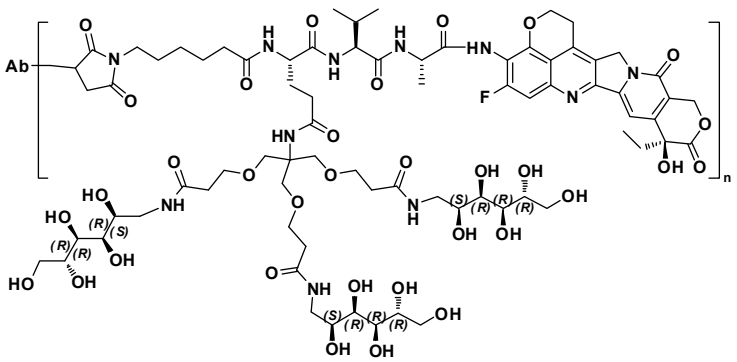
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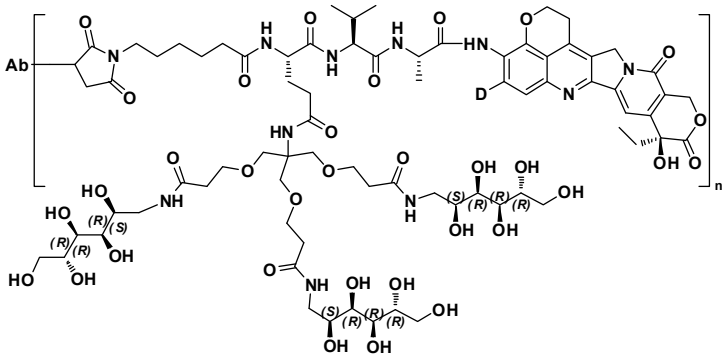
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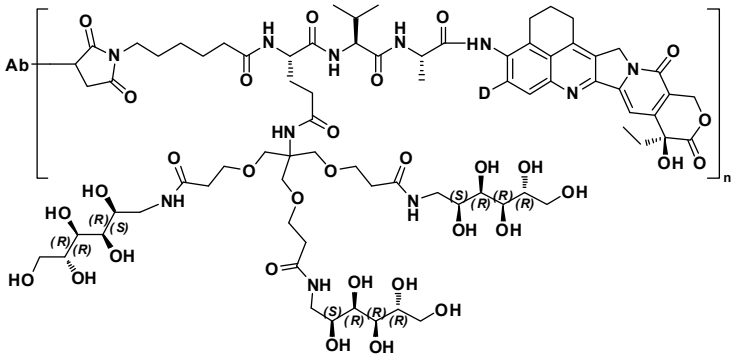
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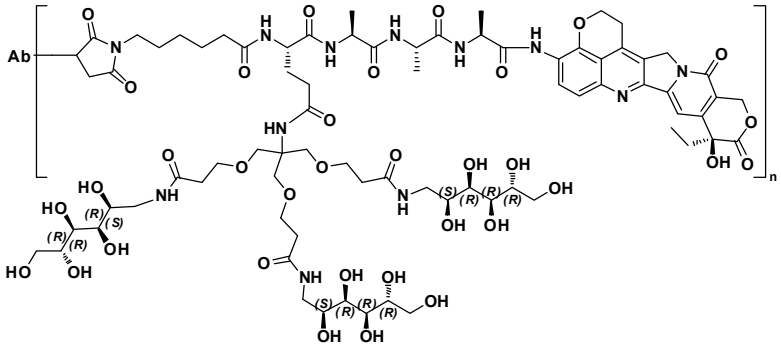
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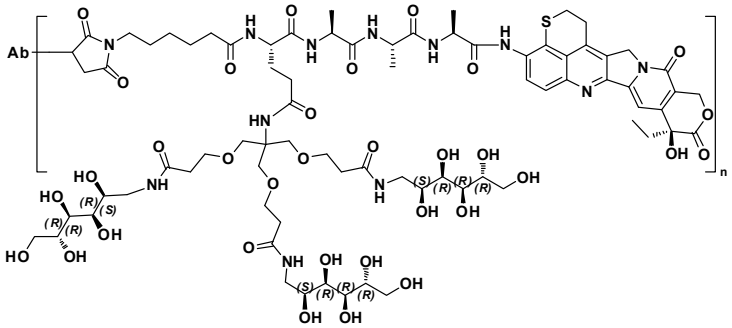
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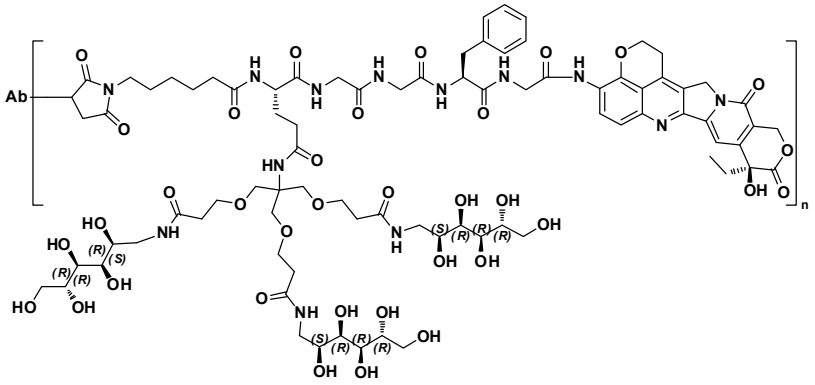
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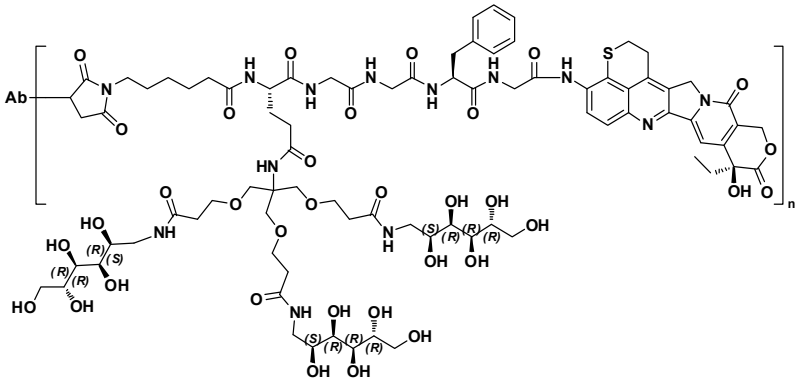
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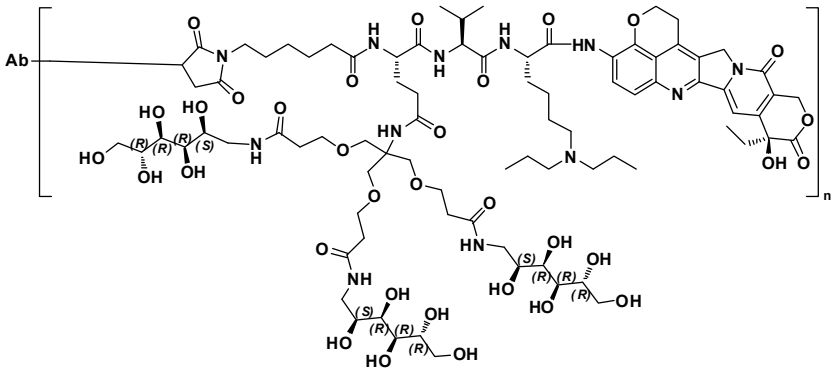
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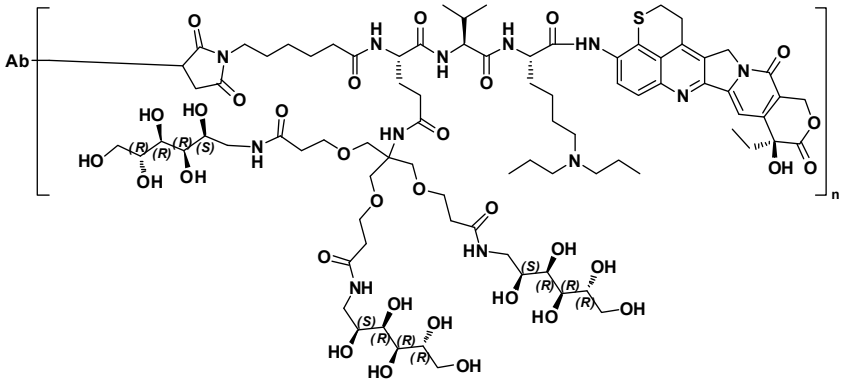
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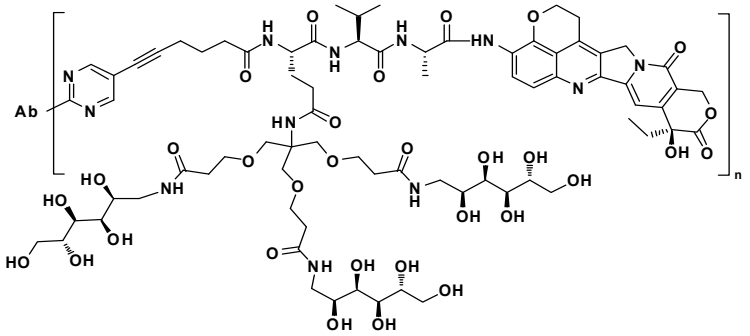
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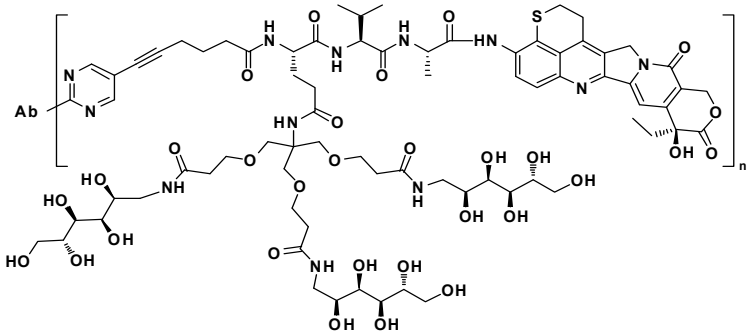
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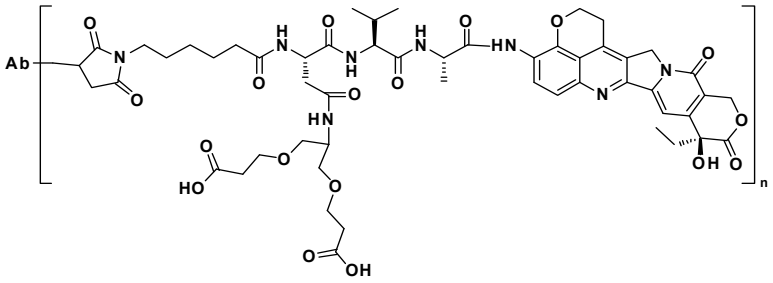
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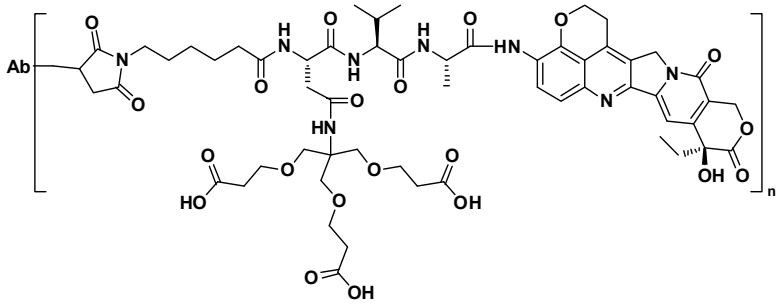
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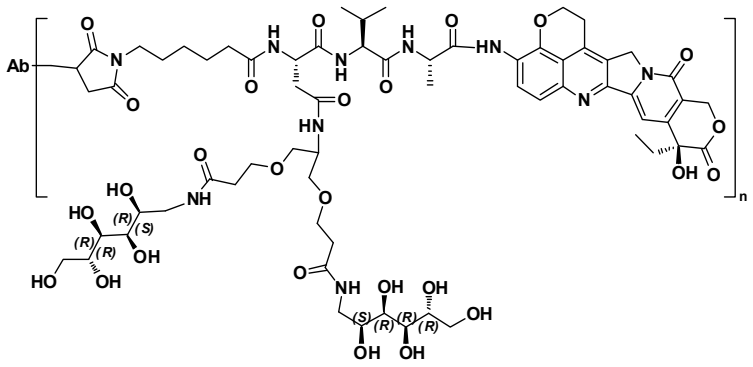
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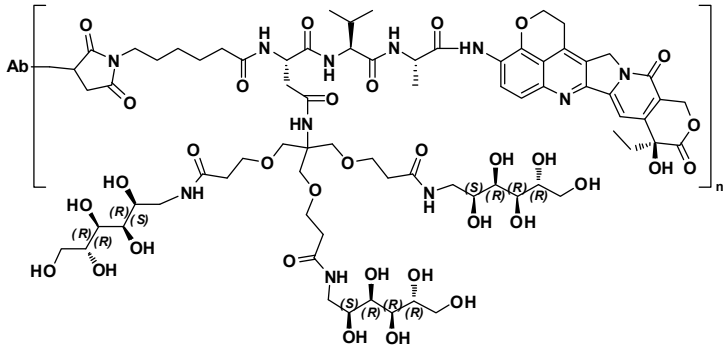
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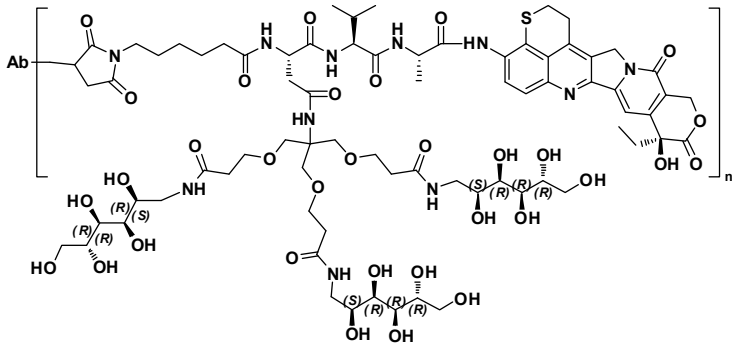
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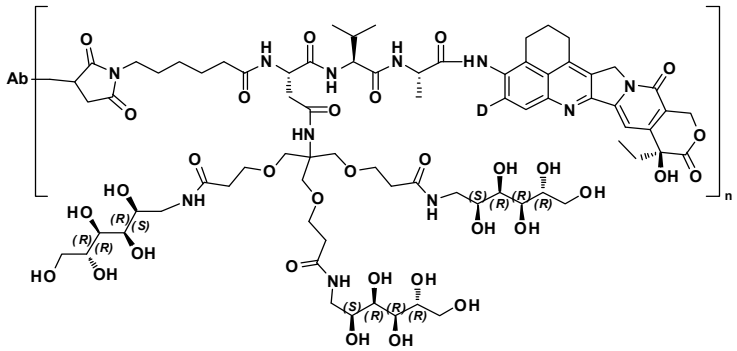
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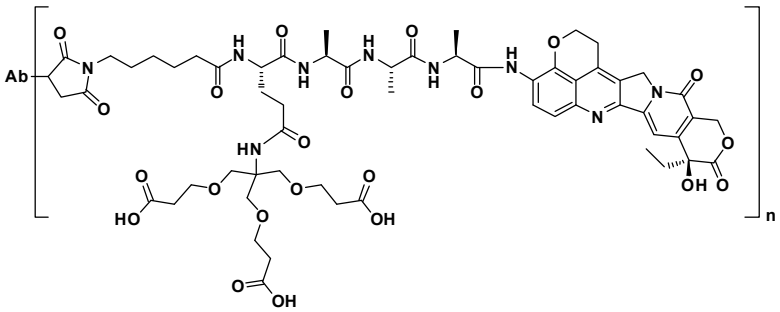
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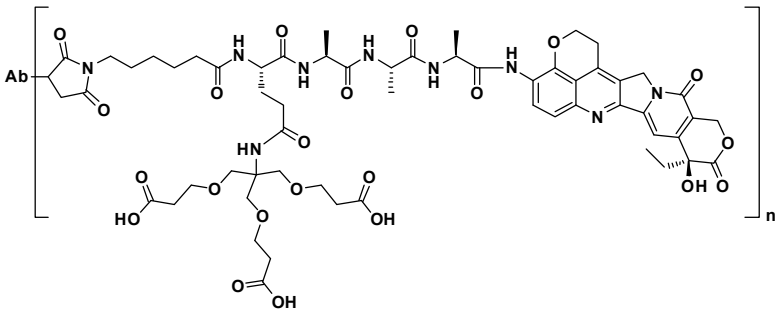
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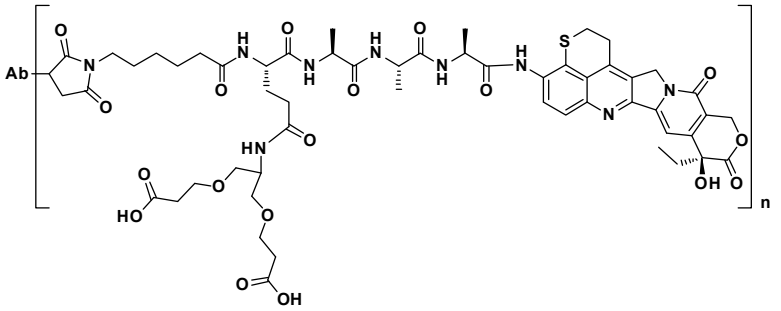
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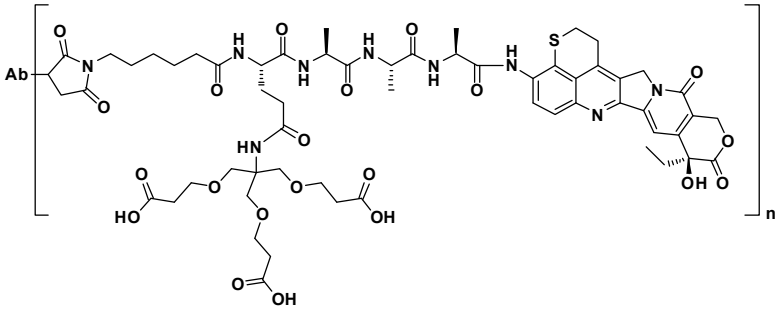
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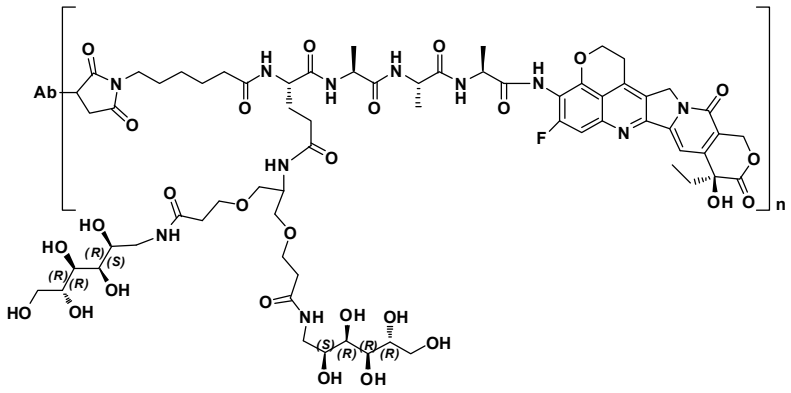
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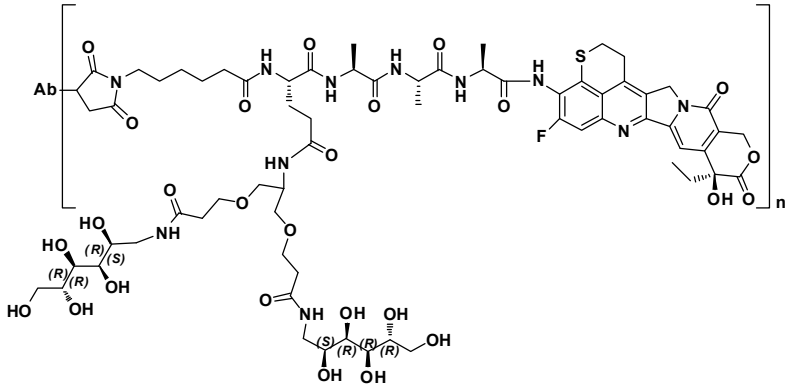
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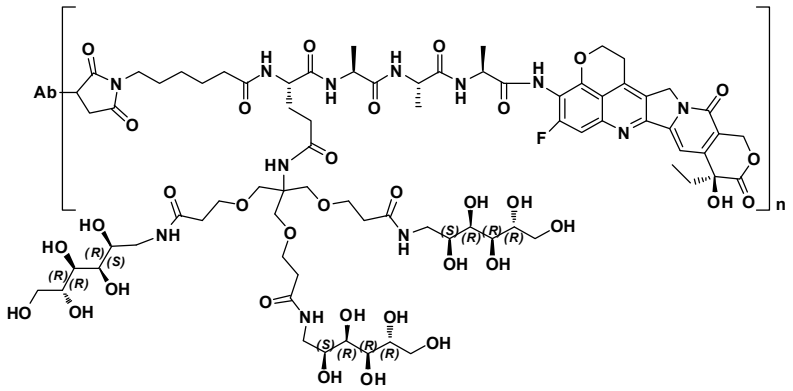
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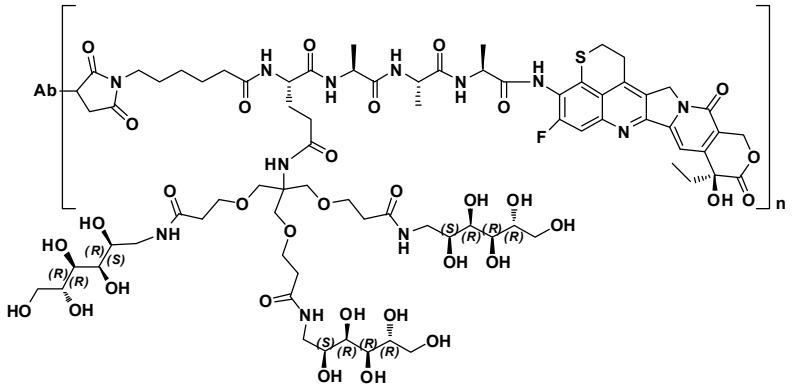
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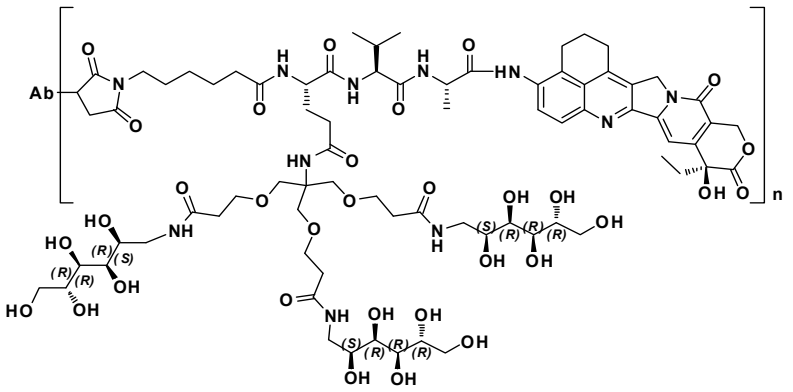
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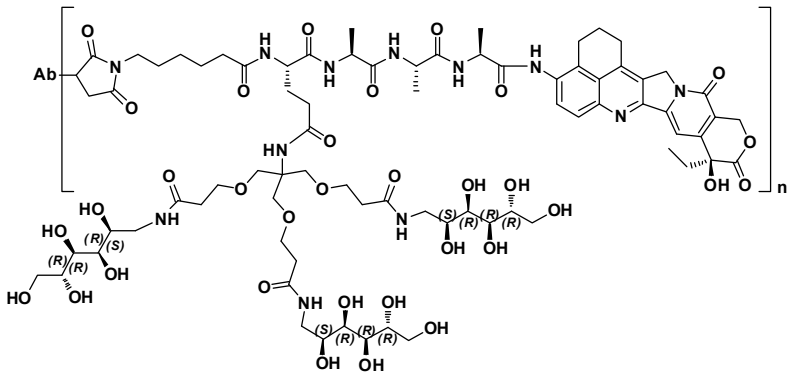
(III')-37



(III')-38



(III')-39



(III')-40,

where n is a number in the range from 1 to 8.

10. The ligand-drug conjugate or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to any of claims 8 to 9, wherein the antibody is selected from the group consisting of mouse-derived antibodies, chimeric antibodies, humanized antibodies and fully humanized antibodies;

or the antibody is mAb;

or, the antibody is bispecific antibody or multispecific antibody;

or, the antibody is antibody fragments, nanobody or fusion protein;

or, the antibody is an antibody capable of binding to CTLA4, CD137, OX40, HER2, HER3, CD19, CD20, CD22, CD30, CD33, CD37, CD45, CD56, CD66e, CD70, CD74, CD79b, CD137, CD138, CD147, CD223, EpCAM, Mucin 1, STEAP1, GPNMB, FGF2, FOLR1, EGFR, EGFRvIII, Tissue factor, c-MET, FGFR, Nectin 4, AGS-16, Guanylyl cyclase C, Mesothelin, SLC44A4, PSMA, EphA2, AGS-5, GPC-3, c-KIT, ROR1, PD-L1, CD27L, 5T4, Mucin 16, NaPi2b, STEAP, SLITRK6, ETBR, BCMA, Trop-2, CEACAM5, SC-16, SLC39A6, Delta-like protein3, or Claudin 18.2 tumor-associated antigen.

11. A pharmaceutical composition comprising a ligand-drug conjugate or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to any of claims 7 to 10; and a pharmaceutically acceptable diluent, carrier or excipient;

preferably, the ligand-drug conjugate has an ADC DAR value in the range from 1 to 8.

12. Use of a ligand-drug conjugate or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to any of claims 7 to 10 in preparation of a medicament for treating a tumor in a subject.

13. The use according to claim 12, wherein the tumor is selected from the group consisting of solid tumor, brain cancer, lung cancer, melanoma, prostate cancer, esophageal squamous cell carcinoma, leukemia, lymphoma, ovarian cancer, colorectal cancer, head and neck cancer, bladder cancer, renal cancer pancreatic cancer, liver cancer, bladder cancer, stomach cancer or breast cancer.

14. A method for preparation of a ligand-drug conjugate or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to any of claims 7 to 10, comprising the following steps of:

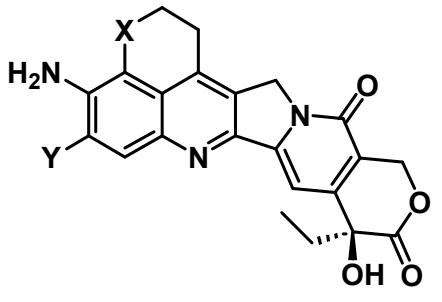
a) reacting a ligand with a reducing agent in a buffer to obtain a reduced ligand; and

b) coupling a compound or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to any of claims 4 to 6 with the reduced ligand obtained in step a) in a mixture of a buffer and an organic solvent to obtain the ligand -drug conjugate;

or comprising the following step of:

coupling a compound or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof according to any of claims 4 to 6 with a ligand in a mixture of a buffer and an organic solvent to obtain the ligand -drug conjugate.

15. A compound of Formula (IV):



(IV),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or isotopic variant thereof, wherein

X is selected from the group consisting of -CH_2-, O, and S; and

Y is selected from the group consisting of H, D, and F;

preferably, the compound is for use in treating a tumor in a subject.