

ANTIBODY-DRUG CONJUGATES OF CAMPTOTHECIN DERIVATIVES AND USES THEREOF

FIELD OF THE INVENTION

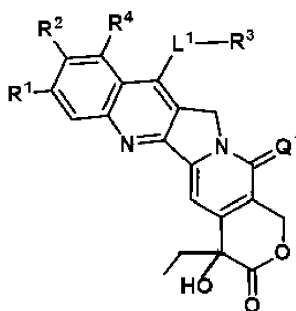
The disclosure provides compounds as well as their compositions and methods of use. The compounds include camptothecin derivatives and antibody-drug conjugates (ADCs) thereof. The compounds are useful in the treatment of various diseases including cancer.

BACKGROUND

Antibody Drug Conjugates (ADCs) include a payload attached to an antibody, typically via a linker. ADCs can be used for the targeted delivery of cytotoxic agents to tumor cells. Camptothecin is a pentacyclic alkaloid that exhibits antitumor activity by inhibiting topoisomerase I. However, camptothecin and many of its derivatives have poor solubility and inactivity at physiological conditions. Accordingly, there is a need for new camptothecin derivatives and antibody-drug conjugates with the new camptothecin derivatives.

SUMMARY

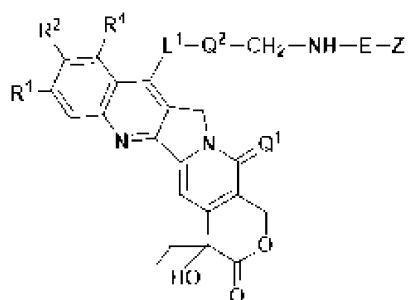
The present disclosure provides, *inter alia*, a compound of Formula (I')



Formula (I')

or a pharmaceutically acceptable salt thereof, wherein constituent variables are defined herein.

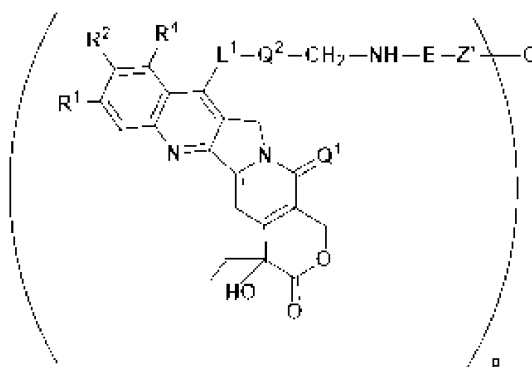
The present disclosure further provides, *inter alia*, a compound of Formula (II')



Formula (II')

or a pharmaceutically acceptable salt thereof, wherein constituent variables are defined herein.

5 The present disclosure further provides, *inter alia*, a compound of Formula (III')



Formula (III')

or a pharmaceutically acceptable salt thereof, wherein constituent variables are defined herein.

10 The present disclosure further provides methods of treating a disease or disorder in a patient comprising administering to the patient a therapeutically effective amount of a compound of the disclosure, or a pharmaceutically acceptable salt thereof.

DESCRIPTION OF DRAWINGS

FIG. 1A depicts a reverse phase chromatograph of a Trastuzumab-PL1 ADC.

15 FIG. 1B depicts a reverse phase chromatograph of a Trastuzumab-PL3 ADC.

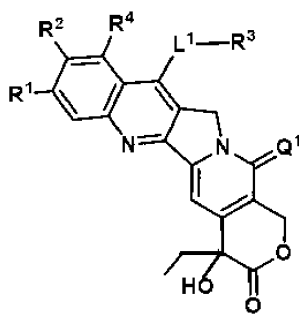
FIG. 1C depicts a reverse phase chromatograph of a Trastuzumab-PL9 ADC.

- FIG. 1D depicts a reverse phase chromatograph of a Trastuzumab-PL11 ADC.
FIG. 1E depicts a reverse phase chromatograph of a Trastuzumab-PL13 ADC.
FIG. 1F depicts a reverse phase chromatograph of a Trastuzumab-PL15 ADC.
FIG. 2A depicts a size exclusion chromatograph of a Trastuzumab-PL1 ADC.
5 FIG. 2B depicts a size exclusion chromatograph of a Trastuzumab-PL3 ADC.
FIG. 2C depicts a size exclusion chromatograph of a Trastuzumab-PL9 ADC.
FIG. 2D depicts a size exclusion chromatograph of a Trastuzumab-PL11 ADC.
FIG. 2E depicts a size exclusion chromatograph of a Trastuzumab-PL13 ADC.
FIG. 2F depicts a size exclusion chromatograph of a Trastuzumab-PL15 ADC.
10 FIG. 3 depicts a graph of hydrophobic interaction chromatography profiles of ADCs with Trastuzumab.
FIG. 4 depicts a graph showing the *in vitro* cytotoxicity of payloads on SK-BR-3 cell lines.
FIG. 5 depicts a graph showing the *in vitro* cytotoxicity of ADCs with
15 Trastuzumab on SK-BR-3 cell lines.
FIG. 6 depicts a graph showing the *in vivo* efficacy of ADCs with Trastuzumab.
FIG. 7 depict a graph showing the body weight change of mice.
FIG. 8 depicts a graph showing the *in vivo* efficacy of ADCs with Trastuzumab.
FIG. 9 depict a graph showing the body weight change of mice.
20 FIG. 10A depicts a graph showing total antibody concentration and concentration of antibody-drug conjugate over time for Trastuzumab-PL1 ADC.
FIG. 10B depicts a graph showing total antibody concentration and concentration of antibody-drug conjugate over time for Trastuzumab-deruxtecan ADC.
FIG. 11 depicts a graph showing body weight change of mice treated with
25 Trastuzumab-PL20 ADC.
FIG. 12 depicts structure of Trastuzumab-PL20.

DETAILED DESCRIPTION

Compounds

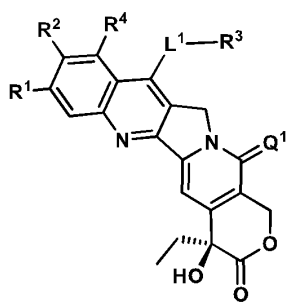
The present disclosure provides, a compound of Formula (I'):



Formula (I')

5 or a pharmaceutically acceptable salt thereof.

The present disclosure provides, a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof.

wherein in Formula (I') and Formula (I):

10 R¹ is selected from H, OH, halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

R² is selected from H, OH, halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

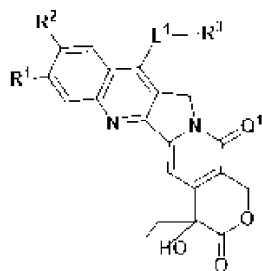
Q¹ is S or O;

R³ is selected from OH, SH, -NH₂, -NHC(=O)-C₁₋₆ alkylene-OH and -NHC(=S)-C₁₋₆ alkylene-OH;

15 L¹ is C₁₋₆ alkylene; and

R⁴ is H; or R⁴ together with L¹ form a 5-8 membered carbocycle.

In some embodiments, the compound of Formula (I') is a compound of Formula (Ia')

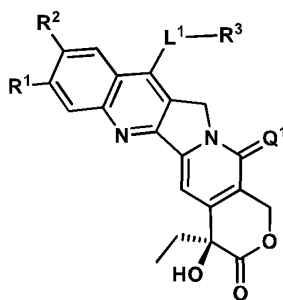


Formula (Ia')

or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, L¹, and Q¹ are as defined herein.

In some embodiments, the compound of Formula (I) is a compound of Formula

5 (Ia)

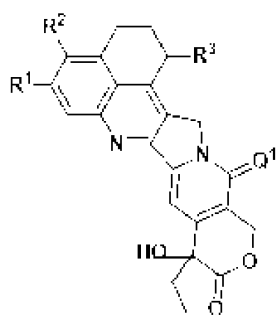


Formula (Ia)

or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, L¹, and Q¹ are as defined herein.

In some embodiments, the compound of Formula (I') is a compound of Formula

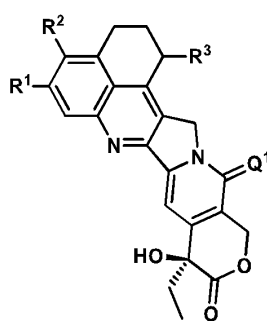
10 (Ib')



Formula (Ib')

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^3 , and Q^1 are as defined herein.

In some embodiments, the compound of Formula (I) is a compound of Formula (Ib)



Formula (Ib)

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^3 , and Q^1 are as defined herein.

In Formula (I'), (I), (Ia'), (Ia), (Ib') and (Ib), R^1 can be H, OH, halo, C_{1-6} alkyl or C_{1-6} alkoxy. In some embodiments, R^1 is halo. In some embodiments, R^1 is fluoro, chloro, or bromo. In some embodiments, R^1 is fluoro. In some embodiments, R^1 is C_{1-6} alkyl or C_{1-6} alkoxy. In some embodiments, R^1 is C_{1-6} alkyl. In some embodiments, R^1 is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl. In some embodiments, R^1 is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^1 is methyl. In some embodiments, R^1 is ethyl. In some embodiments, R^1 is n-propyl. In some embodiments, R^1 is isopropyl. In some embodiments, R^1 is C_{1-6} alkoxy. In some embodiments, R^1 is methoxy or ethoxy. In some embodiments, R^1 is methoxy. In some embodiments, R^1 is ethoxy. In some embodiments, R^1 is H. In some embodiments, R^1 is OH.

In Formula (I'), (I), (Ia'), (Ia), (Ib') and (Ib), R^2 can be halo, C_{1-6} alkyl or C_{1-6} alkoxy. In some embodiments, R^2 is C_{1-6} alkyl or C_{1-6} alkoxy. In some embodiments, R^2 is C_{1-6} alkyl. In some embodiments, R^2 is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl. In some embodiments, R^2 is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^2 is methyl. In some embodiments, R^2 is ethyl. In some embodiments, R^2 is n-propyl. In some embodiments, R^2 is isopropyl. In some embodiments, R^2 is C_{1-6} alkoxy. In some embodiments, R^2 is methoxy or ethoxy. In some

embodiments, R^2 is methoxy. In some embodiments, R^2 is ethoxy. In some embodiments, R^2 is halo. In some embodiments, R^2 is fluoro, chloro, or bromo.

In Formula (I'), (I), (Ia'), (Ia), (Ib') and (Ib), Q^1 can be O or S. In some embodiments, Q^1 is O. In some embodiments, Q^1 is S.

5 In Formula (I'), (I), (Ia'), (Ia), (Ib') and (Ib), R^3 can be OH, $-NH_2$, $-NHC(=O)-C_{1-6}$ alkylene-OH and $-NHC(=S)-C_{1-6}$ alkylene-OH. In some embodiments, R^3 is selected from OH, $-NH_2$, $-NHC(=O)-C_{1-6}$ alkylene-OH and $-NHC(=S)-C_{1-6}$ alkylene-OH. In some embodiments, R^3 is OH. In some embodiments, R^3 is $-NHC(=O)-C_{1-6}$ alkylene-OH. In some embodiments, R^3 is NH_2 .

10 In Formula (I'), (I), (Ia'), and (Ia), L^1 can be C_{3-4} alkylene. In some embodiments, L^1 is C_{3-4} alkylene.

In Formula (I'), (I), (Ia'), and (Ia), $-L^1-R^3$ can be $-CH_2CH_2CH_2OH$ or $-CH_2CH_2CH_2CH_2OH$. In some embodiments, $-L^1-R^3$ is $-CH_2CH_2CH_2OH$. In some embodiments, $-L^1-R^3$ is $-CH_2CH_2CH_2CH_2OH$.

15 In Formula (I') and (I), R^4 can be H. In some embodiments, R^4 is H.

In Formula (I') and (I), R^4 together with L^1 can form a 5-8 membered carbocycle. In some embodiments, R^4 together with L^1 form a 5-8 membered carbocycle. In some embodiments, R^4 together with L^1 form a 6-membered carbocycle. In some embodiments, R^4 together with L^1 form a 6-membered carbocycle, and R^3 is selected from $-NH_2$,
20 $-NHC(=O)-C_{1-6}$ alkylene-OH and $-NHC(=S)-C_{1-6}$ alkylene-OH. In some embodiments, R^4 together with L^1 form a 6-membered carbocycle, and R^3 is selected from $-NH_2$, $-NHC(=O)-CH_2-OH$ and $-NHC(=S)-CH_2-OH$.

In some embodiments, in Formula (I') and (I), R^1 is selected from halo, C_{1-6} alkyl, and C_{1-6} alkoxy; R^2 is selected from H, OH, C_{1-6} alkyl, and C_{1-6} alkoxy; Q^1 is S or O; R^3 is OH; L^1 is C_{1-6} alkylene; and R^4 is H.
25

In some embodiments, in Formula (I') and (I), R^1 is halo; R^2 is selected from H, OH, C_{1-6} alkyl, and C_{1-6} alkoxy; Q^1 is S or O; R^3 is OH; L^1 is C_{1-6} alkylene; and R^4 is H.

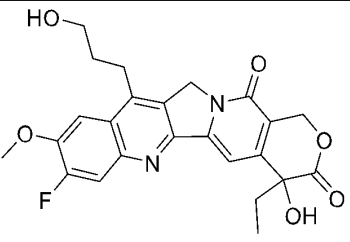
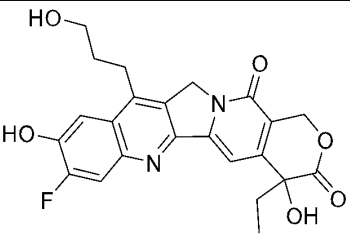
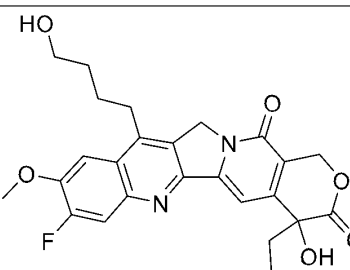
In some embodiments, in Formula (I') and (I), R^1 is fluoro; R^2 methoxy; Q^1 is O; and $-L^1-R^3$ is $-CH_2CH_2CH_2OH$. In some embodiments, R^1 is selected from halo, C_{1-6} alkyl, and C_{1-6} alkoxy; R^2 is selected from H, OH, C_{1-6} alkyl, and C_{1-6} alkoxy; Q^1 is S or
30

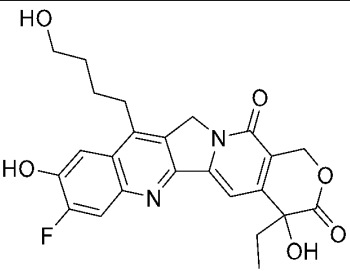
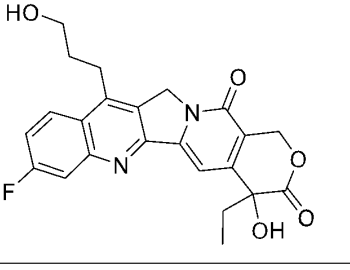
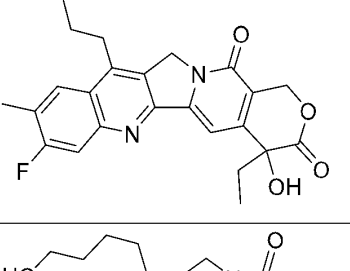
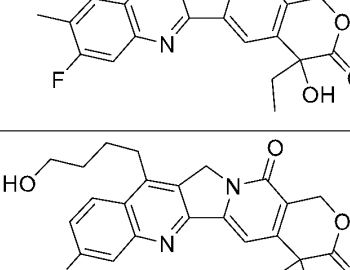
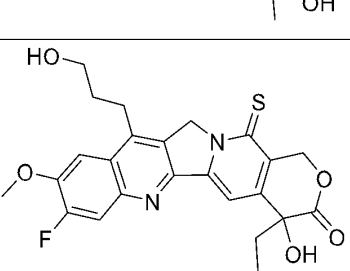
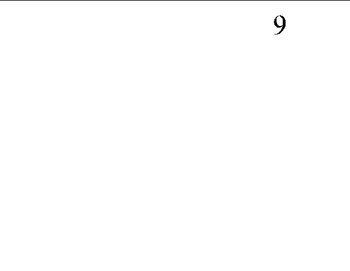
O; R³ is selected from OH, SH, -NH₂, -NHC(=O)-C₁₋₆ alkylene-OH and -NHC(=S)-C₁₋₆ alkylene-OH; and R⁴ together with L¹ form a 5-8 membered carbocycle.

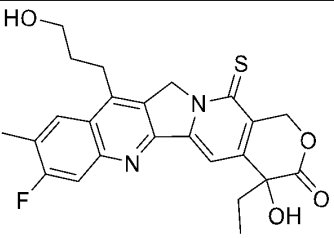
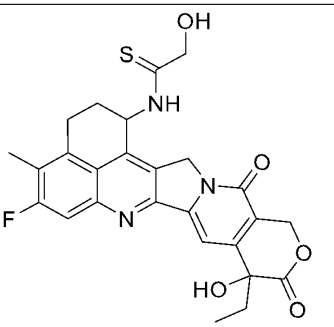
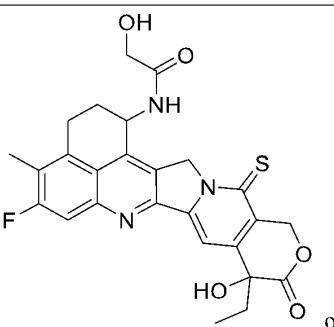
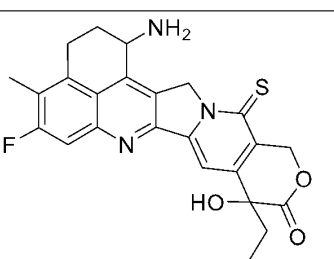
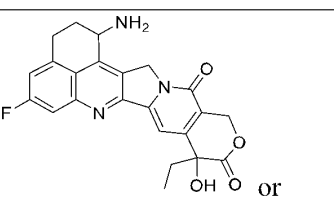
In some embodiments, in Formula (I') and (I), R¹ is halo; R² is C₁₋₆ alkyl; Q¹ is S or O; R³ is selected from OH, SH, -NH₂, -NHC(=O)-C₁₋₆ alkylene-OH and -NHC(=S)-C₁₋₆ alkylene-OH; and R⁴ together with L¹ form a 5-8 membered carbocycle.

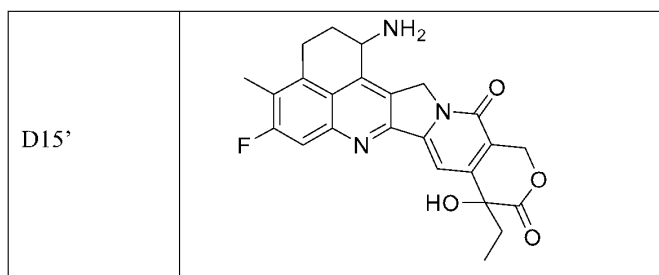
In some embodiments, the compound of Formula (I'), (I), (Ia'), (Ia), (Ib') and (Ib), is a payload in an ADC.

In some embodiments, the compound of Formula (I') is:

D1'	
D2'	
D3'	

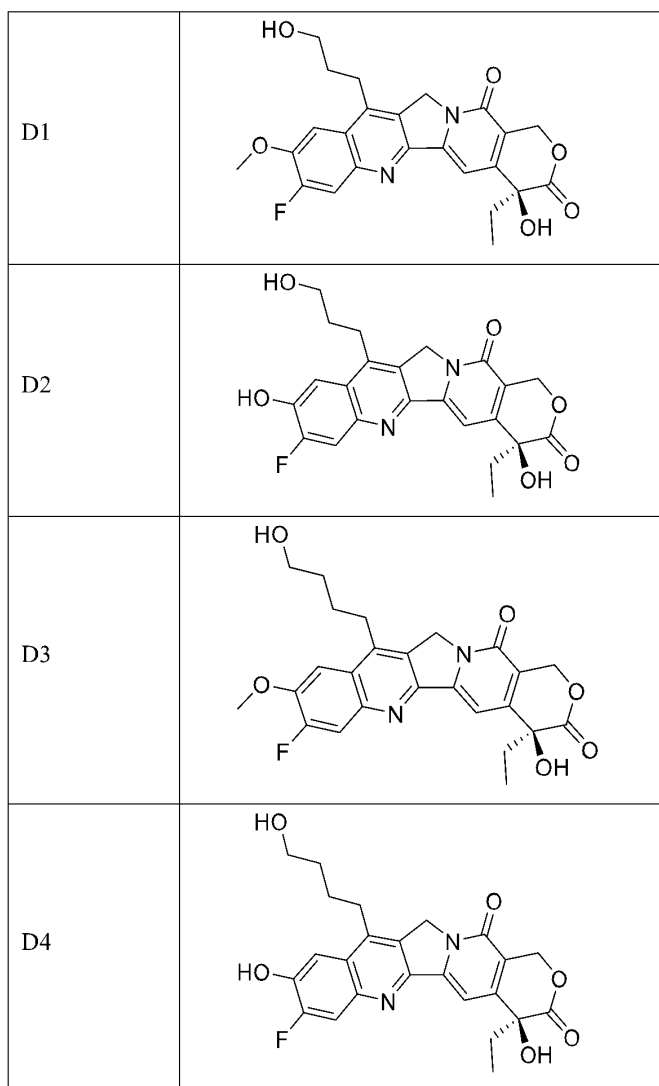
D4'	
D5'	
D6'	
D7'	
D8'	
D9'	

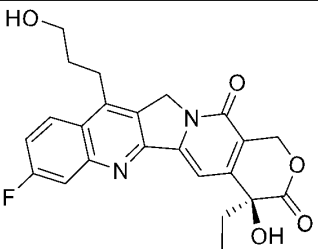
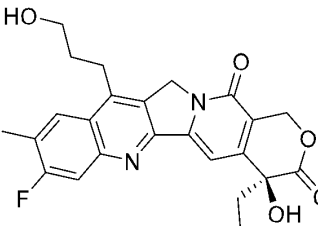
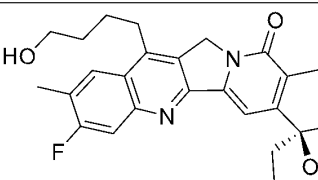
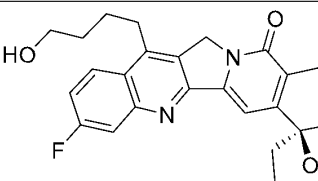
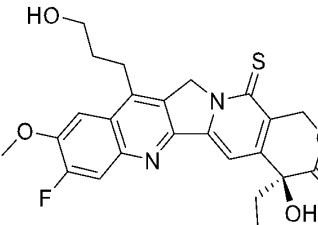
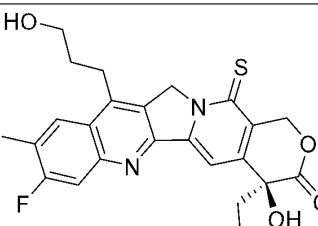
D10'	
D11'	
D12'	
D13'	
D14'	

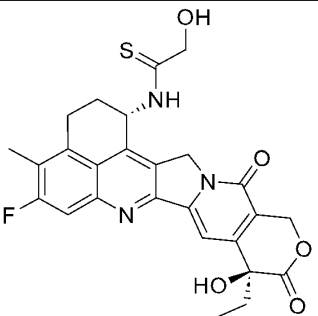
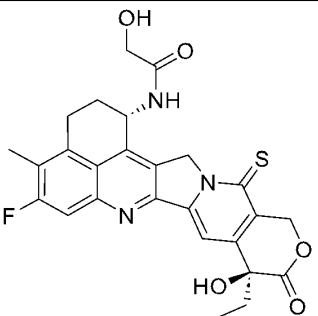
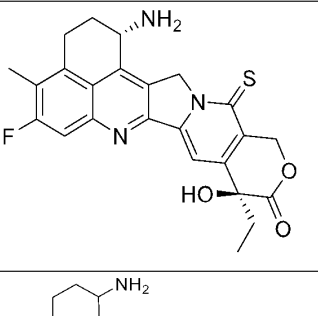
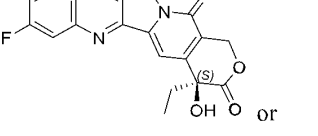
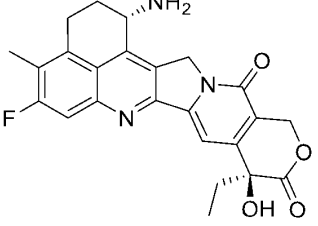


or pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) is:



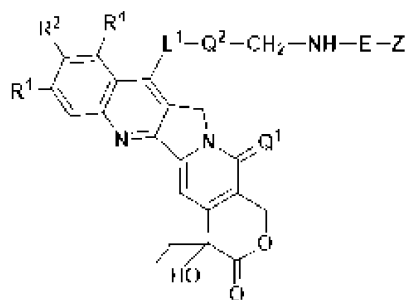
D5	
D6	
D7	
D8	
D9	
D10	

D11	
D12	
D13	
D14	
D15	

or a pharmaceutically acceptable salt thereof.

The present disclosure further provides an antibody-drug conjugate comprising a drug and an antibody, wherein the drug includes a compound of Formula (I'), (I), (Ia'), (Ia), (Ib') or (Ib), or a derivative thereof. In some embodiments, the drug attaches to the antibody via a linker.

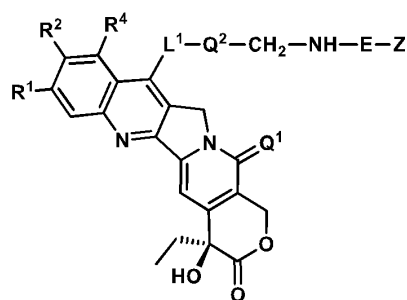
5 The present disclosure further provides, a compound of Formula (II'):



Formula (II')

or a pharmaceutically acceptable salt thereof.

The present disclosure further provides, a compound of Formula (II):



Formula (II)

10 or a pharmaceutically acceptable salt thereof.

wherein in Formula (II') and Formula (II):

R¹ is selected from halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

R² is selected from H, -OH, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

Q¹ is S or O;

15 L¹ is C₁₋₆ alkylene;

R⁴ is H; or

R⁴ together with L¹ form 5-8 membered carbocycle;

Q^2 is selected from $-S-$, $-O-$, $^*-NHC(=O)-C_{1-6}$ alkylene- $O-$ and $^*-NHC(=S)-C_{1-6}$ alkylene- $O-$, wherein the asterisk represents to point of attachment to L^1 ;

E is a peptide including 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol;

5 the N terminal of the peptide is covalently attached to Z;

Z is $-C(=O)-L^2-Y$;

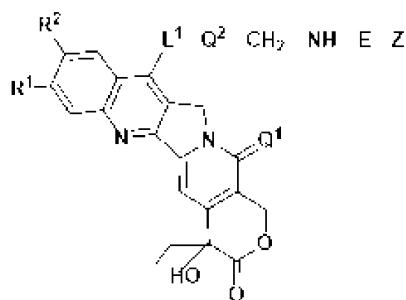
L^2 is selected from C_{1-6} alkylene, $-(CH_2CH_2-O)_n-C_{1-6}$ alkylene- * , and $-C_{1-6}$ alkylene- $(O-CH_2CH_2)_n-^*$;

n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

10 the asterisk (*) represents the point of attachment to Y; and

Y is a reactive group, preferably an electrophilic group.

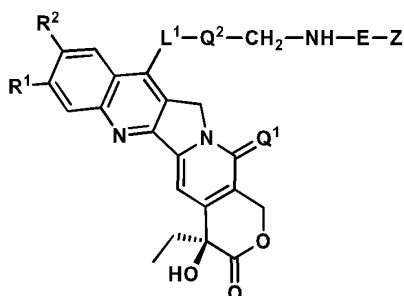
In some embodiments, the compound of Formula (II') is a compound of Formula (IIa')



Formula (IIa')

15 or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , L^1 , Q^1 , Q^2 , E and Z are as defined herein.

In some embodiments, the compound of Formula (II) is a compound of Formula (IIa)



Formula (IIa)

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , L^1 , Q^1 , Q^2 , E and Z are as defined herein.

In Formula (II'), (II), (IIa') and (IIa), R^1 can be halo, C_{1-6} alkyl or C_{1-6} alkoxy. In some embodiments, R^1 is halo. In some embodiments, R^1 is fluoro, chloro or bromo. In some embodiments, R^1 is fluoro. In some embodiments, R^1 is C_{1-6} alkyl or C_{1-6} alkoxy. In some embodiments, R^1 is C_{1-6} alkyl. In some embodiments, R^1 is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl. In some embodiments, R^1 is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^1 is methyl. In some embodiments, R^1 is ethyl. In some embodiments, R^1 is n-propyl. In some embodiments, R^1 is isopropyl. In some embodiments, R^1 is C_{1-6} alkoxy. In some embodiments, R^1 is methoxy or ethoxy. In some embodiments, R^1 is methoxy. In some embodiments, R^1 is ethoxy.

In Formula (II'), (II), (IIa') and (IIa), R^2 can be C_{1-6} alkyl or C_{1-6} alkoxy. In some embodiments, R^2 is C_{1-6} alkyl or C_{1-6} alkoxy. In some embodiments, R^2 is C_{1-6} alkyl. In some embodiments, R^2 is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl. In some embodiments, R^2 is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^2 is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^2 is methyl. In some embodiments, R^2 is ethyl. In some embodiments, R^2 is n-propyl. In some embodiments, R^2 is isopropyl. In some embodiments, R^2 is C_{1-6} alkoxy. In some embodiments, R^2 is methoxy or ethoxy. In some embodiments, R^2 is methoxy. In some embodiments, R^2 is ethoxy.

In Formula (II'), (II), (IIa') and (IIa), Q^1 can be O or S. In some embodiments, Q^1 is O. In some embodiments, Q^1 is S.

In Formula (II'), (II), (IIa') and (IIa), L^1 can be C_{3-4} alkylene. In some embodiments, L^1 is C_{3-4} alkylene.

In Formula (II'), (II), (IIa') and (IIa), Q^2 can be O or S. In some embodiments, Q^2 is O. In some embodiments, Q^2 is S.

5 In Formula (II'), (II), (IIa') and (IIa), $-L^1-Q^2$ can be $^*-CH_2CH_2CH_2O-$ or $^*-CH_2CH_2CH_2CH_2O-$, wherein the asterisk (*) represents the point of attachment to L^1 . In some embodiments, $-L^1-Q^2$ is $^*-CH_2CH_2CH_2O-$, wherein the asterisk (*) represents the point of attachment to L^1 . In some embodiments, $-L^1-Q^2$ is $^*-CH_2CH_2CH_2CH_2O-$, wherein the asterisk (*) represents the point of attachment to L^1 .

10 In Formula (II') and (II), R^4 can be H. In some embodiments, R^4 is H.

In Formula (II') and (II), R^4 together with L^1 can form a 5-8 membered carbocycle. In some embodiments, R^4 together with L^1 form a 5-8 membered carbocycle. In some embodiments, R^4 together with L^1 form a 6-membered carbocycle. In some embodiments, R^4 together with L^1 form a 6-membered carbocycle, and Q^2 is selected from $^*-NHC(=O)-C_{1-6}$ alkylene-O- and $^*-NHC(=S)-C_{1-6}$ alkylene-O-, wherein the asterisk (*) represents to point of attachment to L^1 . In some embodiments, R^4 together with L^1 form a 6-membered carbocycle, and Q^2 is selected from $^*-NHC(=O)-CH_2-O-$ and $^*-NHC(=S)-CH_2-O-$, wherein the asterisk (*) represents to point of attachment to L^1 .

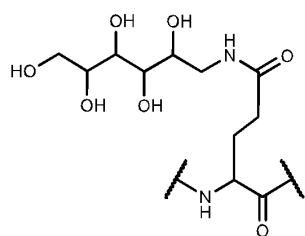
20 In some embodiments, in Formula (II') and (II), R^1 is halo; R^2 is selected from H, $-OH$, C_{1-6} alkyl, and C_{1-6} alkoxy; Q^1 is S or O; R^4 is H; L^1 is C_{1-6} alkylene; Q^2 is selected from $-S-$, and $-O-$; E is a peptide including 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol; the N terminal of the peptide is covalently attached to Z; Z is $-C(=O)-L^2-Y$; L^2 is selected from C_{1-6} alkylene, $-(CH_2CH_2O)_n-C_{1-6}$ alkylene-*, and $-C_{1-6}$ alkylene-($O-CH_2CH_2$) $_n$ -*; n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; the asterisk (*) represents the point of attachment to Y; and Y is a reactive group, preferably an electrophilic group.

25 In some embodiments, in Formula (II') and (II), R^1 is halo; R^2 is C_{1-6} alkoxy; Q^1 is O; R^4 is H; L^1 is C_{1-6} alkylene; Q^2 is $-O-$; E is a peptide including 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol; the N terminal of the peptide is covalently attached to Z; Z is $-C(=O)-L^2-Y$; L^2 is $-(CH_2CH_2O)_n-C_{1-6}$

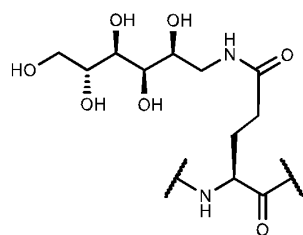
alkylene-*; n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; the asterisk (*) represents the point of attachment to Y; and Y is an electrophilic group.

In Formula (II'), (II), (IIa'), and (IIa), E can be a peptide including 2 to 10 amino acids, and the N terminal of the peptide is covalently attached to Z. In some

- 5 embodiments, E is a peptide including 2 to 10 amino acids, and the N terminal of the peptide is covalently attached to Z. In some embodiments, E is a peptide including 2 to 8 amino acids, and the N terminal of the peptide is covalently attached to Z. In some embodiments, E is a peptide including 2 to 6 amino acids, and the N terminal of the peptide is covalently attached to Z. In some embodiments, E is a peptide including 2 to 4
- 10 amino acids, and the N terminal of the peptide is covalently attached to Z. In some embodiments, E is a peptide including 2 to 3 amino acids, and the N terminal of the peptide is covalently attached to Z. In some embodiments, each amino acid of E is an L amino acid, or at least one amino acid of E is a D amino acid. In some embodiments, E includes one or more amino acids selected from glycine, alanine, valine, glutamine,
- 15 glutamic acid, phenylalanine, and leucine. In some embodiments, one or more amino acid of E is substituted with one or more polyol. In some embodiments, one or more of the glutamine or glutamic acid of E is substituted with one or more polyol. In some embodiments, E includes an amino acid having the following structure,

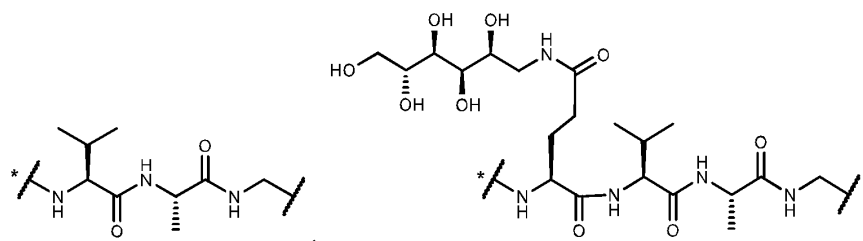


- 20 . In some embodiments, E includes an amino acid having the following structure,



. In some embodiments, E is selected from -Ala-Val-*, -Val-Ala-*, -Gly-Gly-*, -Val-Cit-*, -Cit-Val-*, -Leu-Ala-*, -Ala-Leu-*, -Leu-Cit-*, -Cit-Leu-*, -Leu-Ala-*, -Ala-Leu-*, -Lys-Lys-*, -Ala-Lys-*, -Lys-Ala-*, -Val-Lys-*, -Lys-Val-*, -Tyr-Arg-*, -Arg-Tyr-*, -Arg-Arg-*, -Ala-Ala-*, -Phe-Lys-*, -Lys-Phe-*, -Thr-Thr-*, -Thr-Met-*, -Met-Thr-*, -Met-Tyr-*, -Tyr-Met-*, -Phe-Gln-*, -Gln-Phe-*, -Gly-Ser-*, -Leu-Gln-*, -Gln-Leu-*, -Ser-Ala-*, -Ser-Gly-*, -Val-Thr-*, -Thr-Val-*, -Val-Gln-*, -Ser-Val-*, -Val-Ser-*, -Ala-Met-*, -Met-Ala-*, -Val-Arg-*, -Arg-Val-*, -Phe-Ala-*, -Ala-Phe-*, -Cit-Val-*, -Gln-Val-*, -Phe-Arg-*, -Arg-Phe-*, -Ala-Val-Glu-*, -Ala-Ala-Ala-*, -Gly-Gly-Gly-*, -Ala-Val-Ala-*, -Gly-Val-Gly-*, -Ala-Val-Gly-*, -Gly-Phe-Lys-*, -Lys-Phe-Gly-*, -Leu-Ala-Leu-*, -Val-Ala-Leu-*, -Leu-Ala-Val-*, -Val-Ala-Val-*, -Ala-Val-Ala-Gly-*, -Gly-Phe-Gly-Gly-*, -Gly-Gly-Phe-Gly-*, -Ala-Val-Gly-Gly-*, -Ala-Ala-Ala-Ala-*, -Ala-Val-Ala-Ala-*, -Ala-Leu-Ala-Leu-*, -Leu-Ala-Leu-Ala-*, -Gly-Phe-Leu-Gly-*, and -Gly-Leu-Phe-Gly-*, wherein the Glu is optionally substituted with a polyol, and wherein (*) represents the N-terminal of the peptides covalently attached to Z. In some embodiments, E is selected from -Ala-Val-*, -Val-Ala-*, -Val-Lys-*, -Val-Arg-*, -Val-Cit-*, -Val-Arg-*, -Val-Cit-*, -Val-Lys-*, -Val-Arg-*, -Arg-Arg-*, -Ala-Ala-*, -Ala-Lys-*, -Ala-Arg-*, -Ala-Val-Glu-*, -Ala-Ala-Ala-*, -Ala-Val-Ala-*, -Ala-Ala-Gly-*, and -Ala-Val-Gly-*, wherein the Glu is optionally substituted with a polyol, and wherein (*) represents the N-terminal of the peptides covalently attached to Z. In some embodiments, E is selected from -Ala-Val-* and -Ala-Val-Glu-*, wherein the Glu is optionally substituted with a polyol, and wherein (*) represents the N-terminal of the peptides covalently attached to Z. In some embodiments, E is -Ala-Val-*, wherein (*) represents the N-terminal of the peptides covalently attached to Z. In some embodiments, E is -Ala-Val-Glu-*, wherein the Glu is substituted with a polyol, and wherein (*) represents the N-terminal of the peptides covalently attached to Z.

In some embodiments, in Formula (II'), (II), (IIa'), and (IIa), -E-NH-CH₂- has one of the following structures, wherein (*) represents the N-terminal of the peptides covalently attached to Z:

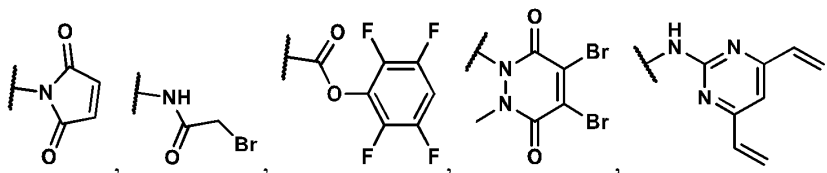


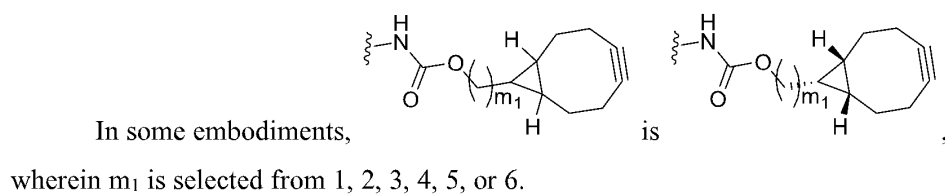
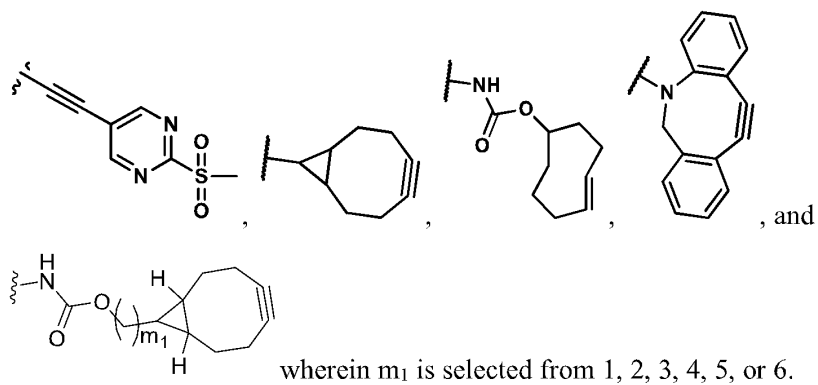
5 wherein (*) represents the N-terminal of the peptides covalently attached to Z.

In Formula (II'), (II), (IIa'), and (IIa), L² can be C₁₋₆ alkylene, -(CH₂CH₂-O)_n-C₁₋₆ alkylene-*, or -C₁₋₆ alkylene-(O-CH₂CH₂)_n*, wherein n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and wherein the asterisk (*) represents the point of attachment to Y. In some embodiments, L² is C₁₋₆ alkylene. In some embodiments, L² is C₃₋₆ alkylene. In some embodiments, L² is -(CH₂)₅-. In some embodiments, L² is selected from -(CH₂CH₂-O)_n-C₁₋₆ alkylene-*, and -C₁₋₆ alkylene-(O-CH₂CH₂)_n*, wherein n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and wherein the asterisk (*) represents the point of attachment to Y. In some embodiments, n is 2, 3, 4 or 5. In some embodiments, n is 2, 3 or 4. In some embodiments, n is 3 or 4. In some embodiments, n is 4.

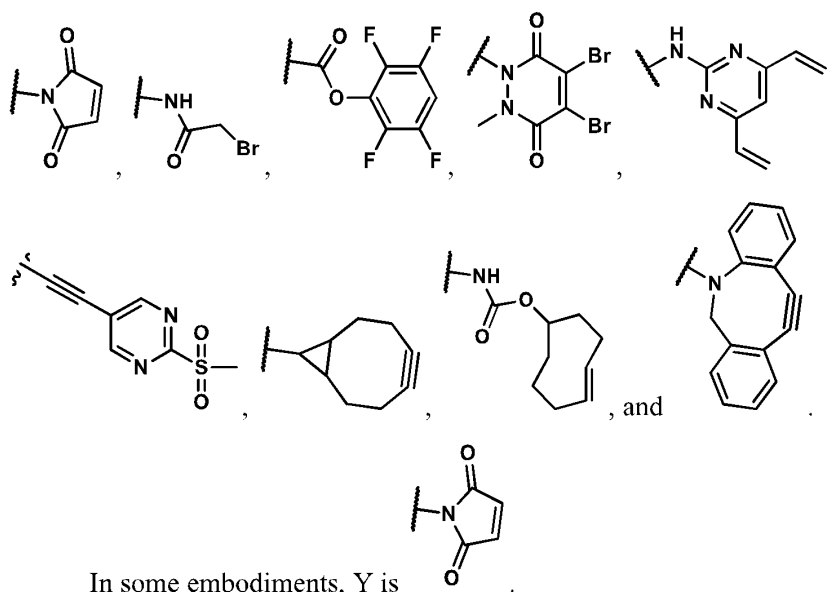
15 In Formula (II'), (II), (IIa'), and (IIa), L² can be -(CH₂CH₂-O)₄-C₁₋₄ alkylene-*, and -C₁₋₄ alkylene-(O-CH₂CH₂)₄*, wherein the asterisk (*) represents the point of attachment to Y. In some embodiments, L² is selected from -(CH₂CH₂-O)₄-C₁₋₄ alkylene-*, and -C₁₋₄ alkylene-(O-CH₂CH₂)₄*, wherein the asterisk (*) represents the point of attachment to Y. In some embodiments, L² is selected from -(CH₂CH₂-O)₄-CH₂CH₂*, and -CH₂CH₂-(O-CH₂CH₂)₄*, and wherein the asterisk (*) represents the point of attachment to Y.

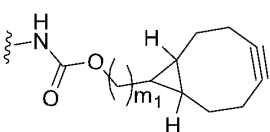
In some embodiments, in Formula (II'), (II), (IIa'), and (IIa), Y is selected from

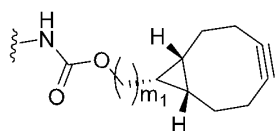




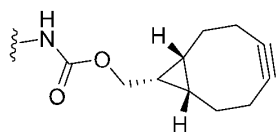
5 In some embodiments, in Formula (II'), (II), (IIa'), and (IIa), Y is selected from



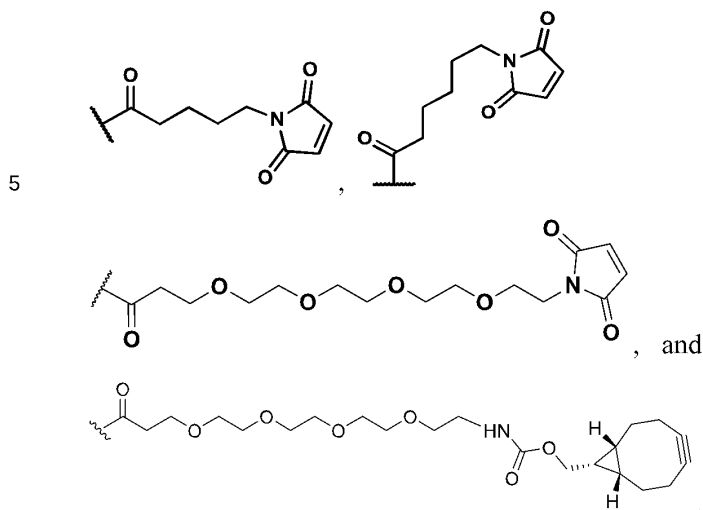
In some embodiments, Y is , preferably



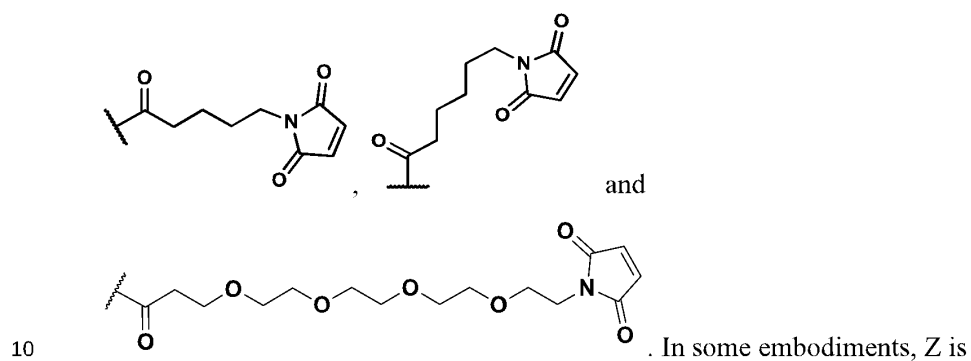
wherein m_1 is defined as above, more preferably



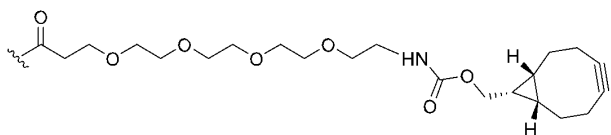
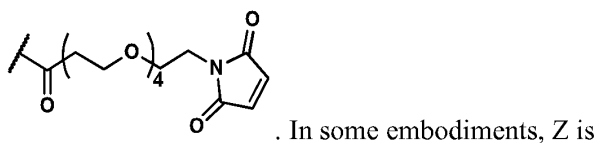
In some embodiments, in Formula (II'), (II), (IIa'), and (IIa), Z is selected from



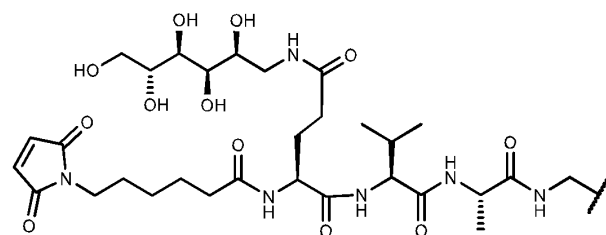
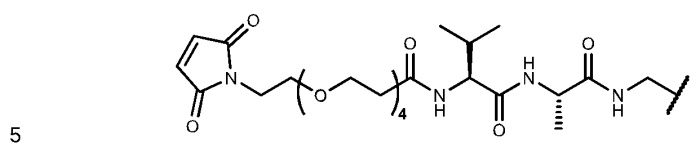
In some embodiments, in Formula (II'), (II), (IIa'), and (IIa), Z is selected from



. In some embodiments, Z is

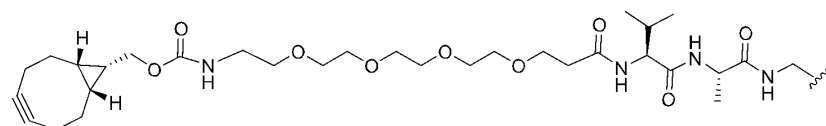


In some embodiments, in Formula (II'), (II), (IIa'), and (IIa), $-\text{CH}_2\text{-NH-E-Z}$ has one of the following structures:



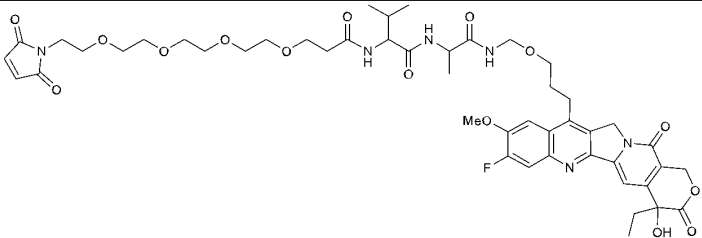
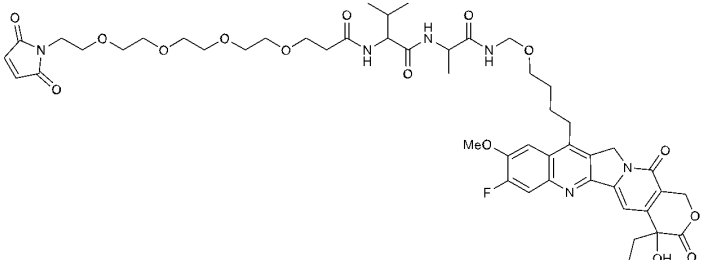
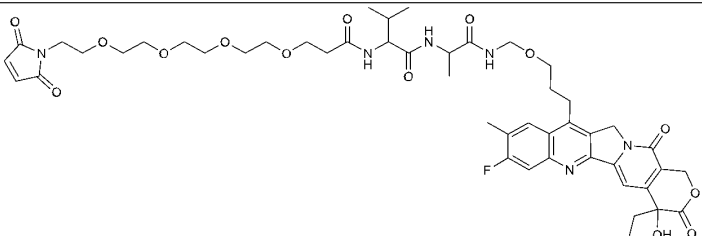
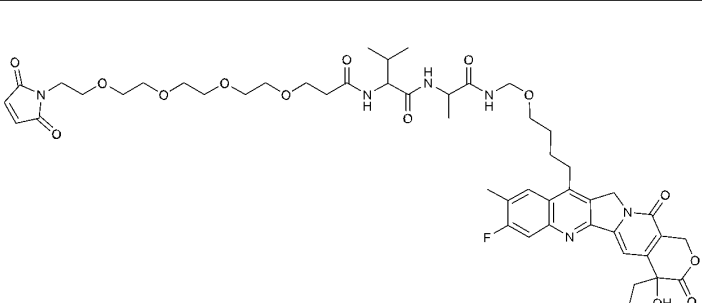
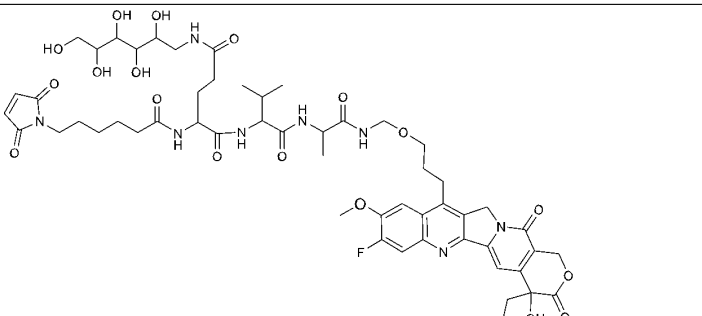
In some embodiments, in Formula (II'), (II), (IIa'), and (IIa), $-\text{CH}_2\text{-NH-E-Z}$ has the following structures:

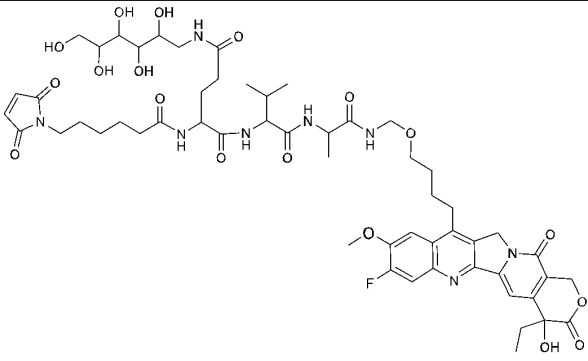
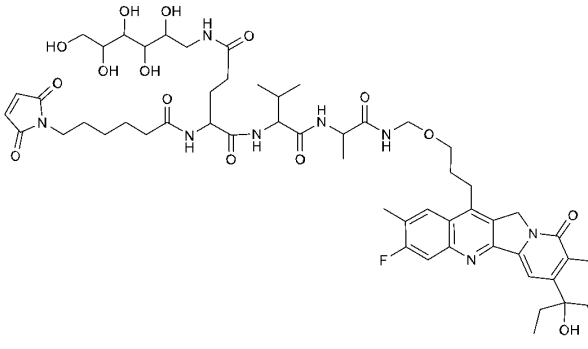
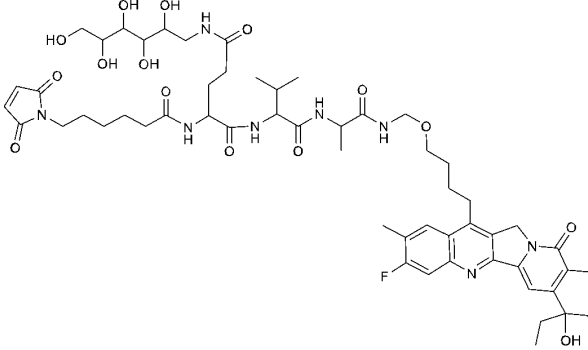
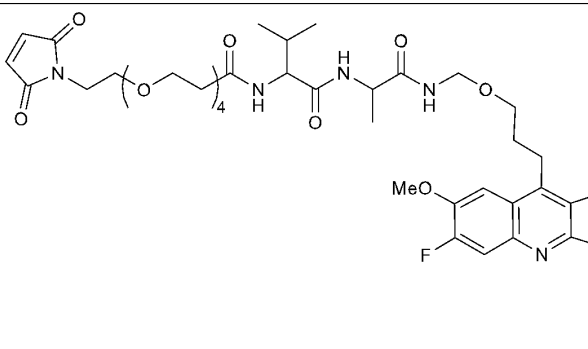
10



In some embodiments, the compound of Formula (II'), (II), (IIa') and (IIa) is a payload and linker in an ADC.

In some embodiments, the compound of Formula (II') is:

PL1'	
PL2'	
PL3'	
PL4'	
PL5'	

PL6'	
PL7'	
PL8'	
PL9'	

PL10'	Chemical structure of PL10': A molecule featuring a 2,5-dioxolane ring substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group. This is connected via a 3-(2,2,4,4-tetramethyl-1,3-dioxane-6-yl)propan-1-yl chain to a 2,5-dioxolane ring. The 2,5-dioxolane ring is further substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group. The 2,5-dioxolane ring is also substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group.
PL11'	Chemical structure of PL11': A molecule featuring a 2,5-dioxolane ring substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group. This is connected via a 3-(2,2,4,4-tetramethyl-1,3-dioxane-6-yl)propan-1-yl chain to a 2,5-dioxolane ring. The 2,5-dioxolane ring is further substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group. The 2,5-dioxolane ring is also substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group.
PL12'	Chemical structure of PL12': A molecule featuring a 2,5-dioxolane ring substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group. This is connected via a 3-(2,2,4,4-tetramethyl-1,3-dioxane-6-yl)propan-1-yl chain to a 2,5-dioxolane ring. The 2,5-dioxolane ring is further substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group. The 2,5-dioxolane ring is also substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group.
PL13'	Chemical structure of PL13': A molecule featuring a 2,5-dioxolane ring substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group. This is connected via a 3-(2,2,4,4-tetramethyl-1,3-dioxane-6-yl)propan-1-yl chain to a 2,5-dioxolane ring. The 2,5-dioxolane ring is further substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group. The 2,5-dioxolane ring is also substituted with a 4-methoxy-6-fluoro-1,2,3,4-tetrahydroquinazolin-2-ylmethyl group.

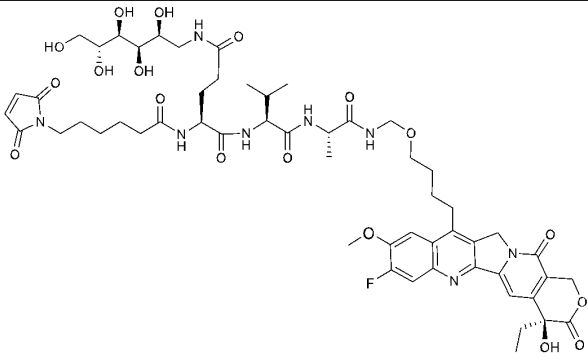
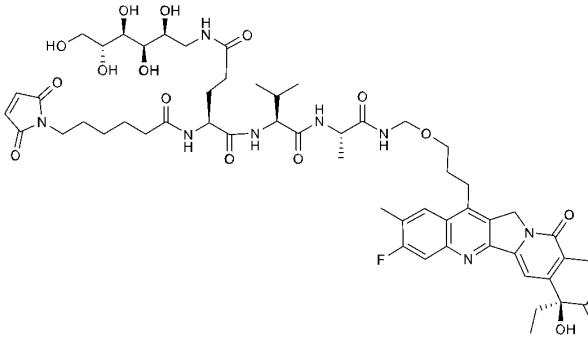
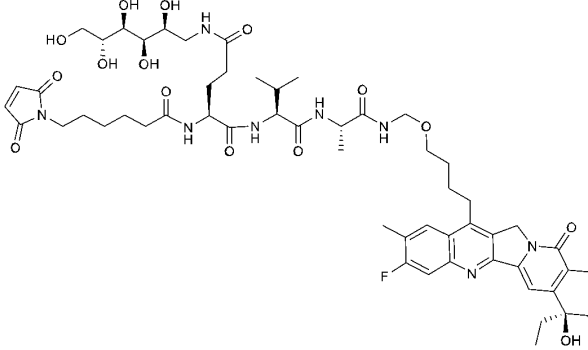
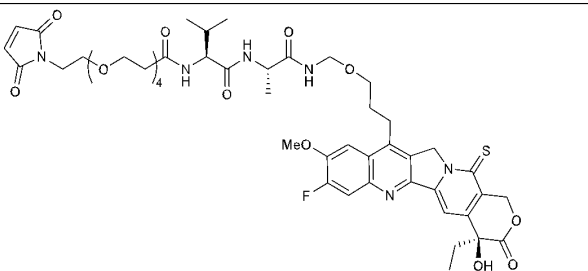
PL14'	Chemical structure of PL14' is a complex molecule. It features a pyridine ring substituted with a fluorine atom and a methyl group. This ring is connected via a methylene chain to a thiazole ring, which is further substituted with a methyl group and a hydroxyl group. The thiazole ring is linked to a side chain containing a hydroxyl group, a carbonyl group, and a methyl group. This side chain is connected to a long chain containing a hydroxyl group, a carbonyl group, and a methyl group. The chain ends with a pyridine ring substituted with a fluorine atom and a methyl group.
PL15'	Chemical structure of PL15' is a complex molecule. It features a pyridine ring substituted with a fluorine atom and a methyl group. This ring is connected via a methylene chain to a thiazole ring, which is further substituted with a methyl group and a hydroxyl group. The thiazole ring is linked to a side chain containing a hydroxyl group, a carbonyl group, and a methyl group. This side chain is connected to a long chain containing a hydroxyl group, a carbonyl group, and a methyl group. The chain ends with a pyridine ring substituted with a fluorine atom and a methyl group.
PL16'	Chemical structure of PL16' is a complex molecule. It features a pyridine ring substituted with a fluorine atom and a methyl group. This ring is connected via a methylene chain to a thiazole ring, which is further substituted with a methyl group and a hydroxyl group. The thiazole ring is linked to a side chain containing a hydroxyl group, a carbonyl group, and a methyl group. This side chain is connected to a long chain containing a hydroxyl group, a carbonyl group, and a methyl group. The chain ends with a pyridine ring substituted with a fluorine atom and a methyl group.
PL17'	Chemical structure of PL17' is a complex molecule. It features a pyridine ring substituted with a fluorine atom and a methyl group. This ring is connected via a methylene chain to a thiazole ring, which is further substituted with a methyl group and a hydroxyl group. The thiazole ring is linked to a side chain containing a hydroxyl group, a carbonyl group, and a methyl group. This side chain is connected to a long chain containing a hydroxyl group, a carbonyl group, and a methyl group. The chain ends with a pyridine ring substituted with a fluorine atom and a methyl group.

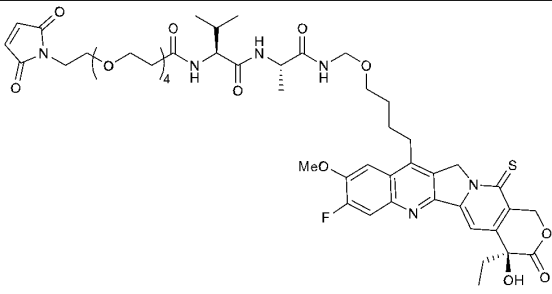
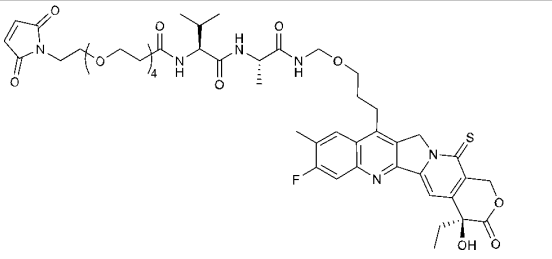
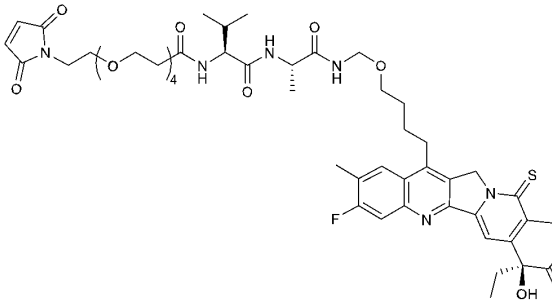
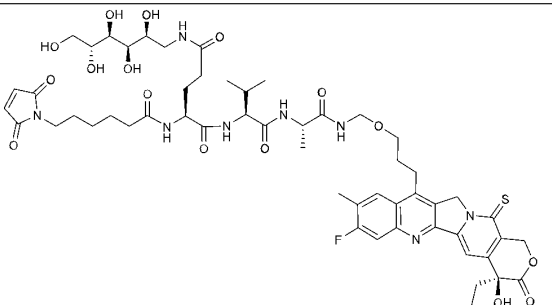
PL18'	Chemical structure of PL18' is a complex molecule. It features a succinimide ring on the left, connected via a polyether chain to a series of amide linkages. These linkages are connected to a central aromatic ring, which is further linked to a complex polycyclic system on the right. This system includes a quinoline-like core with a fluorine substituent and a fused lactone ring.
PL19'	Chemical structure of PL19' is a complex molecule. It features a succinimide ring on the left, connected via a polyether chain to a series of amide linkages. These linkages are connected to a central aromatic ring, which is further linked to a complex polycyclic system on the right. This system includes a quinoline-like core with a fluorine substituent and a fused lactone ring. or
PL20'	Chemical structure of PL20' is a complex molecule. It features a bicyclic system on the left, connected via a polyether chain to a series of amide linkages. These linkages are connected to a central aromatic ring, which is further linked to a complex polycyclic system on the right. This system includes a quinoline-like core with a fluorine substituent and a fused lactone ring.

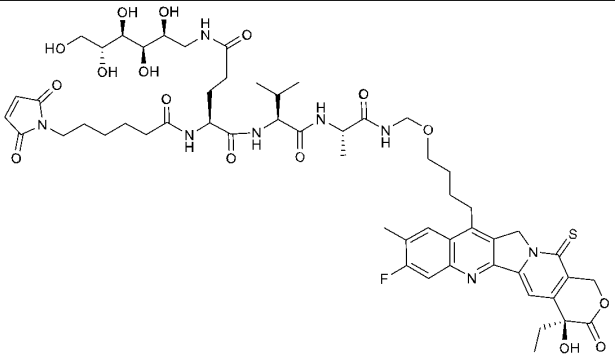
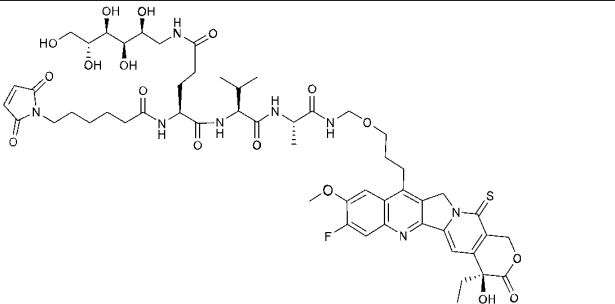
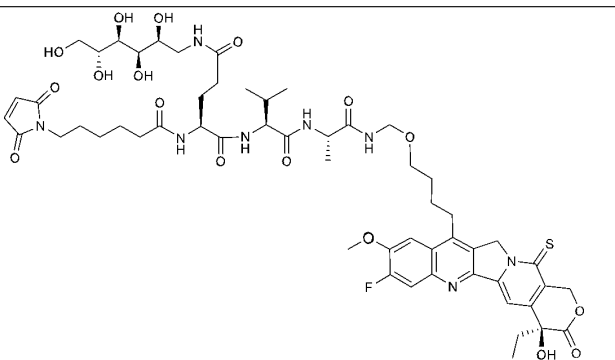
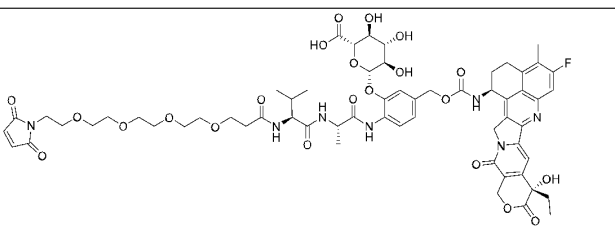
In some embodiments, the compound of Formula (II) is:

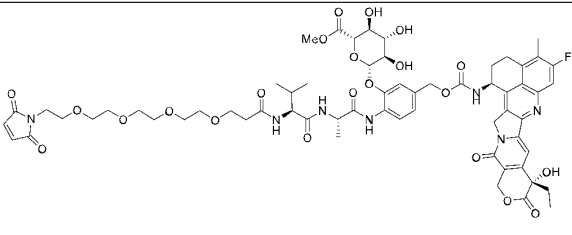
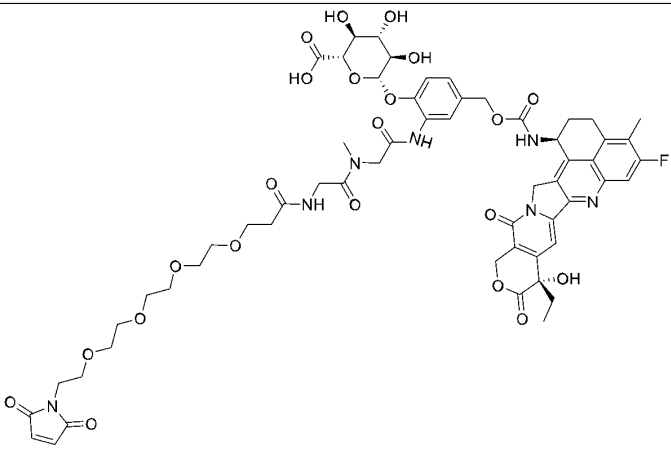
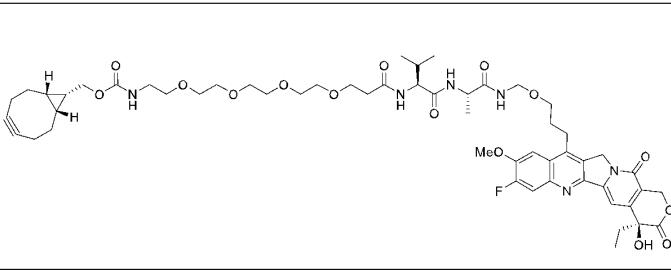
PL1	Chemical structure of PL1 is a complex molecule. It features a succinimide ring on the left, connected via a polyether chain to a series of amide linkages. These linkages are connected to a central aromatic ring, which is further linked to a complex polycyclic system on the right. This system includes a quinoline-like core with a fluorine substituent and a fused lactone ring.
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PL2	
PL3	
PL4	
PL5	

PL6	
PL7	
PL8	
PL9	

PL10	
PL11	
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PL13	

PL14	
PL15	
PL16	
PL17	

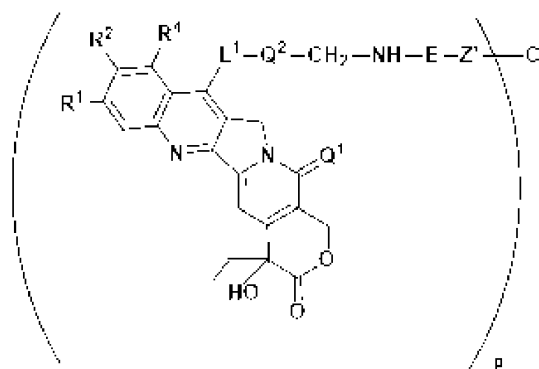
PL18	
PL19	
PL20	

or pharmaceutically acceptable salt thereof.

The present disclosure further provides an antibody-drug conjugate comprising a drug and an antibody, wherein the drug includes a compound of Formula (II'), (II), (IIa') or (IIa), or a derivative thereof.

5

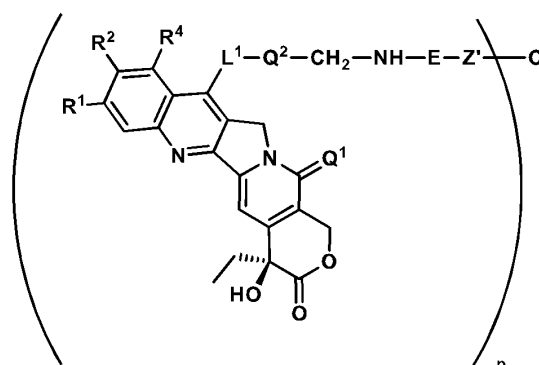
The present disclosure further provides, a compound of Formula (III'):



Formula (III'),

or a pharmaceutically acceptable salt thereof.

The present disclosure further provides, a compound of Formula (III):



Formula (III),

or a pharmaceutically acceptable salt thereof.

wherein in Formula (III') and Formula (III):

C is a cell binding agent;

R¹ is selected from halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

R² is selected from H, -OH, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

Q¹ is S or O;

L¹ is C₁₋₆ alkylene;

Q² is selected from -S-, -O-, *-NHC(=O)-C₁₋₆ alkylene-O- and *-NHC(=S)-C₁₋₆ alkylene-O-*, wherein the asterisk (*) represents the point of attachment to L¹;

E is a peptide including 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol;

the N terminal of the peptide is covalently attached to Z;

Z' is $-C(=O)-L^2-Y'$,

L^2 is selected from C_{1-6} alkylene, $-(CH_2CH_2-O)_n-C_{1-6}$ alkylene-*, and $-C_{1-6}$ alkylene- $(O-CH_2CH_2)_n$ -*,

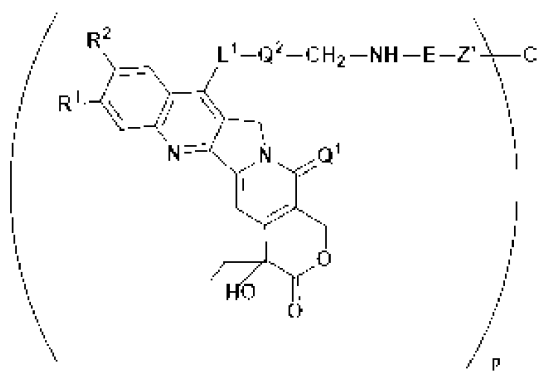
n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

the asterisk (*) represents the point of attachment to Y' ;

Y' is a group formed by a reaction of an electrophilic group with a reactive nucleophilic group present on the cell binding agent; and

p is the drug to antibody ratio (DAR) and p has a value between 1 to 18, for example, a value between 2-10, 4-8, 7-8, or 3.2 to 8.0, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

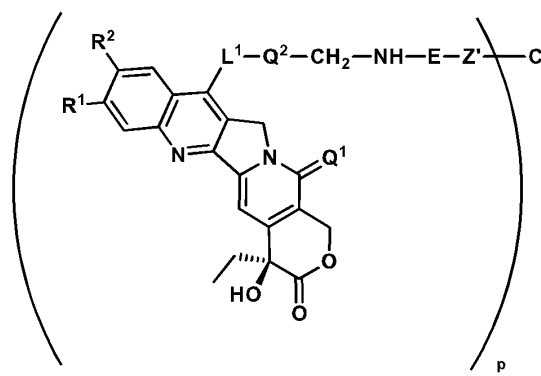
In some embodiments, the compound of Formula (III') is a compound of Formula (IIIa'),



Formula (IIIa'),

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , L^1 , Q^1 , Q^2 , E , Z' , and C are as defined herein.

In some embodiments, the compound of Formula (III) is a compound of Formula (IIIa),



Formula (IIIa),

or a pharmaceutically acceptable salt thereof, wherein R¹, R², L¹, Q¹, Q², E, Z', and C are as defined herein.

In Formula (III'), (III), (IIIa') and (IIIa), R¹ can be halo, C₁₋₆ alkyl or C₁₋₆ alkoxy.

5 In some embodiments, R¹ is halo. In some embodiments, R¹ is fluoro, chloro, or bromo. In some embodiments, R¹ is fluoro. In some embodiments, R¹ is C₁₋₆ alkyl or C₁₋₆ alkoxy. In some embodiments, R¹ is C₁₋₆ alkyl. In some embodiments, R¹ is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl. In some embodiments, R¹ is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R¹ is methyl. In some
10 embodiments, R¹ is ethyl. In some embodiments, R¹ is n-propyl. In some embodiments, R¹ is isopropyl. In some embodiments, R¹ is C₁₋₆ alkoxy. In some embodiments, R¹ is methoxy or ethoxy. In some embodiments, R¹ is methoxy. In some embodiments, R¹ is ethoxy.

In Formula (III'), (III), (IIIa') and (IIIa), R² can be C₁₋₆ alkyl or C₁₋₆ alkoxy. In
15 some embodiments, R² is C₁₋₆ alkyl or C₁₋₆ alkoxy. In some embodiments, R² is C₁₋₆ alkyl. In some embodiments, R² is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl. In some embodiments, R² is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R² is methyl. In some embodiments, R² is ethyl. In some
20 embodiments, R² is n-propyl. In some embodiments, R² is isopropyl. In some embodiments, R² is C₁₋₆ alkoxy. In some embodiments, R² is methoxy or ethoxy. In some embodiments, R² is methoxy. In some embodiments, R² is ethoxy.

In Formula (III'), (III), (IIIa') and (IIIa), Q¹ can be O or S. In some embodiments, Q¹ is O. In some embodiments, Q¹ is S.

In Formula (III'), (III), (IIIa') and (IIIa), L^1 can be C_{3-4} alkylene. In some embodiments, L^1 is C_{3-4} alkylene.

In Formula (III'), (III), (IIIa') and (IIIa), Q^2 can be O or S. In some embodiments, Q^2 is O. In some embodiments, Q^2 is S.

5 In Formula (III'), (III), (IIIa') and (IIIa), $-L^1-Q^2$ can be $^*-CH_2CH_2CH_2O-$ or $^*-CH_2CH_2CH_2CH_2O-$, wherein the asterisk (*) represents the point of attachment to L^1 . In some embodiments, $-L^1-Q^2$ is $^*-CH_2CH_2CH_2O-$, wherein the asterisk (*) represents the point of attachment to L^1 . In some embodiments, $-L^1-Q^2$ is $^*-CH_2CH_2CH_2CH_2O-$, wherein the asterisk (*) represents the point of attachment to L^1 .

10 In Formula (III') and (III), R^4 can be H. In some embodiments, R^4 is H.

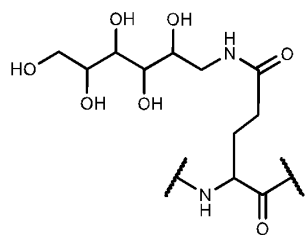
In Formula (III') and (III), R^4 together with L^1 can form a 5-8 membered carbocycle. In some embodiments, R^4 together with L^1 form a 5-8 membered carbocycle. In some embodiments, R^4 together with L^1 form a 6-membered carbocycle. In some embodiments, R^4 together with L^1 form a 6-membered carbocycle, and Q^2 is selected from $^*-NHC(=O)-C_{1-6}$ alkylene-O- and $^*-NHC(=S)-C_{1-6}$ alkylene-O-, wherein the asterisk represents to point of attachment to L^1 . In some embodiments, R^4 together with L^1 form a 6-membered carbocycle, and Q^2 is selected from $^*-NHC(=O)-CH_2-O-$ and $^*-NHC(=S)-CH_2-O-$, wherein the asterisk (*) represents the point of attachment to L^1 .

20 In some embodiments, in Formula (III') and (III), R^1 is fluoro; R^2 is C_{1-4} alkyl or C_{1-4} alkoxy; Q^1 is S or O; R^4 is H; L^1 is C_{1-6} alkylene; Q^2 is $-S-$ or $-O-$; E is a peptide including 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol; the N terminal of the peptide is covalently attached to Z' ; Z' is $-C(=O)-L^2-Y'$, L^2 is selected from C_{1-6} alkylene, $-(CH_2CH_2-O)_n-C_{1-6}$ alkylene-*, and $-C_{1-6}$ alkylene-(O- CH_2CH_2) $_n$ -, n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; the asterisk (*) represents the point of attachment to Y' ; Y' is a group formed by a reaction of an electrophilic group with a reactive nucleophilic group present on the cell binding agent; and p is the drug to antibody ratio (DAR) and p has a value between 1 to 18.

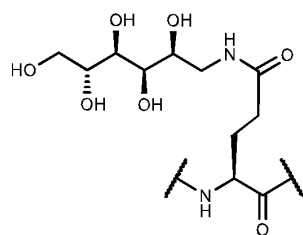
25 In some embodiments, in Formula (III') and (III), R^1 is fluoro; R^2 is C_{1-4} alkoxy; Q^1 is O; R^4 is H; L^1 is C_{1-6} alkylene; Q^2 is $-O-$; E is a peptide including 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol; the N

terminal of the peptide is covalently attached to Z'; Z' is -C(=O)-L²-Y', L² is -(CH₂CH₂-O)_n-C₁₋₆ alkylene-*, n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; the asterisk (*) represents the point of attachment to Y'; Y' is a group formed by a reaction of an electrophilic group with a reactive nucleophilic group present on the cell binding agent; and p is the drug to antibody ratio (DAR) and p has a value between 1 to 18.

In Formula (III'), (III), (IIIa') and (IIIa), E can be a peptide including 2 to 10 amino acids, and the N terminal of the peptide is covalently attached to Z'. In some embodiments, E is a peptide including 2 to 10 amino acids, and the N terminal of the peptide is covalently attached to Z'. In some embodiments, E is a peptide including 2 to 8 amino acids, and the N terminal of the peptide is covalently attached to Z'. In some embodiments, E is a peptide including 2 to 6 amino acids, and the N terminal of the peptide is covalently attached to Z'. In some embodiments, E is a peptide including 2 to 4 amino acids, and the N terminal of the peptide is covalently attached to Z'. In some embodiments, E is a peptide including 2 to 3 amino acids, and the N terminal of the peptide is covalently attached to Z'. In some embodiments, each amino acid of E is an L amino acid, or at least one amino acid of E is a D amino acid. In some embodiments, E includes one or more amino acids selected from glycine, alanine, valine, glutamine, glutamic acid, phenylalanine, and leucine. In some embodiments, one or more amino acid of E is substituted with one or more polyol. In some embodiments, one or more of the glutamine or glutamic acid of E is substituted with one or more polyol. In some embodiments, E includes an amino acid having the following structure,

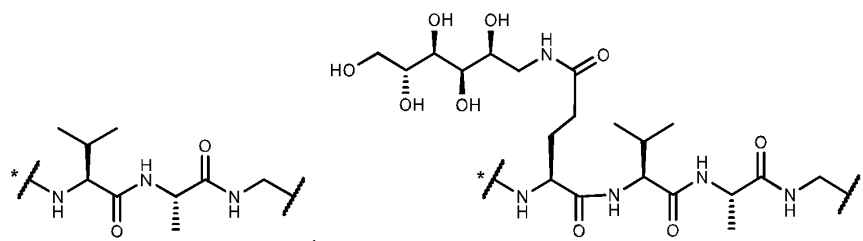


. In some embodiments, E includes an amino acid having the following structure,



. In some embodiments, E is selected from -Ala-Val-*, -Val-Ala-*, -Gly-Gly-*, -Val-Cit-*, -Cit-Val-*, -Leu-Ala-*, -Ala-Leu-*, -Leu-Cit-*, -Cit-Leu-*, -Leu-Ala-*, -Ala-Leu-*, -Lys-Lys-*, -Ala-Lys-*, -Lys-Ala-*, -Val-Lys-*, -Lys-Val-*, -Tyr-Arg-*, -Arg-Tyr-*, -Arg-Arg-*, -Ala-Ala-*, -Phe-Lys-*, -Lys-Phe-*, -Thr-Thr-*, -Thr-Met-*, -Met-Thr-*, -Met-Tyr-*, -Tyr-Met-*, -Phe-Gln-*, -Gln-Phe-*, -Gly-Ser-*, -Leu-Gln-*, -Gln-Leu-*, -Ser-Ala-*, -Ser-Gly-*, -Val-Thr-*, -Thr-Val-*, -Val-Gln-*, -Ser-Val-*, -Val-Ser-*, -Ala-Met-*, -Met-Ala-*, -Val-Arg-*, -Arg-Val-*, -Phe-Ala-*, -Ala-Phe-*, -Cit-Val-*, -Gln-Val-*, -Phe-Arg-*, -Arg-Phe-*, -Ala-Val-Glu-*, -Ala-Ala-Ala-*, -Gly-Gly-Gly-*, -Ala-Val-Ala-*, -Gly-Val-Gly-*, -Ala-Val-Gly-*, -Gly-Phe-Lys-*, -Lys-Phe-Gly-*, -Leu-Ala-Leu-*, -Val-Ala-Leu-*, -Leu-Ala-Val-*, -Val-Ala-Val-*, -Ala-Val-Ala-Gly-*, -Gly-Phe-Gly-Gly-*, -Gly-Gly-Phe-Gly-*, -Ala-Val-Gly-Gly-*, -Ala-Ala-Ala-Ala-*, -Ala-Val-Ala-Ala-*, -Ala-Leu-Ala-Leu-*, -Leu-Ala-Leu-Ala-*, -Gly-Phe-Leu-Gly-*, and -Gly-Leu-Phe-Gly-*, wherein the Glu is optionally substituted with a polyol, and wherein * represents the N-terminal of the peptides covalently attached to Z'. In some embodiments, E is selected from -Ala-Val-*, -Val-Ala-*, -Val-Lys-*, -Val-Arg-*, -Val-Cit-*, -Val-Arg-*, -Val-Cit-*, -Val-Lys-*, -Val-Arg-*, -Arg-Arg-*, -Ala-Ala-*, -Ala-Lys-*, -Ala-Arg-*, -Ala-Val-Glu-*, -Ala-Ala-Ala-*, -Ala-Val-Ala-*, -Ala-Ala-Gly-*, and -Ala-Val-Gly-*, wherein the Glu is optionally substituted with a polyol, and wherein the asterisk (*) represents the N-terminal of the peptides covalently attached to Z'. In some embodiments, E is selected from -Ala-Val-* and -Ala-Val-Glu-*, wherein the Glu is optionally substituted with a polyol, and wherein * represents the N-terminal of the peptides covalently attached to Z'. In some embodiments, E is -Ala-Val-*, wherein the asterisk (*) represents the N-terminal of the peptides covalently attached to Z'. In some embodiments, E is -Ala-Val-Glu-*, wherein the Glu is substituted with a polyol, and wherein the asterisk (*) represents the N-terminal of the peptides covalently attached to Z'.

In some embodiments, in Formula (III'), (III), (IIIa') and (IIIa), -E-NH-CH₂- has one of the following structures, wherein the asterisk (*) represents the N-terminal of the peptides covalently attached to Z':

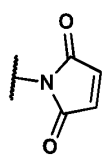


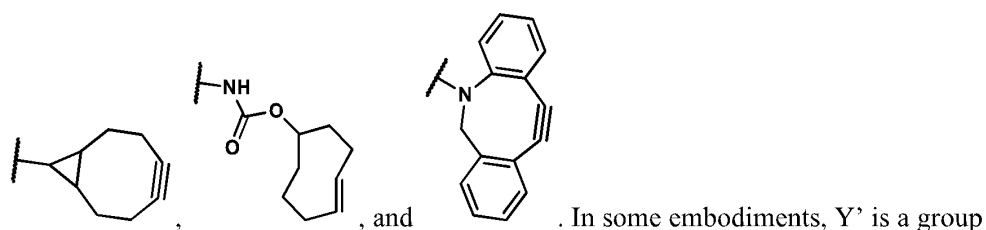
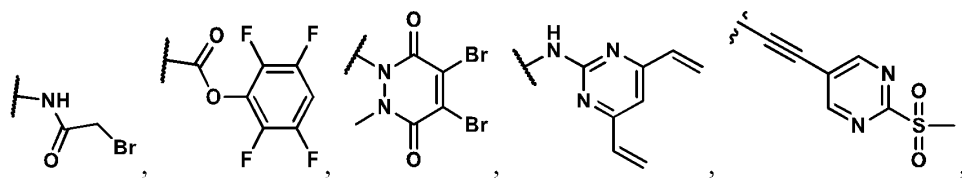
5 wherein (*) represents the N-terminal of the peptides covalently attached to Z'.

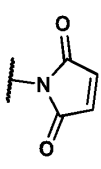
In Formula (III'), (III), (IIIa') and (IIIa), L² can be C₁₋₆ alkylene, -(CH₂CH₂-O)_n-C₁₋₆ alkylene-*, or -C₁₋₆ alkylene-(O-CH₂CH₂)_n*, wherein n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and wherein the asterisk (*) represents the point of attachment to Y'. In some embodiments, L² is C₁₋₆ alkylene. In some embodiments, L² is C₃₋₆ alkylene. In some embodiments, L² is -(CH₂)₅-. In some embodiments, L² is selected from -(CH₂CH₂-O)_n-C₁₋₆ alkylene-*, and -C₁₋₆ alkylene-(O-CH₂CH₂)_n*, wherein n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and wherein the asterisk (*) represents the point of attachment to Y'. In some embodiments, n is 2, 3, 4 or 5. In some embodiments, n is 2, 3 or 4. In some embodiments, n is 3 or 4. In some embodiments, n is 4. In some embodiments, L² is selected from -(CH₂CH₂-O)₄-C₁₋₄ alkylene-*, and -C₁₋₄ alkylene-(O-CH₂CH₂)₄*, wherein the asterisk (*) represents the point of attachment to Y'. In some embodiments, L² is selected from -(CH₂CH₂-O)₄-CH₂CH₂*, and -CH₂CH₂-(O-CH₂CH₂)₄*, and wherein the asterisk (*) represents the point of attachment to Y'.

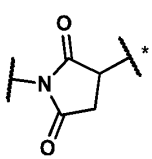
20 In some embodiments, in Formula (III'), (III), (IIIa') and (IIIa), Y' is a group formed by a reaction of a reactive group such as an electrophilic group with another reactive group such as a reactive nucleophilic group present on the cell binding agent, wherein the reactive group is as defined above for group Y.

25 In some embodiments, in Formula (III'), (III), (IIIa') and (IIIa), Y' is a group formed by a reaction of an electrophilic group with a reactive nucleophilic group present

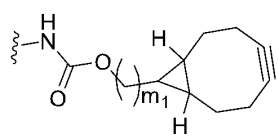
on the cell binding agent, wherein the electrophilic group is selected from ,



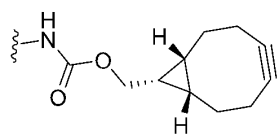
formed by a reaction of  with a reactive nucleophilic group present on the cell

- 5 binding agent. In some embodiments, Y' is , wherein the asterisk (*) represents the point of attachment to C.

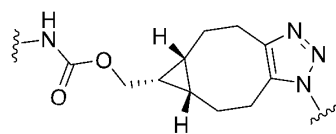
In some embodiments, Y' is a group formed by a reaction of



wherein m_1 is defined as above (preferably



) with a reactive group (such as azide group) present on the cell



binding agent. In some embodiments, Y' is
 asterisk (*) represents the point of attachment to C.

In some embodiments, in Formula (III'), (III), (IIIa') and (IIIa), the cell binding agent is an antibody or an antigen-binding fragment thereof. In some embodiments, the cell binding agent is a monoclonal antibody or an antigen-binding fragment thereof. In some embodiments, the antibody or antigen-binding fragment is an anti-Her2 antibody, an anti-Her3 antibody or antigen-binding fragment, an anti-C-Met antibody or antigen-binding fragment, an anti-B7-H3 antibody or antigen-binding fragment, an anti-B7-H4 antibody or antigen-binding fragment, an anti-CEACAM5 antibody or antigen-binding fragment, an anti-Trop2 antibody or antigen-binding fragment, and/or an anti-CEA antibody or antigen-binding fragment. In some embodiments, the antibody or antigen-binding fragment is an antibody or an antigen-binding fragment against PD-1, OX40, LAG3, CD47, IL23, PCSK9, CTLA4, KRAS, OX40L, CD40, CD40L, HER2 (e.g., Trastuzumab (Herceptin®)), PDE4, FR α , PSMA, BCMA, Claudins, and/or PD-L1. In some embodiments, the antibody or an antigen-binding fragment is an anti-Her2 antibody or antigen-binding fragment, an anti-Her3 antibody or antigen-binding fragment, an anti-C-Met antibody or antigen-binding fragment (e.g., an antibody as disclosed in US8455623B2 or US20150147274A1, which are herein incorporated by reference in their entirety), an anti-B7-H3 antibody or antigen-binding fragment, an anti-B7-H4 antibody or antigen-binding fragment, an anti-CEACAM5 antibody or antigen-binding fragment, and/or an anti-Trop2 antibody or antigen-binding fragment. In some embodiments, the antibody is Trastuzumab.

In some embodiments, the cell binding agent is linked to Y' by a sulfur atom of the cell binding agent.

In some embodiments, the cell binding agent is linked to Y' by a glycan chain of the cell binding agent. In some embodiments, the glycan chain of the cell binding agent is a modified glycan chain. In some embodiments, the glycan chain of the cell binding agent comprises (preferably at the terminus linking to Y') or consists of 2 to 10 (such as

2, 3, 4, 5, 6, 7, 8, 9 or 10) single sugars or derivatives thereof. In some embodiments, the single sugars or derivatives thereof are selected from N- acetyl glucosamine (GlcNAc), fucose (Fuc), Galactose (Gal), mannose (Man), glucose (Glc), N-acetylgalactosamine (GalNAc), glucuronic acid (Gcu), and N-acetylneuraminic acid (sialic acid). In some

5 embodiments, the single sugar or derivative thereof is linked to other sugar(s) or derivative(s) thereof via β (1,4)- or β (1,3)- glucoside linkage and/or α (1,4)- or α (1,3)- glucoside linkage. In some embodiment, the glycan chain comprises or consists of

$$\begin{array}{c} \text{(Fuc)}_b \\ | \\ \text{---GlcNAc---GlcNAcMan---}^* \end{array}$$

wherein b is 0 or 1, the asterisk (*) represents the point of attachment to Y', the left terminus of the glycan chain is linked to the remaining part of

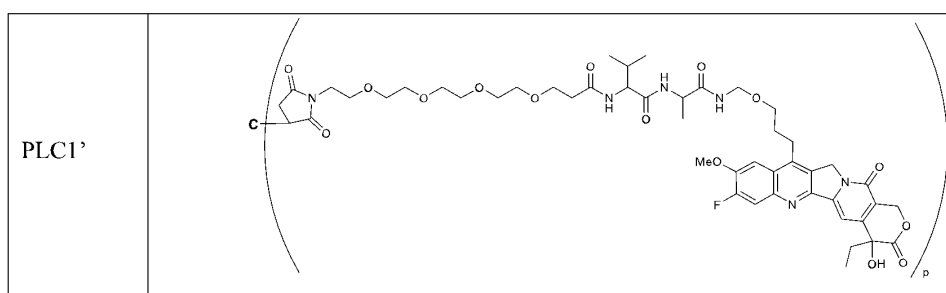
10 the cell binding agent.. In some embodiment, one glycan chain is linked to 1, 2, 3 or 4 linker-payloads. In some embodiment, the glycan chains are present at glycosylation site of Asn 297 of heavy chains.

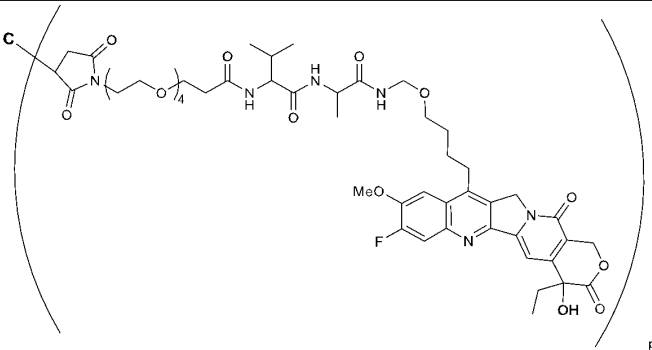
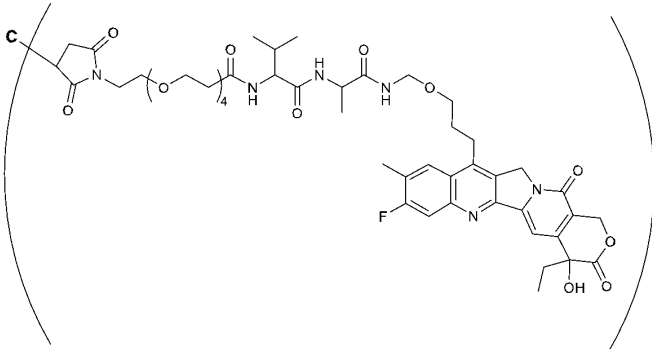
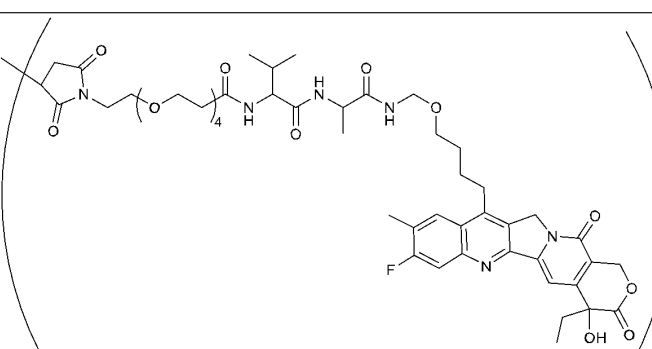
In some embodiments, in Formula (III'), (III), (IIIa') and (IIIa), p has a value

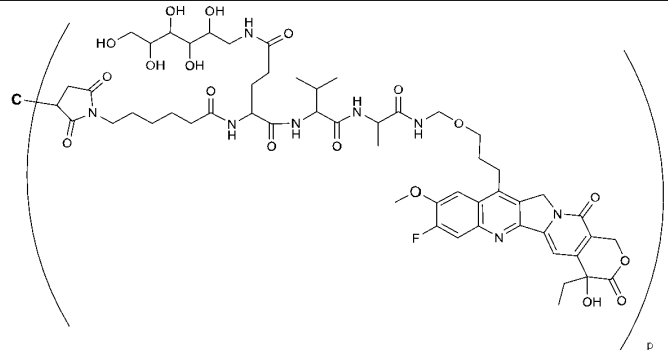
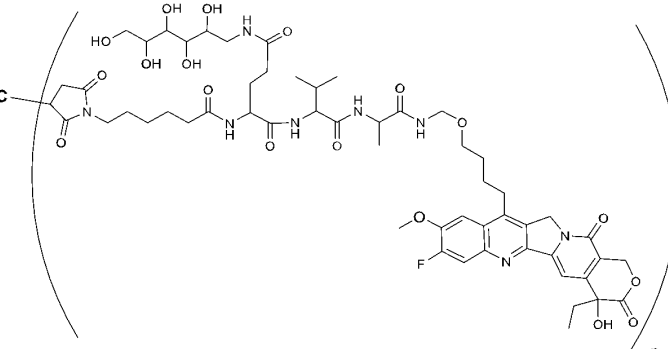
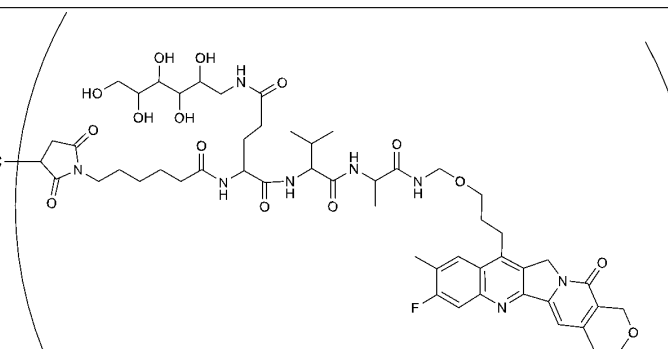
15 between 2-10, 4-8, 7-8, or 3.2 to 8.0.

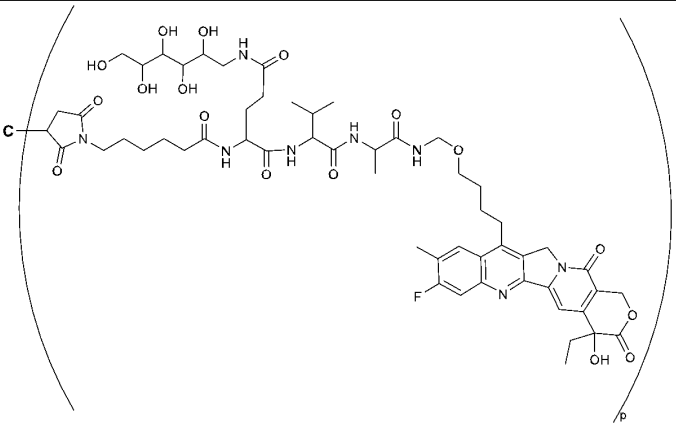
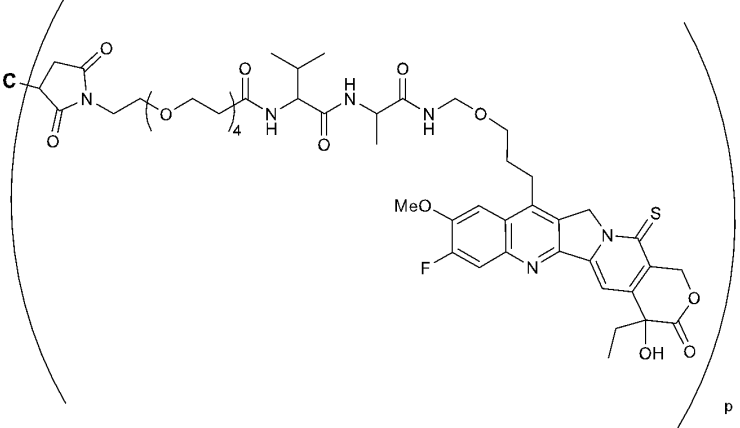
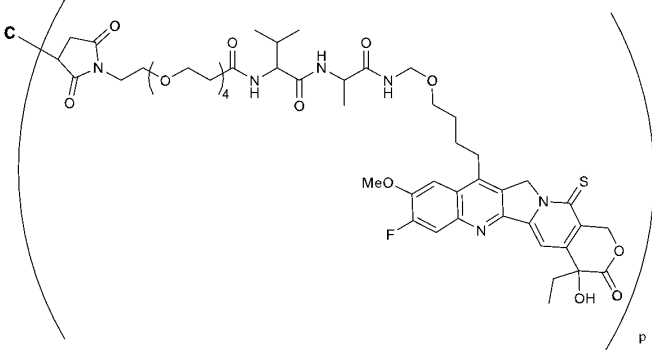
In some embodiments, the compounds of Formula (III'), (III), (IIIa') and (IIIa) are an ADC.

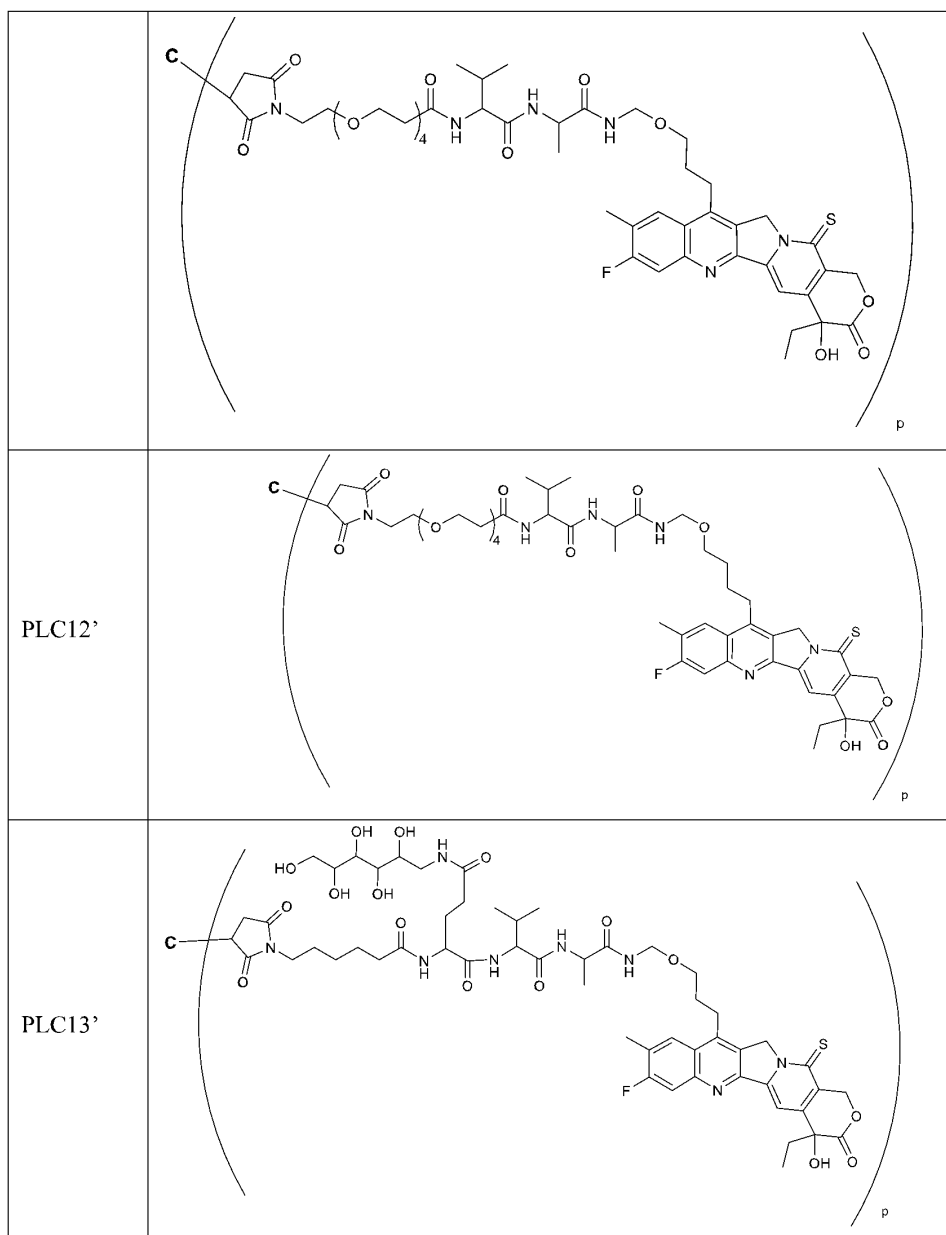
In some embodiments, the compound of Formula (III') is:

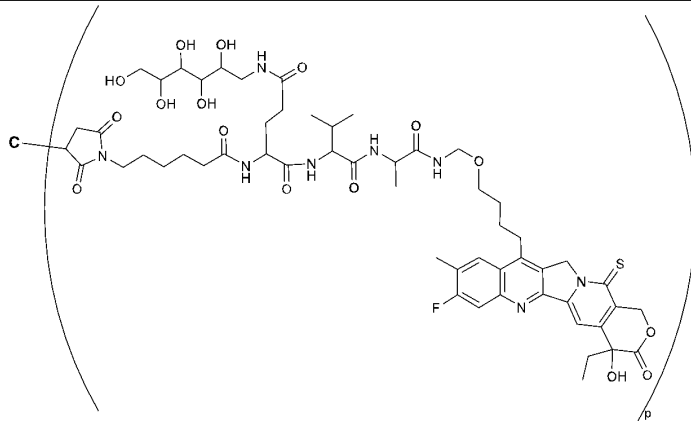
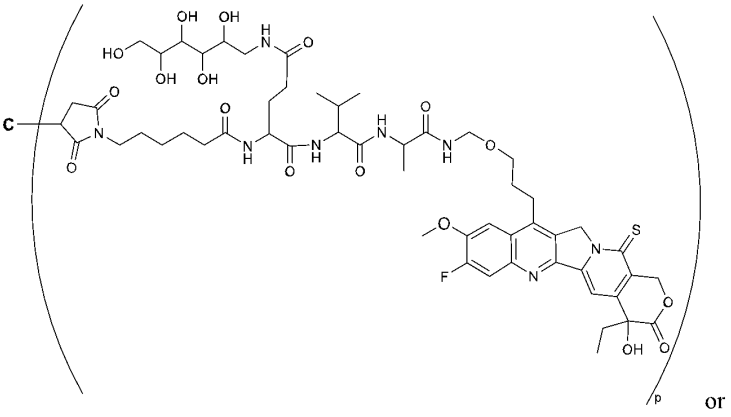
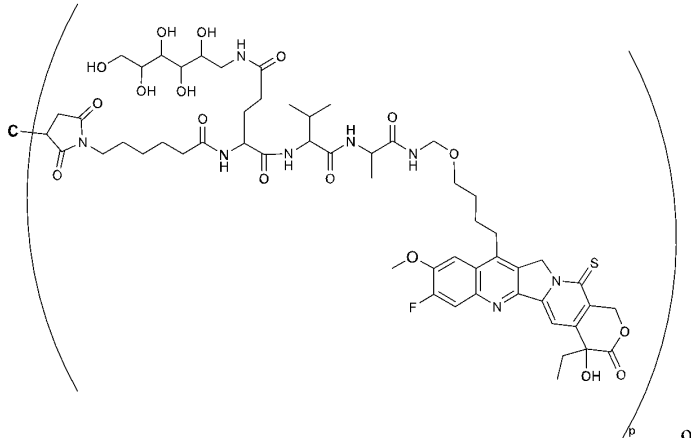


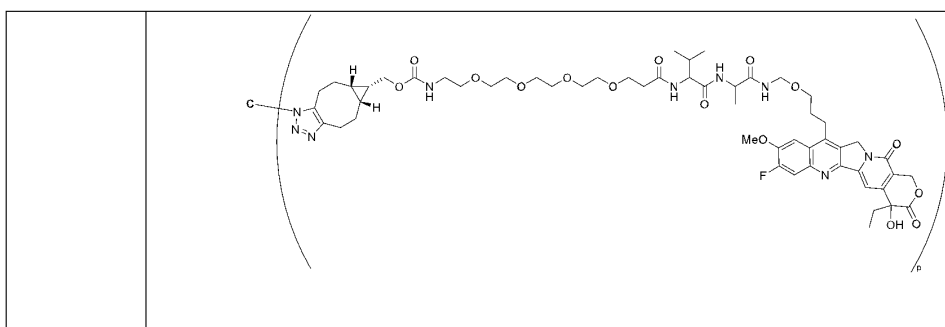
PLC2'	
PLC3'	
PLC4'	

PLC5'	 Chemical structure of PLC5' derivative. The molecule consists of a central linker chain (HO-CH2-CH(OH)-CH(OH)-CH(OH)-CH2-NH-CO-) connected to a 5-membered lactam ring (labeled 'C') and a complex polycyclic system (labeled 'P'). The polycyclic system includes a quinoline-like core with a fluorine atom and a methoxy group, and a fused ring system with a hydroxyl group and a carbonyl group.
PLC6'	 Chemical structure of PLC6' derivative. The molecule consists of a central linker chain (HO-CH2-CH(OH)-CH(OH)-CH(OH)-CH2-NH-CO-) connected to a 5-membered lactam ring (labeled 'C') and a complex polycyclic system (labeled 'P'). The polycyclic system includes a quinoline-like core with a fluorine atom and a methoxy group, and a fused ring system with a hydroxyl group and a carbonyl group.
PLC7'	 Chemical structure of PLC7' derivative. The molecule consists of a central linker chain (HO-CH2-CH(OH)-CH(OH)-CH(OH)-CH2-NH-CO-) connected to a 5-membered lactam ring (labeled 'C') and a complex polycyclic system (labeled 'P'). The polycyclic system includes a quinoline-like core with a fluorine atom and a methoxy group, and a fused ring system with a hydroxyl group and a carbonyl group.

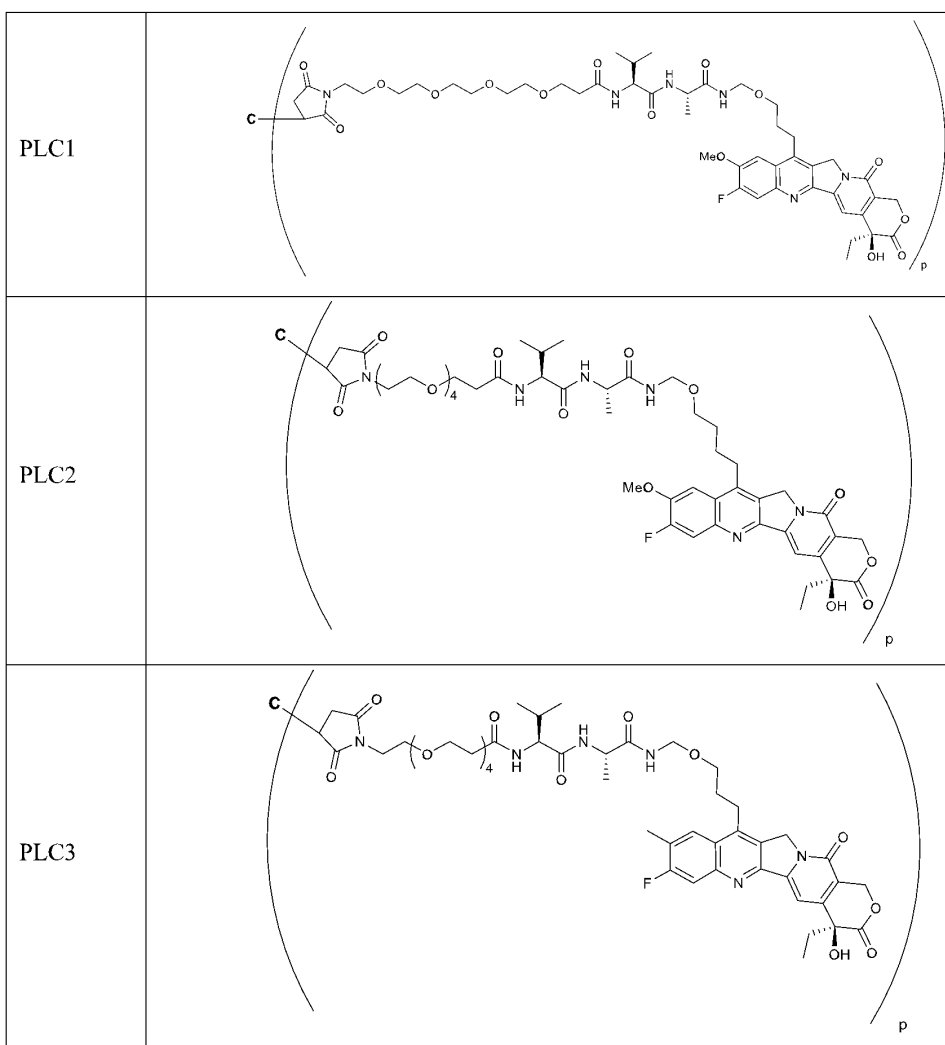
PLC8'	
PLC9'	
PLC10'	
PLC11'	

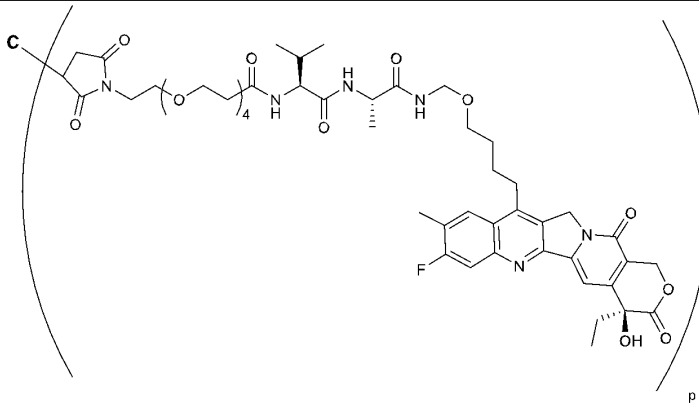
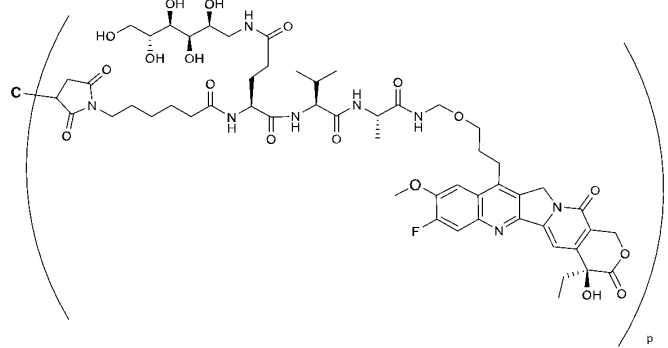
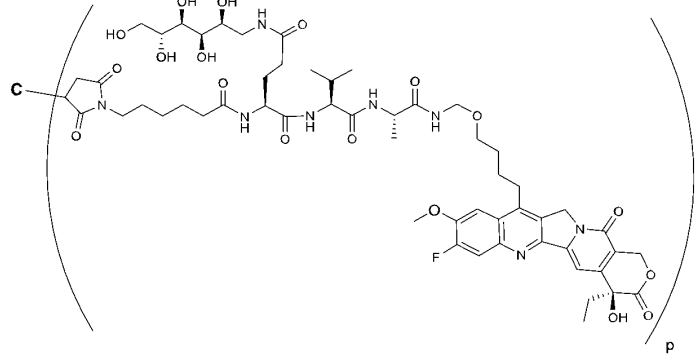


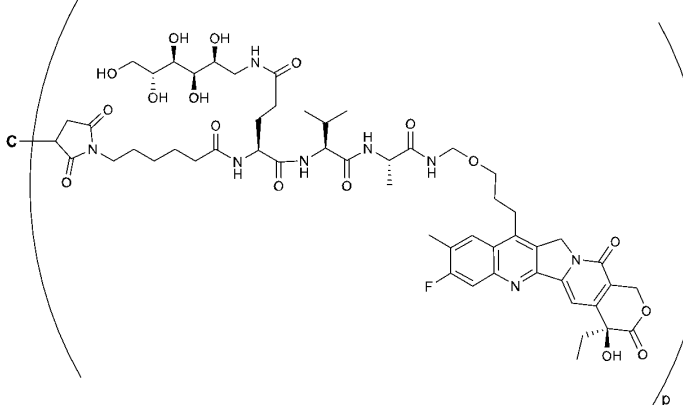
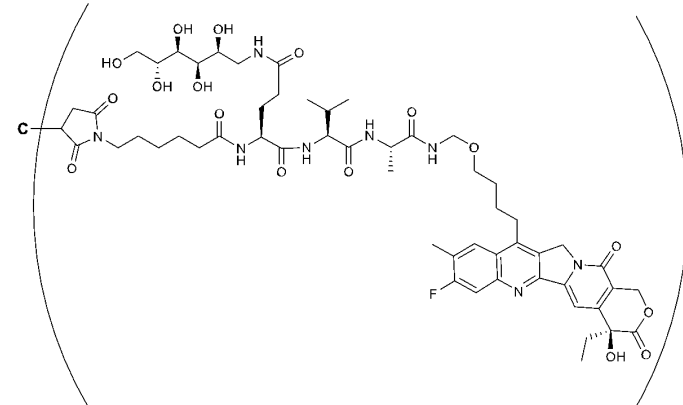
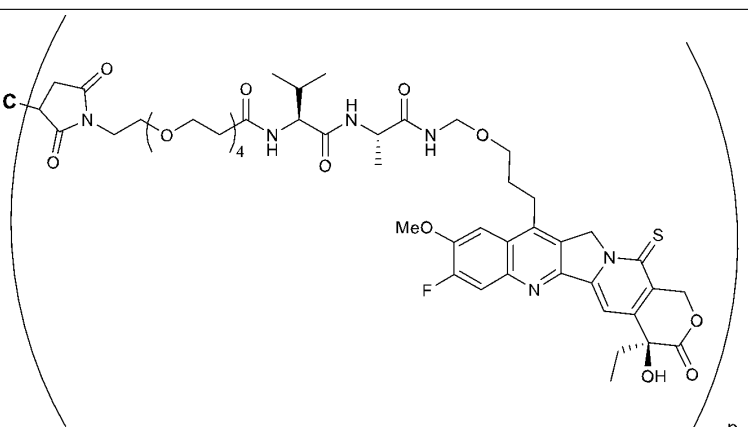
PLC14'	
PLC15'	 or
PLC16'	 or
PLC17'	

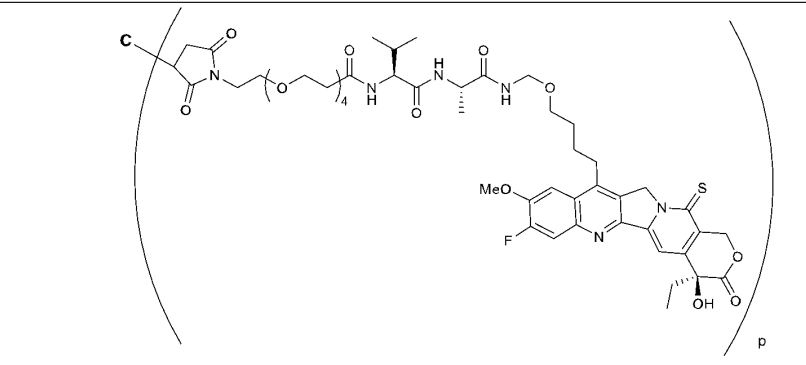
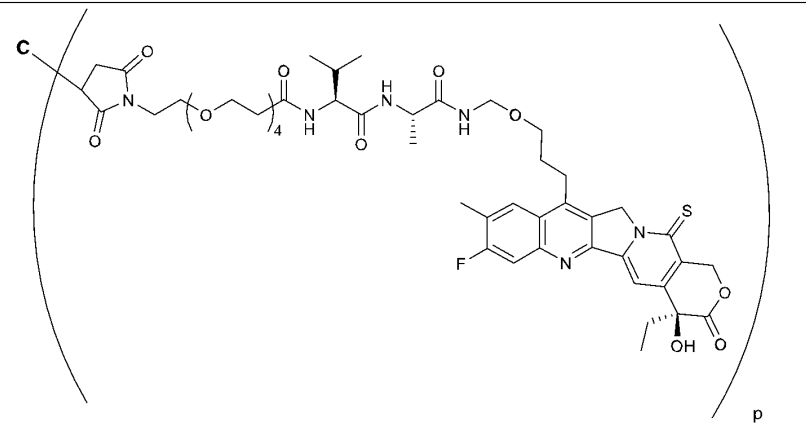
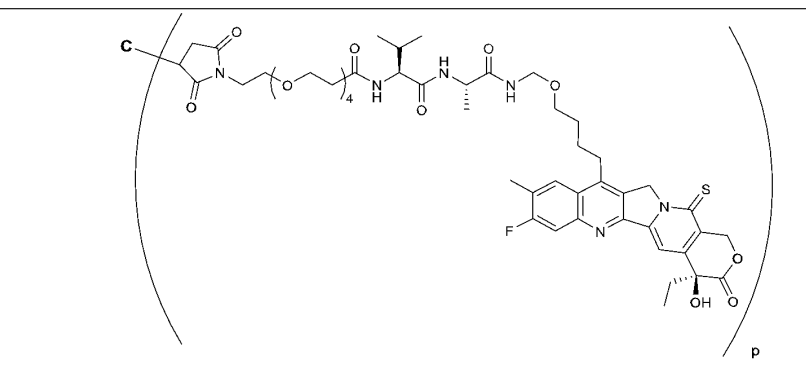


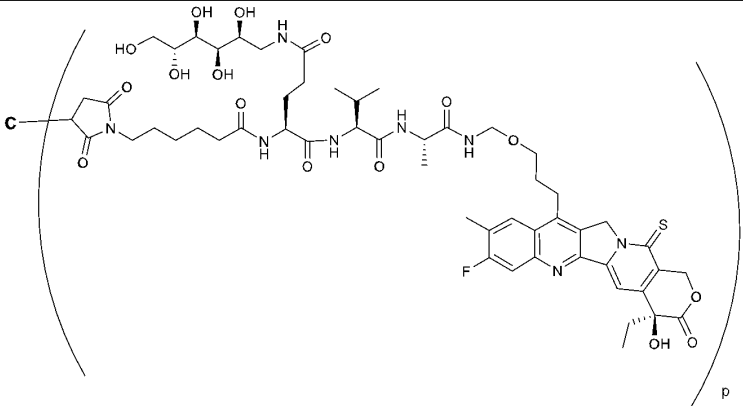
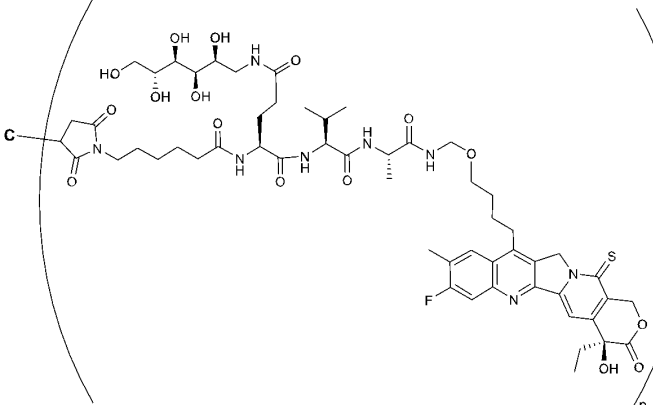
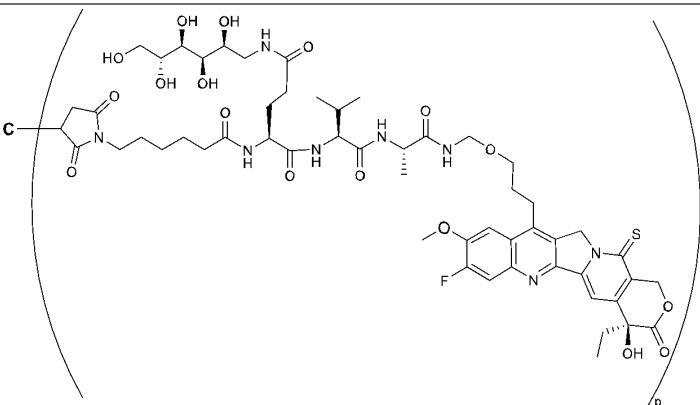
In some embodiments, the compound of Formula (III) is:

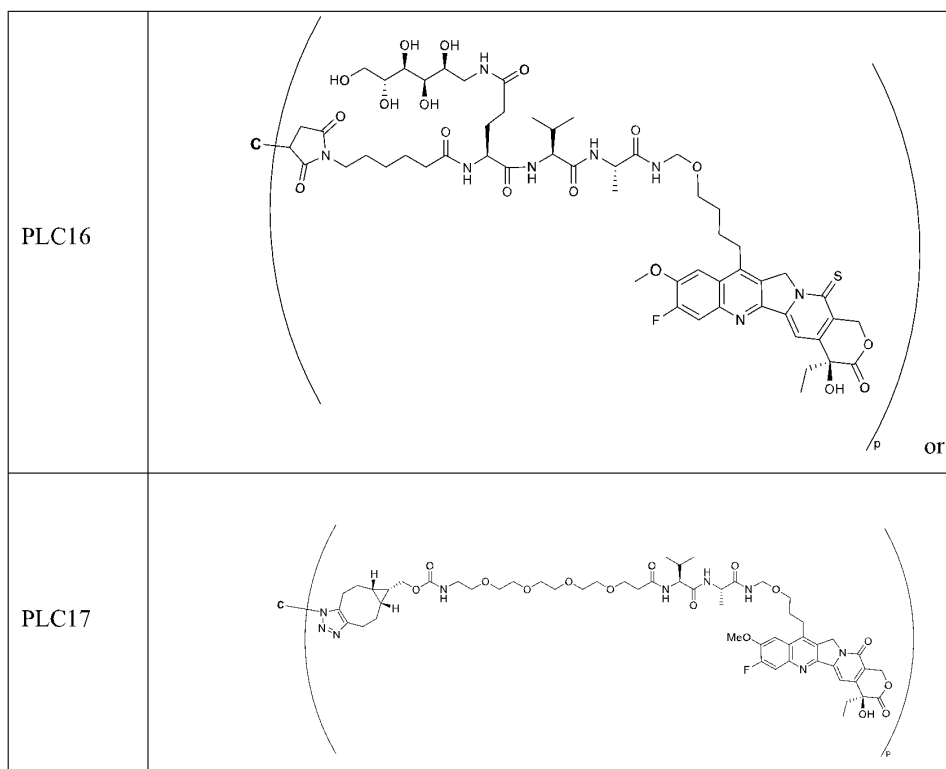


PLC4	 Chemical structure of PLC4, showing a polymer chain (C) with a repeating unit of a poly(ether amide) and a terminal unit of a poly(ether amide) linked to a complex heterocyclic system (P). The heterocyclic system includes a benzimidazole core with a fluorine substituent and a fused lactone ring.
PLC5	 Chemical structure of PLC5, showing a polymer chain (C) with a repeating unit of a poly(ether amide) and a terminal unit of a poly(ether amide) linked to a complex heterocyclic system (P). The heterocyclic system includes a benzimidazole core with a fluorine substituent and a fused lactone ring.
PLC6	 Chemical structure of PLC6, showing a polymer chain (C) with a repeating unit of a poly(ether amide) and a terminal unit of a poly(ether amide) linked to a complex heterocyclic system (P). The heterocyclic system includes a benzimidazole core with a fluorine substituent and a fused lactone ring.

PLC7	 Chemical structure of PLC7, a polymer repeat unit. The structure is enclosed in large parentheses with a subscript 'p' at the bottom right. It features a central chain with a 2,3,4,5-tetrahydroxybutyrate moiety, a 2,3-dihydroxybutyrate moiety, and a 2,3-dihydroxybutyrate moiety. The chain is terminated by a 2,3-dihydroxybutyrate moiety on the left and a 2,3-dihydroxybutyrate moiety on the right. The chain is also terminated by a 2,3-dihydroxybutyrate moiety on the left and a 2,3-dihydroxybutyrate moiety on the right. The chain is also terminated by a 2,3-dihydroxybutyrate moiety on the left and a 2,3-dihydroxybutyrate moiety on the right.
PLC8	 Chemical structure of PLC8, a polymer repeat unit. The structure is enclosed in large parentheses with a subscript 'p' at the bottom right. It features a central chain with a 2,3,4,5-tetrahydroxybutyrate moiety, a 2,3-dihydroxybutyrate moiety, and a 2,3-dihydroxybutyrate moiety. The chain is terminated by a 2,3-dihydroxybutyrate moiety on the left and a 2,3-dihydroxybutyrate moiety on the right. The chain is also terminated by a 2,3-dihydroxybutyrate moiety on the left and a 2,3-dihydroxybutyrate moiety on the right. The chain is also terminated by a 2,3-dihydroxybutyrate moiety on the left and a 2,3-dihydroxybutyrate moiety on the right.
PLC9	 Chemical structure of PLC9, a polymer repeat unit. The structure is enclosed in large parentheses with a subscript 'p' at the bottom right. It features a central chain with a 2,3,4,5-tetrahydroxybutyrate moiety, a 2,3-dihydroxybutyrate moiety, and a 2,3-dihydroxybutyrate moiety. The chain is terminated by a 2,3-dihydroxybutyrate moiety on the left and a 2,3-dihydroxybutyrate moiety on the right. The chain is also terminated by a 2,3-dihydroxybutyrate moiety on the left and a 2,3-dihydroxybutyrate moiety on the right. The chain is also terminated by a 2,3-dihydroxybutyrate moiety on the left and a 2,3-dihydroxybutyrate moiety on the right.

PLC10	 Chemical structure of PLC10, showing a polymer chain (C) with a repeating unit containing a carbonyl group and a methylene group, linked to a complex heterocyclic system (P) via a linker. The heterocyclic system includes a benzimidazole core with a methoxy group (MeO) and a fluorine atom (F) on the benzene ring, and a thiazolidine ring fused to a pyridine ring. The linker consists of a carbonyl group, a methylene group, and a methylene group.
PLC11	 Chemical structure of PLC11, showing a polymer chain (C) with a repeating unit containing a carbonyl group and a methylene group, linked to a complex heterocyclic system (P) via a linker. The heterocyclic system includes a benzimidazole core with a fluorine atom (F) on the benzene ring, and a thiazolidine ring fused to a pyridine ring. The linker consists of a carbonyl group, a methylene group, and a methylene group.
PLC12	 Chemical structure of PLC12, showing a polymer chain (C) with a repeating unit containing a carbonyl group and a methylene group, linked to a complex heterocyclic system (P) via a linker. The heterocyclic system includes a benzimidazole core with a fluorine atom (F) on the benzene ring, and a thiazolidine ring fused to a pyridine ring. The linker consists of a carbonyl group, a methylene group, and a methylene group.

PLC13	 Chemical structure of PLC13, a polymer repeat unit. The structure is enclosed in large parentheses with a subscript 'p'. It features a central polyamide backbone. On the left, a 2,2,6,6-tetramethyl-1,3-dioxane-4,5-dione ring is attached to the backbone. On the right, a complex heterocyclic system is attached, consisting of a benzimidazole core fused to a thiophene ring, which is further substituted with a fluorine atom and a hydroxyl group. The backbone also includes a 1,3,4,5-tetrahydroxybutyl side chain.
PLC14	 Chemical structure of PLC14, a polymer repeat unit. The structure is enclosed in large parentheses with a subscript 'p'. It features a central polyamide backbone. On the left, a 2,2,6,6-tetramethyl-1,3-dioxane-4,5-dione ring is attached to the backbone. On the right, a complex heterocyclic system is attached, consisting of a benzimidazole core fused to a thiophene ring, which is further substituted with a fluorine atom and a hydroxyl group. The backbone also includes a 1,3,4,5-tetrahydroxybutyl side chain.
PLC15	 Chemical structure of PLC15, a polymer repeat unit. The structure is enclosed in large parentheses with a subscript 'p'. It features a central polyamide backbone. On the left, a 2,2,6,6-tetramethyl-1,3-dioxane-4,5-dione ring is attached to the backbone. On the right, a complex heterocyclic system is attached, consisting of a benzimidazole core fused to a thiophene ring, which is further substituted with a fluorine atom and a hydroxyl group. The backbone also includes a 1,3,4,5-tetrahydroxybutyl side chain.



Without wishing to be bound by theory, it is believed that the compounds of the disclosure have a relatively good solubility and potency (*in vitro* growth inhibition and/or *in vivo* tumor growth inhibition) relative to camptothecin. Without wishing to be bound

5 by theory, it is believed that the ADCs of the present disclosure and can provide a relatively good release rate of the payload with relatively little aggregation of the ADCs. Additionally, the structure is believed to provide metabolism pathways to reduce systematic toxicity of payloads after they are released into the circulation system.

It is further appreciated that certain features of the invention, which are, for

10 clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment (while the embodiments are intended to be combined as if written in multiply dependent form). Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination. Thus, it is contemplated

as features described as embodiments of the compounds of the present disclosure can be combined in any suitable combination.

At various places in the present specification, certain features of the compounds are disclosed in groups or in ranges. It is specifically intended that such a disclosure
5 include each and every individual subcombination of the members of such groups and ranges. For example, the term "C₁₋₆ alkyl" is specifically intended to individually disclose (without limitation) methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl and C₆ alkyl.

At various places in the present specification, variables defining divalent linking groups may be described. It is specifically intended that each linking substituent include
10 both the forward and backward forms of the linking substituent. For example, -NR(CR'R'')_n- includes both -NR(CR'R'')_n- and -(CR'R'')_nNR- and is intended to disclose each of the forms individually. Where the structure requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists
15 "alkyl" or "aryl" then it is understood that the "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The term "substituted", unless otherwise indicated, refers to any level of substitution, *e.g.*, mono-, di-, tri-, tetra- or
20 penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by valency. It is to be understood that substitution at a given atom results in a chemically stable molecule. The phrase "optionally substituted" means unsubstituted or substituted. The term
25 "substituted" means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, *e.g.*, oxo, can replace two hydrogen atoms.

The term "C_{n-m}" indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C₁₋₄, C₁₋₆ and the like.

The term "alkyl" employed alone or in combination with other terms, refers to a
30 saturated hydrocarbon group that may be straight-chained or branched. The term "C_{n-m}

alkyl", refers to an alkyl group having n to m carbon atoms. An alkyl group formally corresponds to an alkane with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as 2-methyl-1-butyl, *n*-pentyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl and the like.

The term "alkylene", employed alone or in combination with other terms, refers to a divalent alkyl linking group. An alkylene group formally corresponds to an alkane with two C-H bond replaced by points of attachment of the alkylene group to the remainder of the compound. The term " C_{n-m} alkylene" refers to an alkylene group having n to m carbon atoms. Examples of alkylene groups include, but are not limited to, ethan-1,2-diyl, ethan-1,1-diyl, propan-1,3-diyl, propan-1,2-diyl, propan-1,1-diyl, butan-1,4-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl and the like.

The term "alkoxy", employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group is as defined above. The term " C_{n-m} alkoxy" refers to an alkoxy group, the alkyl group of which has n to m carbons. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, *n*-propoxy and isopropoxy), *t*-butoxy and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the

compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. One method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, *e.g.*, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β -camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α -methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, *N*-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

In some embodiments, the compounds of the invention have the (*R*)-configuration. In other embodiments, the compounds have the (*S*)-configuration. In compounds with more than one chiral centers, each of the chiral centers in the compound may be independently (*R*) or (*S*), unless otherwise indicated.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, *e.g.*, 1*H*- and 3*H*-imidazole, 1*H*-, 2*H*- and 4*H*- 1,2,4-triazole, 1*H*- and 2*H*- isoindole and 1*H*- and 2*H*-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. One or more constituent atoms of the compounds of the invention
5 can be replaced or substituted with isotopes of the atoms in natural or non-natural abundance. In some embodiments, the compound includes at least one deuterium atom. For example, one or more hydrogen atoms in a compound of the present disclosure can be replaced or substituted by deuterium. In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound
10 includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 deuterium atoms. Synthetic methods for including isotopes into organic compounds are known in the art (Deuterium Labeling in Organic Chemistry by Alan F. Thomas (New York, N.Y., Appleton-Century-Crofts, 1971; The Renaissance of H/D Exchange by Jens Atzrodt, Volker Derdau, Thorsten Fey and Jochen Zimmermann, Angew. Chem. Int. Ed. 2007, 7744-7765). Isotopically labeled
15 compounds can be used in various studies such as NMR spectroscopy, metabolism experiments, and/or assays.

Substitution with heavier isotopes such as deuterium, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some
20 circumstances. (A. Kerekes et.al. *J. Med. Chem.* **2011**, 54, 201-210; R. Xu et.al. *J. Label Compd. Radiopharm.* **2015**, 58, 308-312).

The term, "compound," as used herein is meant to include all stereoisomers, geometric isomers, tautomers and isotopes of the structures depicted. The term is also meant to refer to compounds of the inventions, regardless of how they are prepared, e.g.,
25 synthetically, through biological process (e.g., metabolism or enzyme conversion), or a combination thereof.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g., hydrates and solvates) or can be isolated. When in the solid state, the compounds described herein and salts thereof
30 may occur in various forms and may, e.g., take the form of solvates, including hydrates.

The compounds may be in any solid state form, such as a polymorph or solvate, so unless clearly indicated otherwise, reference in the specification to compounds and salts thereof should be understood as encompassing any solid state form of the compound.

5 In some embodiments, the compounds of the present disclosure, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, *e.g.*, a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at
10 least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and
15 animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, "room temperature" as used herein, is understood in the art, and refer generally to a temperature, *e.g.*, a reaction temperature, that is about the temperature of the room in which the reaction is carried out, *e.g.*, a temperature from about 20°C to
20 about 30°C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. The term "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically
25 acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non-toxic salts of the parent compound formed, *e.g.*, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be
30 synthesized from the parent compound which contains a basic or acidic moiety by

conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (*e.g.*, methanol, ethanol, iso-propanol or butanol) or acetonitrile (MeCN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th Ed., (Mack Publishing Company, Easton, 1985), p. 1418, Berge *et al.*, *J. Pharm. Sci.*, **1977**, 66(1), 1-19 and in Stahl *et al.*, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (Wiley, 2002). In some embodiments, the compounds described herein include the N-oxide forms.

Synthesis

The disclosure further provides a method of preparing a conjugate including a cell binding agent and a drug (*e.g.*, a payload such as a compound of Formula (I'), (I), (Ia'), (Ia), (Ib'), or (Ib); or a payload with a linker, such as a compound of Formula (II'), (II), (IIa') or (IIa)), the method including contacting a cell binding agent with a compound of the disclosure, such that a covalent bond forms between the cell binding agent and the compound. In some embodiments, the cell binding agent is an antibody or an antigen-binding fragment thereof. In some embodiments, the cell binding agent is a monoclonal antibody or an antigen-binding fragment thereof.

The disclosure further provides a conjugate including a cell binding agent and a drug, wherein the conjugate is prepared according to the method of the disclosure. In some embodiments, the conjugate includes a cell binding agent that is an antibody or an antigen binding fragment thereof. In some embodiments, the conjugate includes a cell binding agent that is a monoclonal antibody or an antigen-binding fragment thereof.

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, such as those in the Schemes below.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates or products at the temperatures at which the reactions are

carried out, *e.g.*, temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

5 Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups is described, *e.g.*, in Kocienski, *Protecting Groups*, (Thieme, 2007); Robertson, *Protecting Group Chemistry*, (Oxford University Press, 2000); Smith *et al.*, *March's Advanced Organic Chemistry: Reactions,*
10 *Mechanisms, and Structure*, 6th Ed. (Wiley, 2007); Petursson *et al.*, "Protecting Groups in Carbohydrate Chemistry," *J. Chem. Educ.*, 1997, 74(11), 1297; and Wuts *et al.*, *Protective Groups in Organic Synthesis*, 4th Ed., (Wiley, 2006).

Reactions can be monitored according to any suitable method known in the art.
15 For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (*e.g.*, ¹H or ¹³C), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

20 *Methods of Use*

The present disclosure provides a method of treating a cell proliferative disease or disorder or inhibiting abnormal cell growth, the method including administering a compound described herein such as a compound of any of Formula (I'), (I), (Ia'), (Ia), (Ib'), (Ib), (II'), (II), (IIa), (IIa'), (III'), (III), (IIIa'), and (IIIa), or a pharmaceutically
25 acceptable salt thereof. The compounds of the present disclosure can be used alone, in combination with other agents or therapies or as an adjuvant or neoadjuvant for the treatment of diseases or disorders, including cancers. For the uses described herein, any of the compounds of the disclosure, including any of the embodiments thereof, may be used.

A method of treating a cell proliferative disease or disorder or inhibiting abnormal cell growth can include administering to a patient in need thereof a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the cell proliferative disease or disorder or inhibiting abnormal cell growth is cancer. Examples of cancers that are treatable using the compounds of the present disclosure include, but are not limited to, adenocarcinoma, brain cancer, bladder cancer, breast cancer, cervical cancer, choriocarcinoma, a CNS tumor, colon or colorectal cancer, diffuse intrinsic pontine glioma (DIPG), endometrial cancer, esophageal cancer, Ewing's sarcoma, fallopian tube cancer, gall bladder cancer, gastric cancer, glioblastoma, head and neck cancer, hematological cancer, Hodgkin's lymphoma, kidney cancer, laryngeal cancer, leukemia, liver cancer, lung cancer, lymphoma, melanoma, Merkel cell carcinoma, mesothelioma, multiple myeloma, myelodysplastic syndrome (MDS), neuroblastoma, non-Hodgkin's lymphoma, osteosarcoma, pancreatic cancer, peritoneal cancer, prostate cancer, ovarian cancer, renal cancer, rhabdomyosarcoma salivary gland cancer, sarcoma, skin cancer, small intestine cancer, squamous cell carcinoma, testicular cancer, thyroid cancer, uterine cancer, or Wilms tumor.

In some embodiments, the cancer is breast cancer, lung cancer, gastric cancer, prostate cancer, pancreatic cancer, or colon cancer.

Formulation, Dosage Forms and Administration

When employed as pharmaceuticals, a compound of the present disclosure can be administered in the form of pharmaceutical compositions. Thus the present disclosure provides a composition including a compound of Formula (I'), (I), (Ia'), (Ia), (Ib'), (Ib), (II'), (II), (IIa'), (IIa), (III'), (III), (IIIa'), and (IIIa) or any of the formulas as described herein, a compound as described herein, or a pharmaceutically acceptable salt thereof, or any of the embodiments thereof, and at least one pharmaceutically acceptable carrier or excipient. The compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is indicated and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to

mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, *e.g.*, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the present disclosure or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the composition is suitable for topical administration. In making the compositions of the present disclosure, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, *e.g.*, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, *e.g.*, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.*, about 40 mesh.

The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be prepared by processes known in the art see, *e.g.*, WO 2002/000196.

5 Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate and mineral oil; wetting agents; emulsifying and suspending
10 agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

 In some embodiments, the pharmaceutical composition comprises silicified
15 microcrystalline cellulose (SMCC) and at least one compound described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the silicified microcrystalline cellulose comprises about 98% microcrystalline cellulose and about 2% silicon dioxide w/w.

 In some embodiments, the composition is a sustained release composition
20 comprising at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one component selected from microcrystalline cellulose, lactose monohydrate, hydroxypropyl methylcellulose and
25 polyethylene oxide. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate and hydroxypropyl methylcellulose. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose
30 monohydrate and polyethylene oxide. In some embodiments, the composition further

comprises magnesium stearate or silicon dioxide. In some embodiments, the microcrystalline cellulose is Avicel PH102™. In some embodiments, the lactose monohydrate is Fast-flo 316™. In some embodiments, the hydroxypropyl methylcellulose is hydroxypropyl methylcellulose 2208 K4M (*e.g.*, Methocel K4 M Premier™) and/or hydroxypropyl methylcellulose 2208 K100LV (*e.g.*, Methocel K00LV™). In some embodiments, the polyethylene oxide is polyethylene oxide WSR 1105 (*e.g.*, Polyox WSR 1105™).

In some embodiments, a wet granulation process is used to produce the composition. In some embodiments, a dry granulation process is used to produce the composition.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1g). The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The components used to formulate the pharmaceutical compositions can be of high purity and are substantially free of potentially harmful contaminants (*e.g.*, at least National Food grade or a comparable standard in another country, generally at least analytical grade, and more typically at least pharmaceutical grade). For example, suitable formulations may be sterile and/or substantially isotonic and/or in full compliance with all Good Manufacturing Practice regulations of the U.S. Food and Drug Administration or a comparable standard in another country.

The active compound may be effective over a wide dosage range and is generally administered in a therapeutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms and the like.

The therapeutic dosage of a compound of the present invention can vary according to, *e.g.*, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 $\mu\text{g/kg}$ to about 1 g/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, *e.g.*, about 0.1 to about 1000 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release.

A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

5 The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

10 Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect.

15 Compositions can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face mask, tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

20 Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, *e.g.*, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, *e.g.*, glycerinemonostearate, PEG-glycerinemonostearate and cetylstearyl alcohol. Gels can be
25 formulated using isopropyl alcohol and water, suitably in combination with other components such as, *e.g.*, glycerol, hydroxyethyl cellulose, and the like. In some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2 or at least about 5 wt % of the compound of the invention. The topical formulations can be suitably packaged in tubes of, *e.g.*, 100 g

which are optionally associated with instructions for the treatment of the select indication, *e.g.*, psoriasis or other skin condition.

5 The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician
10 depending upon factors such as the severity of the disease, the age, weight and general condition of the patient and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for
15 use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers or stabilizers will result in the formation of pharmaceutical salts.

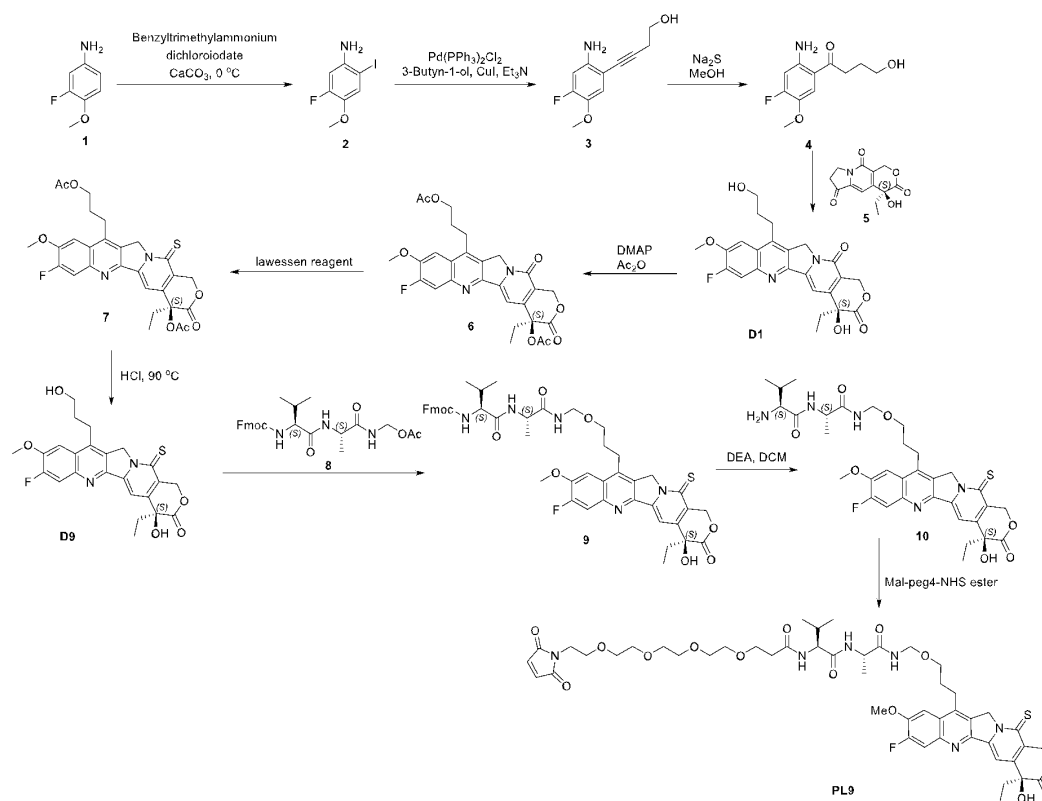
20 The therapeutic dosage of a compound of the present invention can vary according to, *e.g.*, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of
25 factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status
30 of the particular patient, the relative biological efficacy of the compound selected,

formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

In some embodiments, the pharmaceutical compositions include a compound of the present disclosure and a second therapeutic agent.

EXAMPLES

Example 1. Synthesis of 15-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-(((S)-1-(((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methoxy-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-3,6,9,12-tetraoxapentadecanamide (PL9)



5-Fluoro-2-iodo-4-methoxyaniline (2)

To a solution of 3-Fluoro-4-methoxyaniline (0.5 g, 3.5 mmol) in MeOH (4 mL) and DCM (12 mL) were added CaCO₃ (0.7 g, 7.0 mmol) and benzyltrimethylammonium-dichloroiodate (1.28 g, 3.7 mmol) at 0°C. The reaction mixture was stirred for 2 h at 25°C. The mixture was filtered and the filtrate was concentrated under reduced pressure.

- 5 The residue was dissolved into DCM (20 mL) and washed with H₂O (10 mL), saturated aqueous NaHCO₃ (10 mL), brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on a silica gel (petroleum ether/EtOAc = 50:1) to afford compound **2** (0.3 g, 32% yield) as a yellow solid.

10 LC-MS (ESI): m/z 268.0 [M+H]⁺.

4-(2-amino-4-fluoro-5-methoxyphenyl)but-3-yn-1-ol (3)

To a mixture of compound **2** (0.3 g, 1.12 mmol), Pd(PPh₃)₄ (27 mg, 0.03 mmol) and CuI (3 mg, 0.015 mmol) in Et₃N (5 mL) was added 3-Butyn-1-ol (0.6 g, 8.57 mmol) at room temperature under N₂ atmosphere. The reaction mixture was stirred
15 overnight at room temperature. The mixture was diluted with EtOAc (20 mL) and washed with H₂O (10 mL) and brine (10 mL × 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 50:1) to afford compound **3** (0.17 g, 85% yield) as a yellow solid.

20 LC-MS (ESI): m/z 210.2 [M+H]⁺.

1-(2-amino-4-fluoro-5-methoxyphenyl)-4-hydroxybutan-1-one (4)

- 25 To a solution of compound **3** (170 mg, 0.81 mmol) in MeOH (25 mL) was added Na₂S (20.4 mg, 0.26 mmol) at room temperature, then concentrated hydrochloric acid (1 mL, 12 M) was added. The reaction mixture was stirred overnight at 80°C. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved into DCM (20 mL). The resulting mixture was washed with H₂O (10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced

pressure. The residue was purified by column chromatography on silica gel (DCM/MeOH = 20:1) to afford compound **4** (100 mg, 46% yield) as a brown oil.

LC-MS (ESI): m/z 228.4 $[M+H]^+$.

5 **(S)-4-ethyl-8-fluoro-4-hydroxy-11-(3-hydroxypropyl)-9-methoxy-1,12-dihydro-14H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H)-dione (D1)**

To a solution of compound **4** (100 mg, 0.44 mmol) and (S)-4-ethyl-4-hydroxy-7,8-dihydro-1H-pyrano[3,4-f]indolizine-3,6,10(4H)-trione (117 mg, 0.44 mmol) in toluene (5 mL) was added PPTS (55 mg, 0.22 mmol) at room temperature. The reaction mixture was stirred at 120 °C for 16 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 100:1) to afford **D1** (90 mg, 39% yield).

LC-MS (ESI): m/z 455.2 $[M+H]^+$.

15 **(S)-3-(4-acetoxy-4-ethyl-8-fluoro-9-methoxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propyl acetate (6)**

To a solution of **D1** (90 mg, 0.2 mmol) and acetic anhydride (103 mg, 1 mmol) in pyridine (5 mL) was added DMAP (2.5 mg, 0.02 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM and washed with H₂O and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford compound **6** (100 mg, 0.186 mmol, 93% yield).

LC-MS (ESI): m/z 539.2 $[M+H]^+$.

25 **(S)-3-(4-acetoxy-4-ethyl-8-fluoro-9-methoxy-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propyl acetate (7)**

To a solution of **6** (100 mg, 0.186 mmol) in 1,4-dioxane (10 mL) was added lawesson reagent (150 mg, 0.372 mmol) at room temperature. The reaction mixture was stirred at 90 °C for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 50:1) to afford compound **7** as a yellow solid (95 mg, 0.171 mmol, 92.3% yield).

LC-MS (ESI): m/z 555.2 $[M+H]^+$.

(S)-4-ethyl-8-fluoro-4-hydroxy-11-(3-hydroxypropyl)-9-methoxy-14-thioxo-12,14-dihydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-3(4H)-one (D9)

Compound 7 (95 mg, 0.171 mmol) was added to concentrated hydrochloric acid (5 ml). The reaction was stirred at 90 °C for 40 min. the solution was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 50:1) to afford **D9** as a yellow solid (78 mg, 0.166 mmol, 97% yield).

LC-MS (ESI): m/z 471.1 $[M+H]^+$.

(9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methoxy-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (9)

To a solution of **D9** (78 mg, 0.17 mmol) and compound 8 (120 mg, 0.25 mmol) in 1,4-dioxane (10 mL) was added $Zn(OAc)_2$ (25 mg, 0.14 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 50:1) to afford compound **9** as a yellow solid (89 mg, 0.1 mmol, 59% yield).

LC-MS (ESI): m/z 892.3 $[M+H]^+$.

20

(S)-2-amino-N-(((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methoxy-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)-3-methylbutanamide (10)

Compound 9 (89 mg, 0.1 mmol) was dissolved in DCM (5 ml), then diethylamine (2 ml) was added to the solution. The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 10:1) to afford compound **10** as a yellow solid (62 mg, 0.092 mmol, 92% yield).

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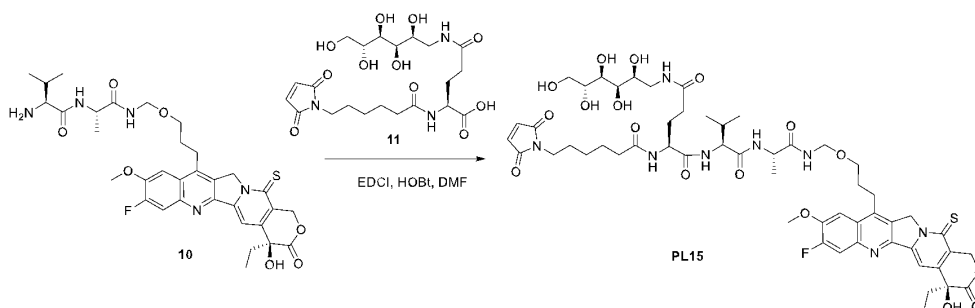
LC-MS (ESI): m/z 670.3 $[M+H]^+$.

15-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methoxy-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-3,6,9,12-tetraoxapentadecanamide (PL9)

To a solution of compound **10** (62 mg, 0.092 mmol) and Mal-Peg4-NHS ester (49 mg, 0.11 mmol) in DCM (10 mL) was added triethylamine (25 mg, 0.25 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 20:1) to afford **PL9** as a yellow solid (35 mg, 0.035 mmol, 38% yield).

LC-MS (ESI): m/z 997.4 $[M+H]^+$.

Example 2. (S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-N1-(((S)-1-(((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methoxy-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-N5-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)pentanediamide (PL15)

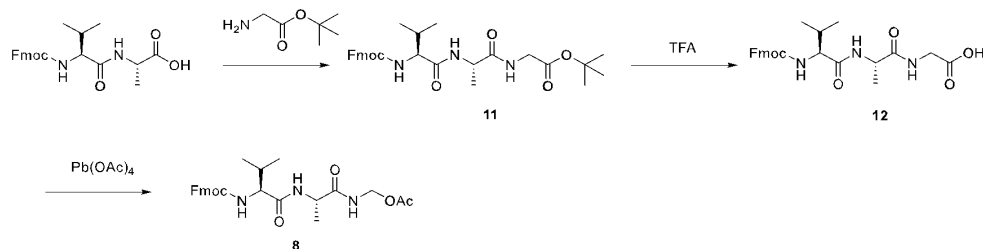


To a solution of compound **10** (50 mg, 0.075 mmol) and compound **11** (38 mg, 0.075 mmol) in DCM (10 mL) was added EDCI (18 mg, 0.09 mmol) and HOBT (12 mg, 0.09 mmol) at room temperature. The reaction mixture was stirred at room temperature

for 30 min. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford **PL15** as a yellow solid (10 mg, 0.009 mmol, 11.6% yield).

LC-MS (ESI): m/z 1155.4 $[M+H]^+$.

5 **Example 3. (5S,8S)-1-(9H-fluoren-9-yl)-5-isopropyl-8-methyl-3,6,9-trioxo-2-oxa-4,7,10-triazaundecan-11-yl acetate (8)**



tert-butyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-valyl-L-alanylglycinate (11)

To a solution of (((9H-fluoren-9-yl)methoxy)carbonyl)-L-valyl-L-alanine (4.1 g, 10 mmol) and tert-butyl glycinate (1.31 g, 10 mmol) in DCM (50 mL) was added EDCI (2.36 g, 12 mmol) and HOBT (1.57 g, 12 mmol) at room temperature. The reaction mixture was stirred at room temperature for 5 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 50:1) to afford compound **11** as a off-white solid (4.4 g, 8.5 mmol, 84% yield).

LC-MS (ESI): m/z 524.3 $[M+H]^+$.

(((9H-fluoren-9-yl)methoxy)carbonyl)-L-valyl-L-alanylglycine (12)

Compound **11** (1 g, 1.9 mmol) was added to TFA (10 mL) and stirred at room temperature for 15 min. the mixture was concentrated under reduced pressure to afford compound **12** as a light-yellow oil (0.89 g, 1.9 mmol, 100% yield).

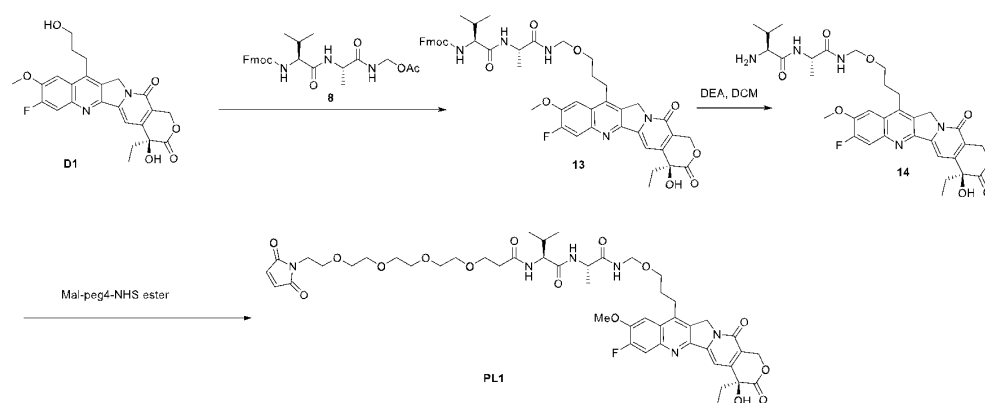
LC-MS (ESI): m/z 466.2 $[M+H]^+$.

(5S,8S)-1-(9H-fluoren-9-yl)-5-isopropyl-8-methyl-3,6,9-trioxo-2-oxa-4,7,10-triazaundecan-11-yl acetate (8)

To a mixture of compound **12** (0.89 g, 1.9 mmol) in THF (15 mL) and toluene (5 mL) were added pyridine (0.18 mL, 2.27 mmol) and Pb(OAc)₄ (1 g, 2.27 mmol). The reaction mixture was refluxed for 5 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 30:1) to afford compound **8** (0.8 g, yield 87%) as a colorless solid.

LC-MS (ESI): *m/z* 482.2 [M+H]⁺.

Example 4. Synthesis of 15-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-(((S)-1-((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methoxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-3,6,9,12-tetraoxapentadecanamide (PL1)



(9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-(((S)-1-((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methoxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (13)

To a solution of **D1** (50 mg, 0.11 mmol) and compound **8** (79 mg, 0.25 mmol) in 1,4-dioxane (10 mL) was added Zn(OAc)₂ (16 mg, 0.088 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on

silica gel (DCM/MeOH = 50:1) to afford compound **9** as a yellow solid (55 mg, 0.062 mmol, 57% yield).

LC-MS (ESI): m/z 876.3 $[M+H]^+$.

(S)-2-amino-N-((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methoxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)-3-methylbutanamide (14)

Compound **13** (55 mg, 0.062 mmol) was dissolved in DCM (5 ml), then diethylamine (2 ml) was added to the solution. The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 10:1) to afford compound **14** as a yellow solid (37 mg, 0.057 mmol, 92% yield).

LC-MS (ESI): m/z 654.3 $[M+H]^+$.

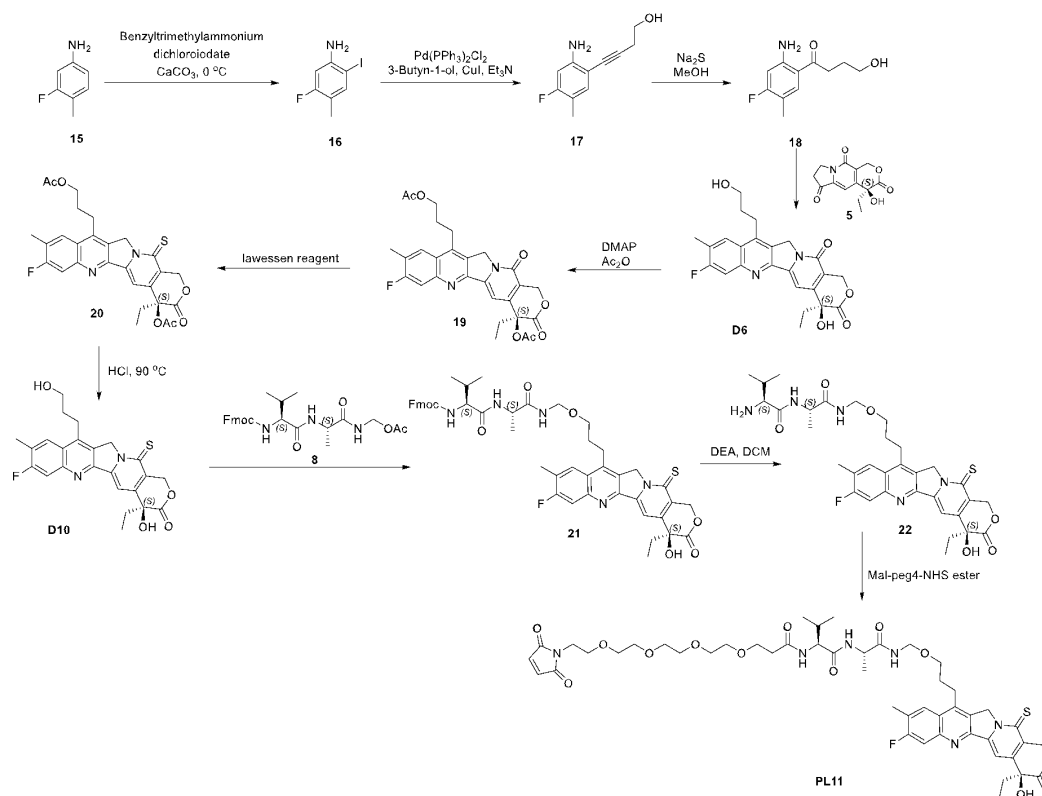
15-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methoxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-3,6,9,12-tetraoxapentadecanamide (PL1)

To a solution of compound **14** (37 mg, 0.057 mmol) and Mal-Peg4-NHS ester (30 mg, 0.068 mmol) in DCM (10 mL) was added triethylamine (11 mg, 0.114 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 20:1) to afford **PL1** as a white solid (24 mg, 0.024 mmol, 42% yield).

LC-MS (ESI): m/z 981.4 $[M+H]^+$.

Example 5. 15-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methyl-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-

oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-3,6,9,12-tetraoxapentadecanamide (PL11)



5-fluoro-2-iodo-4-methylaniline (16)

- 5 To a solution of compound **15** (0.44 g, 3.5 mmol) in MeOH (4 mL) and DCM (12 mL) were added CaCO_3 (0.7 g, 7.0 mmol) and benzyltrimethylammonium-dichloroiodate (1.28 g, 3.7 mmol) at $0\text{ }^\circ\text{C}$. The reaction mixture was stirred for 2 h at $25\text{ }^\circ\text{C}$. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved into DCM (20 mL) and washed with H_2O (10 mL), saturated aqueous NaHCO_3 (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on a silica gel (petroleum ether/ EtOAc = 50:1) to afford compound **16** (0.28 g, 32% yield) as a yellow solid.

LC-MS (ESI): m/z 252.0 $[\text{M}+\text{H}]^+$.

4-(2-amino-4-fluoro-5-methylphenyl)but-3-yn-1-ol (17)

To a mixture of compound **16** (0.28 g, 1.12 mmol), Pd(PPh₃)₄ (27 mg, 0.03 mmol) and CuI (3 mg, 0.015 mmol) in Et₃N (5 mL) was added 3-Butyn-1-ol (0.6 g, 8.57 mmol) at room temperature under N₂ atmosphere. The reaction mixture was stirred overnight at room temperature. The mixture was diluted with EtOAc (20 mL) and washed with H₂O (10 mL) and brine (10 mL × 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 50:1) to afford compound **17** (0.183 g, 85% yield) as a yellow solid.

LC-MS (ESI): m/z 194.2 [M+H]⁺.

1-(2-amino-4-fluoro-5-methylphenyl)-4-hydroxybutan-1-one (18)

To a solution of compound **17** (183 mg, 0.95 mmol) in MeOH (25 mL) was added Na₂S (20.4 mg, 0.26 mmol) at room temperature, then concentrated hydrochloric acid (1 mL) was added. The reaction mixture was stirred overnight at 80°C. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved into DCM (20 mL). The resulting mixture was washed with H₂O (10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM/MeOH = 20:1) to afford compound **18** (93 mg, 46% yield) as a brown solid.

LC-MS (ESI): m/z 212.4 [M+H]⁺.

(S)-4-ethyl-8-fluoro-4-hydroxy-11-(3-hydroxypropyl)-9-methyl-1,12-dihydro-14H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H)-dione (D6)

To a solution of compound **18** (93 mg, 0.44 mmol) and (S)-4-ethyl-4-hydroxy-7,8-dihydro-1H-pyrano[3,4-f]indolizine-3,6,10(4H)-trione (117 mg, 0.44 mmol) in toluene (5 mL) was added PPTS (55 mg, 0.22 mmol) at room temperature. The reaction mixture was stirred at 120°C for 16 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 100:1) to afford **D6** (87 mg, 39% yield).

LC-MS (ESI): m/z 439.2 [M+H]⁺.

(S)-3-(4-acetoxy-4-ethyl-8-fluoro-9-methyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propyl acetate (19)

To a solution of **D6** (87 mg, 0.2 mmol) and acetic anhydride (103 mg, 1 mmol) in pyridine (5 mL) was added DMAP (2.5 mg, 0.02 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM and washed with H₂O and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford compound **19** (97 mg, 0.186 mmol, 93% yield).

LC-MS (ESI): m/z 523.2 [M+H]⁺.

(S)-3-(4-acetoxy-4-ethyl-8-fluoro-9-methyl-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propyl acetate (20)

To a solution of **19** (97 mg, 0.186 mmol) in 1,4-dioxane (10 mL) was added lawesson reagent (145 mg, 0.372 mmol) at room temperature. The reaction mixture was stirred at 90 °C for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 50:1) to afford compound **20** as a yellow solid (92 mg, 0.171 mmol, 92.3% yield).

LC-MS (ESI): m/z 539.2 [M+H]⁺.

(S)-4-ethyl-8-fluoro-4-hydroxy-11-(3-hydroxypropyl)-9-methyl-14-thioxo-12,14-dihydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-3(4H)-one (D10)

Compound **20** (92 mg, 0.171 mmol) was added to concentrated hydrochloric acid (5 mL). The reaction was stirred at 90 °C for 40 min. the solution was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 50:1) to afford **D10** as a yellow solid (75 mg, 0.166 mmol, 97% yield).

LC-MS (ESI): m/z 455.1 [M+H]⁺.

(9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-(((S)-4-ethyl-8-fluoro-4-hydroxy-9-methyl-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (21)

To a solution of **D10** (75 mg, 0.166 mmol) and compound **8** (120 mg, 0.25 mmol) in 1,4-dioxane (10 mL) was added Zn(OAc)₂ (25 mg, 0.14 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 50:1) to afford compound **21** as a yellow solid (87 mg, 0.1 mmol, 59% yield).

LC-MS (ESI): m/z 876.3 [M+H]⁺.

(S)-2-amino-N-((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methyl-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)-3-methylbutanamide (22)

Compound **21** (87 mg, 0.1 mmol) was dissolved in DCM (5 mL), then diethylamine (2 mL) was added to the solution. The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 10:1) to afford compound **22** as a yellow solid (60 mg, 0.092 mmol, 92% yield).

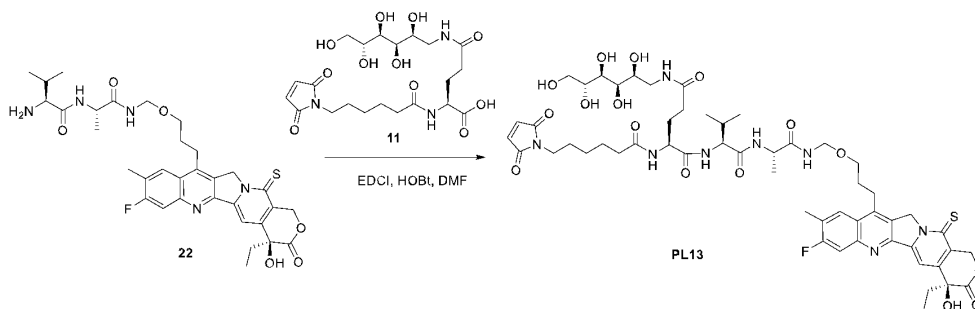
LC-MS (ESI): m/z 654.3 [M+H]⁺.

15-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methyl-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-3,6,9,12-tetraoxapentadecanamide (PL11)

To a solution of compound **22** (60 mg, 0.092 mmol) and Mal-Peg4-NHS ester (49 mg, 0.11 mmol) in DCM (10 mL) was added triethylamine (25 mg, 0.25 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 20:1) to afford **PL11** as a yellow solid (34 mg, 0.035 mmol, 38% yield).

LC-MS (ESI): m/z 981.4 [M+H]⁺.

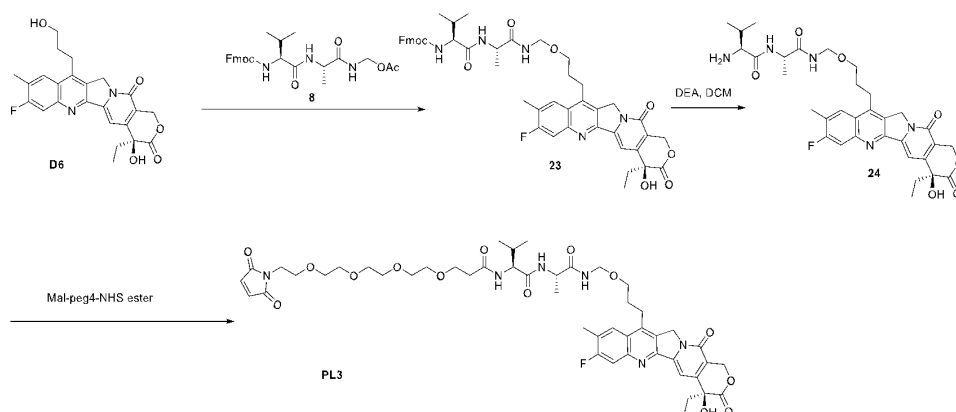
Example 6. (S)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-N1-(((S)-1-(((S)-1-(((3-(((S)-4-ethyl-8-fluoro-4-hydroxy-9-methyl-3-oxo-14-thioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-N5-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)pentanediamide (PL13)



To a solution of compound **22** (48.8 mg, 0.075 mmol) and compound **11** (38 mg, 0.075 mmol) in DCM (10 mL) was added EDCI (18 mg, 0.09 mmol) and HOBT (12 mg, 0.09 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford **PL13** as a yellow solid (9.9 mg, 0.009 mmol, 11.6% yield).

LC-MS (ESI): m/z 1139.4 $[M+H]^+$.

Example 7. 15-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-(((S)-1-(((S)-1-(((3-(((S)-4-ethyl-8-fluoro-4-hydroxy-9-methyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-3,6,9,12-tetraoxapentadecanamide (PL3)



(9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-(((S)-4-ethyl-8-fluoro-4-hydroxy-9-methyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (23)

To a solution of **D6** (48 mg, 0.11 mmol) and compound **8** (79 mg, 0.25 mmol) in 1,4-dioxane (10 mL) was added $\text{Zn}(\text{OAc})_2$ (16 mg, 0.088 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 50:1) to afford compound **23** as a yellow solid (54 mg, 0.062 mmol, 57% yield).

LC-MS (ESI): m/z 860.3 $[\text{M}+\text{H}]^+$.

(S)-2-amino-N-(((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)-3-methylbutanamide (24)

Compound **23** (54 mg, 0.062 mmol) was dissolved in DCM (5 mL), then diethylamine (2 mL) was added to the solution. The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 10:1) to afford compound **24** as a yellow solid (36 mg, 0.057 mmol, 92% yield).

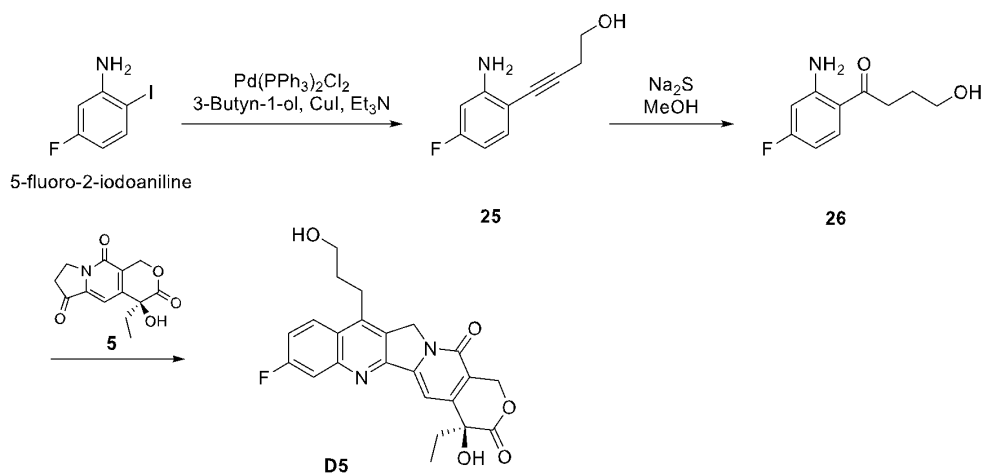
LC-MS (ESI): m/z 638.3 $[\text{M}+\text{H}]^+$.

15-**(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-((S)-1-(((S)-1-(((3-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)propoxy)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)-3,6,9,12-tetraoxapentadecanamide (PL3)**

To a solution of compound **24** (36 mg, 0.057 mmol) and Mal-Peg4-NHS ester (30 mg, 0.068 mmol) in DCM (10 mL) was added triethylamine (11 mg, 0.114 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 20:1) to afford **PL3** as a white solid (23.6 mg, 0.024 mmol, 42% yield).

LC-MS (ESI): m/z 965.4 $[M+H]^+$.

Example 8. (S)-4-ethyl-8-fluoro-4-hydroxy-11-(3-hydroxypropyl)-1,12-dihydro-14H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H)-dione (D5)



4-(2-amino-4-fluorophenyl)but-3-yn-1-ol (25)

To a mixture of 5-fluoro-2-iodoaniline (0.265 g, 1.12 mmol), $Pd(PPh_3)_4$ (27 mg, 0.03 mmol) and CuI (3 mg, 0.015 mmol) in Et_3N (5 mL) was added 3-Butyn-1-ol (0.6 g,

8.57 mmol) at room temperature under N₂ atmosphere. The reaction mixture was stirred overnight at room temperature. The mixture was diluted with EtOAc (20 mL) and washed with H₂O (10 mL) and brine (10 mL × 2), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 50:1) to afford compound **25** (0.146 g, 85% yield) as a yellow solid.

LC-MS (ESI): m/z 180.2 [M+H]⁺.

1-(2-amino-4-fluorophenyl)-4-hydroxybutan-1-one (26)

To a solution of compound **25** (146 mg, 0.81 mmol) in MeOH (25 mL) was added Na₂S (20.4 mg, 0.26 mmol) at room temperature, then adding concentrate hydrochloric acid (1 mL). The reaction mixture was stirred overnight at 80°C. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved into DCM (20 mL). The resulting mixture was washed with H₂O (10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM/MeOH = 20:1) to afford compound **26** (87 mg, 46% yield) as a brown oil.

LC-MS (ESI): m/z 198.4 [M+H]⁺.

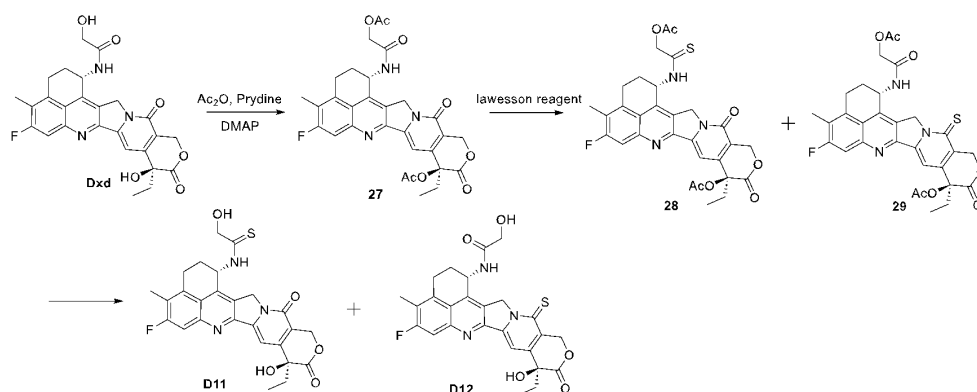
(S)-4-ethyl-8-fluoro-4-hydroxy-11-(3-hydroxypropyl)-1,12-dihydro-14H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H)-dione (D5)

To a solution of compound **26** (87 mg, 0.44 mmol) and (S)-4-ethyl-4-hydroxy-7,8-dihydro-1H-pyrano[3,4-f]indolizine-3,6,10(4H)-trione (117 mg, 0.44 mmol) in toluene (5 mL) was added PPTS (55 mg, 0.22 mmol) at room temperature. The reaction mixture was stirred at 120°C for 16 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 100:1) to afford **D5** (84 mg, 39% yield).

LC-MS (ESI): m/z 455.2 [M+H]⁺.

Example 9. N-((1S,9S)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-hydroxyethanethioamide (D11) and N-((1S,9S)-9-ethyl-5-fluoro-9-

hydroxy-4-methyl-10-oxo-13-thioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-hydroxyacetamide (D12)



2-(((1S,9S)-9-acetoxy-9-ethyl-5-fluoro-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-2-oxoethyl acetate (27)

To a solution of **Dxd** (98 mg, 0.2 mmol) and acetic anhydride (103 mg, 1 mmol) in pyridine (5 mL) was added DMAP (2.5 mg, 0.02 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM and washed with H₂O and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford compound **27** (100 mg, 0.186 mmol, 93% yield).

LC-MS (ESI): *m/z* 577.2 [M+H]⁺.

2-(((1S,9S)-9-acetoxy-9-ethyl-5-fluoro-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-2-thioxoethyl acetate/2-(((1S,9S)-9-acetoxy-9-ethyl-5-fluoro-4-methyl-10-oxo-13-thioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-2-oxoethyl acetate (28/29)

To a solution of **27** (100 mg, 0.186 mmol) in 1,4-dioxane (10 mL) was added lawesson reagent (145 mg, 0.372 mmol) at room temperature. The reaction mixture was

stirred at 90 °C for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 50:1) to afford compound **28** and **29** mixture as a yellow solid (94 mg, 47:53, 0.171 mmol, 92.3% yield).

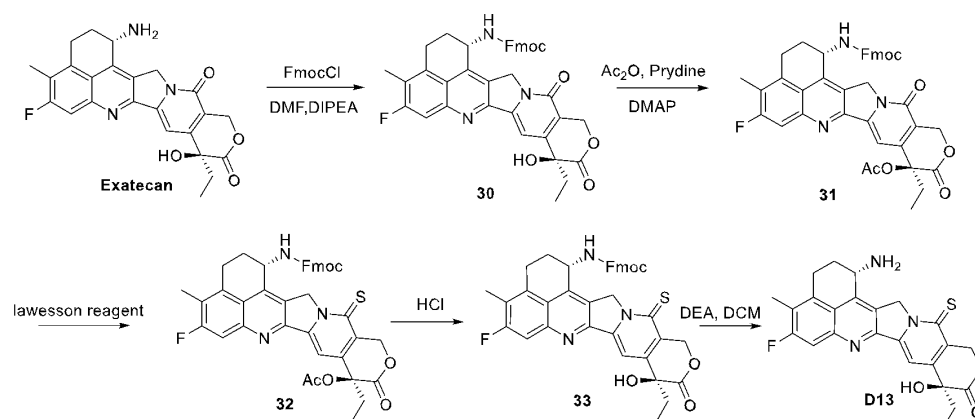
LC-MS (ESI): m/z 594.2 $[M+H]^+$.

5 **(S)-4-ethyl-8-fluoro-4-hydroxy-11-(3-hydroxypropyl)-9-methyl-14-thioxo-12,14-dihydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-3(4H)-one (D11 and D12)**

Compound **28** and **29** mixture (94 mg, 0.171 mmol) was added to concentrated hydrochloric acid (5 ml). The reaction was stirred at 90 °C for 40 min. the solution was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford **D11** (12 mg) and **D12** (15 mg) as a yellow solid (total yield 31%).

LC-MS (ESI): m/z 510.1 $[M+H]^+$.

Example 10. (1S,9S)-1-amino-9-ethyl-5-fluoro-9-hydroxy-4-methyl-13-thioxo-1,2,3,9,13,15-hexahydro-10H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-10-one (D13)



15

(9H-fluoren-9-yl)methyl ((1S,9S)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)carbamate (30)

To a solution of exatecan (100 mg, 0.23 mmol) and Fmoc chloride (89 mg, 0.344 mmol) in 1,4-dioxane (10 mL) was added DIPEA (0.2 mL) at room temperature. The

20

reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 100:1) to afford compound **30** as a white solid (127 mg, 84% yield).

LC-MS (ESI): m/z 658.2 $[M+H]^+$.

5 **(1S,9S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-9-ethyl-5-fluoro-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl acetate (31)**

To a solution of **30** (127 mg, 0.19 mmol) and acetic anhydride (103 mg, 1 mmol) in pyridine (5 mL) was added DMAP (2.5 mg, 0.02 mmol) at room temperature. The
10 reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM and washed with H₂O and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford compound **31** (126 mg, 0.18 mmol, 95% yield).

LC-MS (ESI): m/z 700.2 $[M+H]^+$.

15 **(1S,9S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-9-ethyl-5-fluoro-4-methyl-10-oxo-13-thioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl acetate (32)**

To a solution of **31** (126 mg, 0.18 mmol) in 1,4-dioxane (10 mL) was added lawesson reagent (145 mg, 0.372 mmol) at room temperature. The reaction mixture was
20 stirred at 90 °C for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH = 50:1) to afford compound **32** mixture as a yellow solid (111 mg, 0.155 mmol, 86.5% yield).

LC-MS (ESI): m/z 716.2 $[M+H]^+$.

25 **(9H-fluoren-9-yl)methyl ((1S,9S)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10-oxo-13-thioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)carbamate (33)**

Compound **32** (111 mg, 0.155 mmol) was added to concentrated hydrochloric acid (5 mL). the reaction was stirred at 90 °C for 40 min. the solution was concentrated

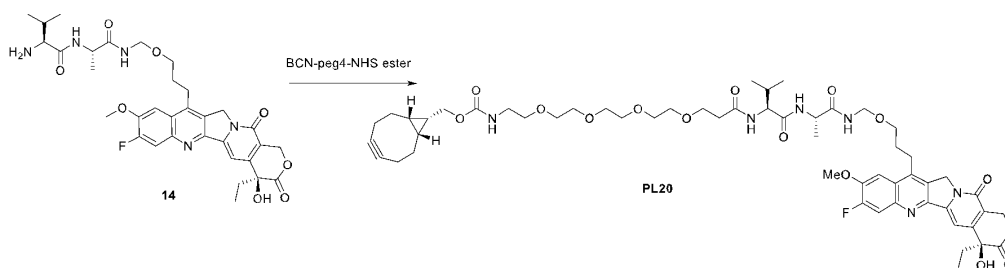
under reduced pressure. The residue was purified by prep-HPLC to afford compound **33** (100 mg, 0.15 mmol, 98% yield)

LC-MS (ESI): m/z 659.1 $[M+H]^+$.

(1S,9S)-1-amino-9-ethyl-5-fluoro-9-hydroxy-4-methyl-13-thioxo-1,2,3,9,13,15-hexahydro-10H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-10-one (D13)

Compound **33** (20 mg, 0.03 mmol) was dissolved in DCM (5 ml), then diethylamine (2 ml) was added to the solution. The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford **D13** as a yellow solid (8 mg, 0.018 mmol, 59% yield). LC-MS (ESI): m/z 452.2 $[M+H]^+$.

Example 11. ((1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-yl)methyl ((16S,19S)-26-((S)-4-ethyl-8-fluoro-4-hydroxy-9-methoxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-11-yl)-16-isopropyl-19-methyl-14,17,20-trioxo-3,6,9,12,23-pentaoxa-15,18,21-triazahexacosyl)carbamate (PL20)



To a solution of compound **14** (20 mg, 0.031 mmol) and endo-BCN-PEG4-NHS ester (16.5 mg, 0.031 mmol) in DMF (1 mL) was added DIPEA (15.8 mg, 0.12 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h. The mixture was diluted with acetonitrile (1 mL). The mixture was purified by prep-HPLC to afford **PL20** as a yellow solid (3 mg, 0.0028 mmol, 9% yield). LC-MS (ESI): m/z 1077.5 $[M+H]^+$.

Example 12. Conjugation

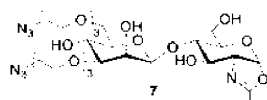
Method A

Trastuzumab solution (<10 mg/mL in 20 mM Histidine buffer, pH 6.5) was reduced with certain amount (12 eq.) of TCEP. The mixture was incubated in a water bath at 30 °C for 1 hour. In the conjugation reaction, 10 % (v/v) DMSO was added in the Trastuzumab solution, followed by the addition of **PL1** DMSO solution. The reaction was kept away from light at 30 °C on a rotational mixer for 1.5 hours. The ADC sample was purified by Zebm™ Spin desalting columns to remove the excess linker-payload before being transferred in 20 mM Histidine 5.5 buffer. The concentration of ADC was determined by Nano Drop (280 nm).

Additional ADC such as Trastuzumab-PL3, Trastuzumab-PL9, Trastuzumab-PL11, Trastuzumab-PL13, and Trastuzumab-PL15 were prepared according to the same method as above by replacing linker-payload PL1 with corresponding linker-payload (PL3, PL9, PL11, PL13, and PL15, respective).

Method B

To a solution of trastuzumab in 50 mM PB buffer (20 mg/mL, pH = 7.0) was added Endo-S2 (0.1% w/w, purchased from Glycogene Inc., product No. SE-3002) and



ManGlcNAc oxazoline(**7**) (30 eq, prepared according to the procedure described in WO2022226420, vide Fig 9 of said PCT publication), and the

5 solution was kept at 30 °C for 1~2 hour until complete consumption of the starting material as monitored by LC-MS. The intermediate was purified by Protein A column and buffer-exchanged to 50 mM PB buffer (pH = 7.0). To the solution of the glycan-engineered antibody, 10 % (v/v) DMSO was added, followed by the addition of PL20 DMSO solution. The reaction was kept away from light at 30 °C on a rotational mixer
10 overnight. The ADC product was purified by Zebm™ Spin desalting columns to remove the excess linker-payload before being transferred in 20 mM Histidine 5.5 buffer. Trastuzumab-PL20 was obtained, DAR is 4. The concentration of ADC was determined by Nano Drop (280 nm). Trastuzumab-PL20 has the structure as shown in Fig 12.

15

Example 13. Reverse phase chromatography

A 50 µg ADC sample was reduced with 20 mM DTT in 37 °C for 1 h. The pH of the reduction buffer was adjusted with 1.5 ul of 1M Tris 7.4 buffer. A volume of 10 µl reduced samples were injected into a Waters, BioResolve RP mAb Polyphenyl column
20 (Mobile phase A: 0.1 % TFA in MilliQ water, Mobile phase B: 0.1 % TFA in acetonitrile) at a rate of 0.3 mL/min for 45 min (with a gradient of B from 30 % to 42 % in 30 min). The reduced sample species were separated at the column temperature of 70 °C, and monitored at 280 nm and 360 nm UV absorbance. Reverse phase chromatographs of Trastuzumab-PL1, Trastuzumab-PL3, Trastuzumab-PL9, Trastuzumab-PL11,
25 Trastuzumab-PL13, and Trastuzumab-PL15 ADC are shown in FIGS. 1A-F, respectively.

Example 14. Size Exclusion Chromatography (SEC)

SEC was used to determine the ADC purity and aggregate content. ~30 µg ADC was injected into a Zenix-C SEC-300 (7.8 × 30 cm, 3 µm) column (the mobile phase was 0.15 M phosphate buffer, pH 7.0) at a rate of 0.75 mL/min for 16 min. The aggregate and monomer species in the ADC were monitored at 280 nm and 360 nm UV absorbance, and reported as the percent of the total areas for all protein related peaks. Size exclusion chromatographs of Trastuzumab-PL1, Trastuzumab-PL3, Trastuzumab-PL9, Trastuzumab-PL11, Trastuzumab-PL13, and Trastuzumab-PL15 ADC are shown in FIGS. 2A-F, respectively.

Example 15. Free drug analysis.

To determine the amount of free drug (linker-payload and any related species) in ADC products, protein precipitation was performed by adding 3M NaCl salt, and an acetonitrile and DMSO mixture. The samples were mixed and incubated at -40 °C for 1 hour, and centrifuged at 120,000 RPM for 30 minutes. The supernatant was collected and analyzed by an Acquity UPLC BEH C18 column (Mobile phase A: 0.1 % TFA in MilliQ water, Mobile phase B: 0.1 % TFA in acetonitrile) at a rate of 0.3 mL/min for 20 min (with a gradient of B from 10 % to 100 % in 10 min, and a column temperature of 40 °C). UV detection was monitored at 360 nm for analysis using an external calibration curve from series of free linker payload concentrations. In this experiment, a control sample for the recovery percentage of residual free drug was measured with 5 % of linker payload spiked in trastuzumab solution in addition to the un-spiked ADC sample simultaneously. All samples were observed to contain less than 5 % free drug.

Example 16. Aqueous Solubility of Payloads

Payloads were suspended in distilled water, the mixture was sonicated for 1h and stirred at 25 °C for 6 h. Insoluble payload was removed by filtration by 20 µm filter, and the payload concentration in the filtrate was determined by HPLC. The aqueous solubility of the payload molecules is presented in Table 1.

Table 1. Aqueous solubility of the payload molecules.

Samples	D1	D5	D6
Aqueous solubility (mg/ml)	0.036	0.001	0.0005

Example 17. Hydrophilicity

An Agilent 1260 Infinity II and Thermo MabPac butyl column were used for the DAR analysis at a flow rate of 0.75 mL/min by hydrophobic interaction chromatography (HIC). HIC was performed under non-denaturing conditions at neutral pH with a gradient from high salt (100 % A mobile phase of 1-1.5M ammonium sulfate) to low salt (100 % B mobile phase) for 25 minutes, with 20 % isopropanol. Even though some of the inter-chain disulfides were disrupted due to the conjugation reaction (while some remained intact), the combination of covalent binding and strong non-covalent forces between the chains were sufficient to keep the mAb intact during analysis.

FIG. 3 depicts a graph of hydrophobic interaction chromatography profiles of ADCs with Trastuzumab as a function of retention time. The payloads ADCs measured were, Dxd, PLC1, PLC3, PLC11 and PLC13. PLC1 was observed to be the most hydrophilic linker-payload conjugate, followed by PLC13, PLC3, linker-Dxd conjugate and PLC11.

Example A. In Vitro growth inhibition

SK-BR-3 Cells were seeded at a density of 1×10^4 cells/well in 96-well white plate (50 μ L/well) and incubated at 37°C, 5% CO₂. After overnight incubation, 50 μ L of each diluted substance was added. Cell viability was evaluated after 6 days using a CellTiter-Glo Luminescent Cell Viability Assay from Promega Corp. according to the manufacturer's instructions.

FIG. 4 depicts a graph showing the *in vitro* Cytotoxicity of payloads on SK-BR-3 Cell Lines. The cell viability is plotted as a function of concentration of payload. The payloads tested were Exatecan, Dxd, D1, D6, D9, and D10. D9 was observed to be the most cytotoxic payload, followed by D1, D10, Exatecan, D6, and Dxd. D9 was the most

cytotoxic of the compounds tested. The IC₅₀ of the payloads are summarized in Table 2. The enhancements of D9 and D10 were compared relative to D1 and D6, respectively

Table 2. In Vitro Cytotoxicity of Payloads on SK-BR-3 Cell Lines

Samples	Exatecan	Dxd	D9	D10	D1	D6
IC ₅₀ (nM)	1.055	2.165	0.2749	0.7879	0.7492	0.8288
Enhancement			2.7	1.1		

5 FIG. 5 depicts a graph showing the *in vitro* Cytotoxicity of ADCs with Trastuzumab on SK-BR-3 Cell Lines. The cell viability is plotted as a function of concentration. The ADCs tested were Trastuzumab with deruxtecan, PL1, PL3, PL9, PL11, PL13, and PL15. The Trastuzumab-PL13 conjugate was observed to be the most active compound.

10 **Example B. Tumor volume (mm³) and survival curves in a NCI-N87 tumorigenic epithelial cell line xenograft model dosed once intravenously with 2 mg/kg of ADCs**

 The NCI-N87 tumorigenic epithelial cell line was implanted subcutaneously in female CB17/SCID mice (4 weeks old). ADCs from above were dosed once intravenously at a 2 mg/kg dose when tumors had grown to approximately 200 mm³ (day 13, 7 animals per group, assigned to minimize differences in initial tumor volumes between groups). Tumor volume was measured every 3-5 days by a caliper device and was calculated using the formula (L x W²)/2. Mice were sacrificed when the tumor volume exceeded 1000 mm³.

 FIGS. 6 and 8 depict graphs showing the *in vivo* efficacy of ADCs with Trastuzumab, which targets HER2. The tumor volume (in mm³) is plotted as a function of days post tumor implantation. In FIG. 6, the ADCs tested were Trastuzumab with deruxtecan, PL1, and PL5. The Trastuzumab-PL1 conjugate was observed to show the highest potency in tumor growth inhibition. In FIG. 8 the ADCs tested were Trastuzumab

with deruxtecan, PL1, PL9, PL11, PL13, and PL15. The Trastuzumab-PL9 conjugate was observed to show the highest potency in tumor growth inhibition.

FIGS. 7 and 9 depict graphs showing the body weight change of mice for each ADC with Trastuzumab from FIGS. 6 and 8, respectively. The body weight change is plotted as a function of days post tumor implantation. The body weight of mice in each group increased steadily or slightly.

Example C. Pharmacokinetic profile (total antibody concentration over time) in mice following a single intravenous 2 mg/kg dose of ADCs

An ADC of PL1 was injected at 2 mg/kg in male CB17/SCID mice (4-6 weeks old) *via* the tail 30 vein (four animals per dose group, randomly assigned). Blood was drawn into citrate tubes *via* retro-orbital bleeding at various time points and processed to plasma. Total ADC concentration was assessed using a human IgG ELISA kit (Stemcell™ Technologies) according to the manufacturer's protocol. Standard curves of Trastuzumab were used for quantification. Pharmacokinetics parameters (clearance and AUC) were calculated by non-compartmental analysis using Microsoft® Excel® software incorporating PK functions.

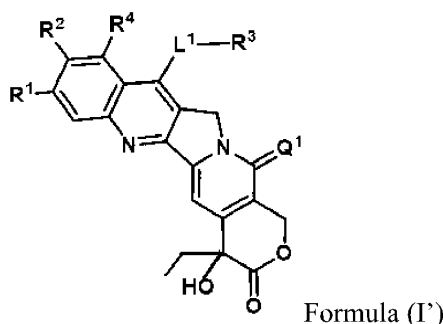
FIG. 10A and FIG. 10B depict graphs showing total antibody concentration (TAB) and concentration of antibody-drug conjugate (ADC) as a function of hours after dose injection of for Trastazumab-PL1 and Trastazumab-deruxtecan, respectively. Several hours after injection, the amount of ADC is greater for PL1 (FIG. 10A) relative to Trastuzumab-deruxtecan (FIG. 10B).

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including without limitation all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

Example D. Single dose toxicity study of Trastuzumab-PL20 in mice
10 female BALB/c mice (6-8 weeks old, Vitalriver) were randomly divided into two groups including IgG group (300 mpk, Equitech-Bio) and Trastuzumab-PL20 group (300 mpk), five mice in each group. Both drugs were administered intravenously once. After administration, body weight was monitored once a day. No mice died in both groups. A transient body weight loss observed in PL20 group and then rapidly recovered since day 3. FIG.11 showing body weight change of mice treated with Trastuzumab-PL20 ADC.

WHAT IS CLAIMED IS:

1. A compound of Formula (I')



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from H, OH, halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

5 R² is selected from H, OH, halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

Q¹ is S or O;

R³ is selected from OH, SH, -NH₂, -NHC(=O)-C₁₋₆ alkylene-OH and -NHC(=S)-C₁₋₆ alkylene-OH;

L¹ is C₁₋₆ alkylene; and

10 R⁴ is H; or R⁴ together with L¹ form a 5-8 membered carbocycle.

2. The compound of claim 1, wherein R¹ is halo.

3. The compound of claim 1, wherein R¹ is fluoro, chloro, or bromo.

4. The compound of claim 1, wherein R¹ is fluoro.

5. The compound of claim 1, wherein R¹ is C₁₋₆ alkyl or C₁₋₆ alkoxy.

15 6. The compound of claim 1, wherein R¹ is C₁₋₆ alkyl.

7. The compound of claim 1, wherein R¹ is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl.

8. The compound of claim 1, wherein R¹ is methyl, ethyl, n-propyl, or isopropyl.

20 9. The compound of claim 1, wherein R¹ is C₁₋₆ alkoxy.

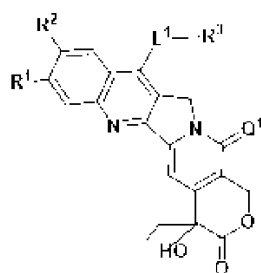
10. The compound of claim 1, wherein R¹ is methoxy or ethoxy.

11. The compound of any one of claims 1-10, wherein R^2 is C_{1-6} alkyl or C_{1-6} alkoxy.
12. The compound of any one of claims 1-10, wherein R^2 is C_{1-6} alkyl.
13. The compound of any one of claims 1-10, wherein R^2 is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl.
14. The compound of any one of claims 1-10, wherein R^2 is methyl, ethyl, n-propyl, or isopropyl.
15. The compound of any one of claims 1-10, wherein R^2 is C_{1-6} alkoxy.
16. The compound of any one of claims 1-10, wherein R^2 is methoxy or ethoxy.
17. The compound of any one of claims 1-16, wherein Q^1 is O.
18. The compound of any one of claims 1-16, wherein Q^1 is S.
19. The compound of any one of claims 1-18, wherein R^3 is selected from OH, $-NH_2$, $-NHC(=O)-C_{1-6}$ alkylene-OH and $-NHC(=S)-C_{1-6}$ alkylene-OH.
20. The compound of any one of claims 1-18, wherein R^3 is OH.
21. The compound of any one of claims 1-18, wherein R^3 is $-NHC(=O)-C_{1-6}$ alkylene-OH.
22. The compound of any one of claims 1-18, wherein R^3 is NH_2 .
23. The compound of any one of claims 1-22, wherein L^1 is C_{3-4} alkylene.
24. The compound of any one of claims 1-22, wherein $-L^1-R^3$ is $-CH_2CH_2CH_2OH$.
25. The compound of any one of claims 1-22, wherein $-L^1-R^3$ is $-CH_2CH_2CH_2CH_2OH$.
26. The compound of any one of claims 1-25, wherein R^4 is H.
27. The compound of any one of claims 1-22, wherein R^4 together with L^1 form a 5-8 membered carbocycle.
28. The compound of any one of claims 1-22, wherein R^4 together with L^1 form a 6-membered carbocycle.

29. The compound of any one of claims 1-22, wherein R^4 together with L^1 form a 6-membered carbocycle, and R^3 is selected from $-NH_2$, $-NHC(=O)-C_{1-6}$ alkylene-OH and $-NHC(=S)-C_{1-6}$ alkylene-OH.

30. The compound of any one of claims 1-22, wherein R^4 together with L^1 form a 6-membered carbocycle, and R^3 is selected from $-NH_2$, $-NHC(=O)-CH_2-OH$ and $-NHC(=S)-CH_2-OH$.

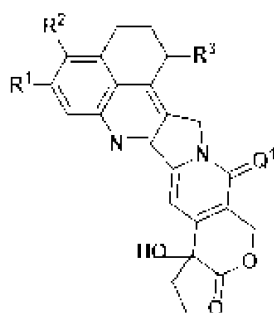
31. The compound of claim 1, wherein the compound is a compound of Formula (Ia')



Formula (Ia')

or a pharmaceutically acceptable salt thereof.

32. The compound of claim 1, wherein the compound is a compound of Formula (Ib')



Formula (Ib')

or a pharmaceutically acceptable salt thereof.

33. The compound of claim 1, wherein:

R^1 is selected from halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^2 is selected from H, OH, C_{1-6} alkyl, and C_{1-6} alkoxy;

Q^1 is S or O;

R³ is OH;

L¹ is C₁₋₆ alkylene; and

R⁴ is H.

34. The compound of claim 1, wherein:

R¹ is halo;

R² is selected from H, OH, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

Q¹ is S or O;

R³ is OH;

L¹ is C₁₋₆ alkylene; and

R⁴ is H.

35. The compound of claim 1, wherein:

R¹ is fluoro;

R² methoxy;

Q¹ is O; and

-L¹-R³ is -CH₂CH₂CH₂OH.

36. The compound of claim 1, wherein:

R¹ is selected from halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

R² is selected from H, OH, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

Q¹ is S or O;

R³ is selected from OH, SH, -NH₂, -NHC(=O)-C₁₋₆ alkylene-OH and -NHC(=S)-C₁₋₆ alkylene-OH; and

R⁴ together with L¹ form a 5-8 membered carbocycle.

37. The compound of claim 1, wherein:

R¹ is halo;

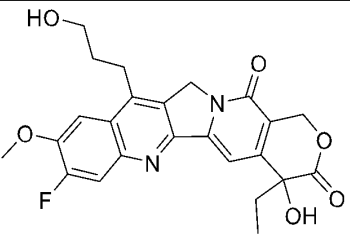
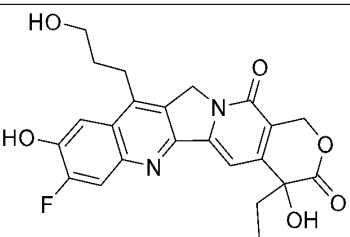
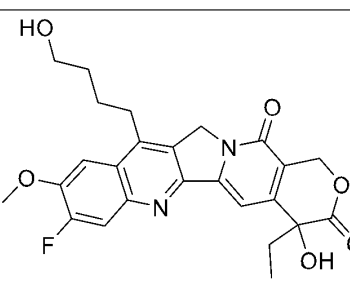
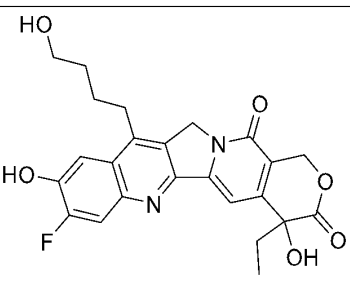
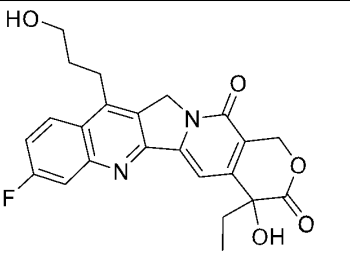
R² is C₁₋₆ alkyl;

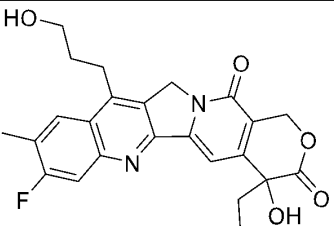
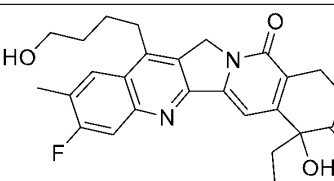
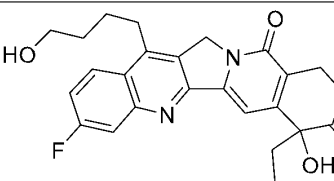
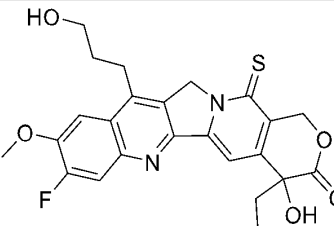
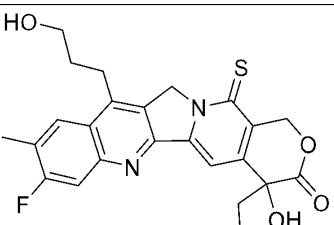
Q¹ is S or O;

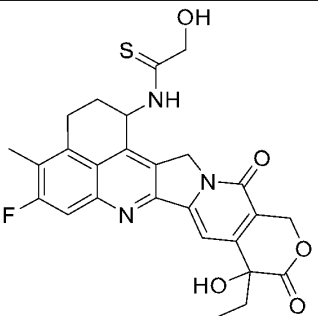
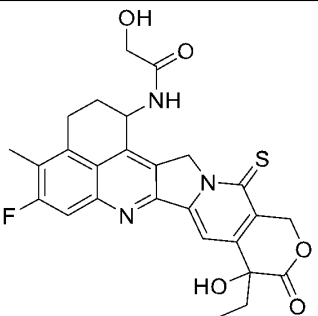
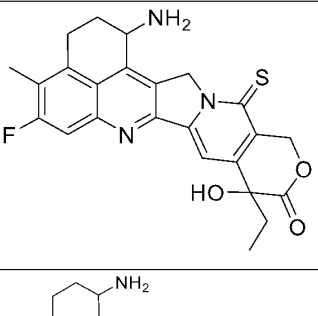
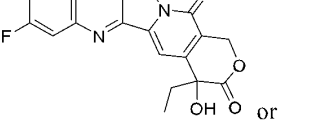
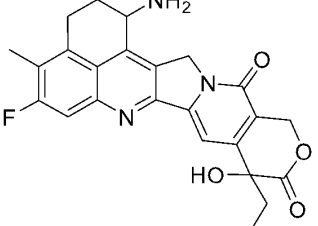
R³ is selected from OH, SH, -NH₂, -NHC(=O)-C₁₋₆ alkylene-OH and -NHC(=S)-C₁₋₆ alkylene-OH; and

R⁴ together with L¹ form a 5-8 membered carbocycle.

38. The compound of claim 1, wherein the compound is:

D1'	
D2'	
D3'	
D4'	
D5'	
D6'	

	
D7'	
D8'	
D9'	
D10'	

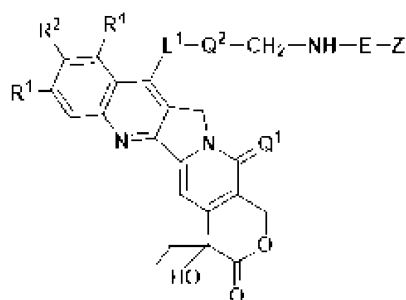
D11'	
D12'	
D13'	
D14'	
D15'	

or a pharmaceutically acceptable salt thereof.

39. An antibody-drug conjugate comprising a drug and an antibody, wherein the drug comprises a compound of any one of claim 1-38, or a derivative thereof.

40. The antibody-drug conjugate of claim 39, wherein the drug attaches to the antibody via a linker.

41. A compound of Formula (II')



Formula (II')

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from H, OH, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

10 R^2 is selected from H, OH, C_{1-6} alkyl, and C_{1-6} alkoxy;

Q^1 is S or O;

L^1 is C_{1-6} alkylene;

R^4 is H; or

R^4 together with L^1 form 5-8 membered carbocycle;

15 Q^2 is selected from $-S-$, $-O-$, $^*-NHC(=O)-C_{1-6}$ alkylene- $O-$ and $^*-NHC(=S)-C_{1-6}$ alkylene- $O-$, wherein the asterisk (*) represents the point of attachment to L^1 ;

E is a peptide comprising 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol;

the N terminal of the peptide is covalently attached to Z;

20 Z is $-C(=O)-L^2-Y$;

L^2 is selected from C_{1-6} alkylene, $-(CH_2CH_2-O)_n-C_{1-6}$ alkylene-*, and $-C_{1-6}$ alkylene- $(O-CH_2CH_2)_n-$;

n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

the asterisk (*) represents the point of attachment to Y; and

Y is a reactive group, preferably an electrophilic group.

42. The compound of claim 41, wherein R¹ is halo.
43. The compound of claim 41, wherein R¹ is fluoro, chloro or bromo.
44. The compound of claim 41, wherein R¹ is fluoro.
- 5 45. The compound of claim 41, wherein R¹ is C₁₋₆ alkyl or C₁₋₆ alkoxy.
46. The compound of claim 41, wherein R¹ is C₁₋₆ alkyl.
47. The compound of claim 41, wherein R¹ is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl.
- 10 48. The compound of claim 41, wherein R¹ is methyl, ethyl, n-propyl, or isopropyl.
49. The compound of claim 41, wherein R¹ is C₁₋₆ alkoxy.
50. The compound of claim 41, wherein R¹ is methoxy or ethoxy.
51. The compound of any one of claims 41-50, wherein R² is C₁₋₆ alkyl or C₁₋₆ alkoxy.
- 15 52. The compound of any one of claims 41-50, wherein R² is C₁₋₆ alkyl.
53. The compound of any one of claims 41-50, wherein R² is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl.
54. The compound of any one of claims 41-50, wherein R² is methyl, ethyl, n-propyl, or isopropyl.
- 20 55. The compound of any one of claims 41-50, wherein R² is C₁₋₆ alkoxy.
56. The compound of any one of claims 41-50, wherein R² is methoxy or ethoxy.
57. The compound of any one of claims 41-56, wherein Q¹ is O.
58. The compound of any one of claims 41-56, wherein Q¹ is S.
- 25 59. The compound of any one of claims 41-58, wherein L¹ is C₃₋₄ alkylene.
60. The compound of any one of claims 41-59, wherein Q² is O.
61. The compound of any one of claims 41-59, wherein Q² is S.
62. The compound of any one of claims 41-58, wherein -L¹-Q² is *-CH₂CH₂CH₂O-, wherein the asterisk (*) represents the point of attachment to L¹.

63. The compound of any one of claims 41-58, wherein $-L^1-Q^2$ is $^*-CH_2CH_2CH_2CH_2O-$, wherein the asterisk (*) represents the point of attachment to L^1 .

64. The compound of claim any one of claims 41-63, wherein R^4 is H.

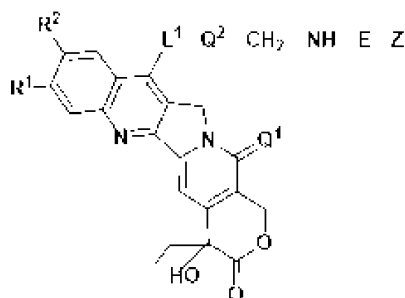
65. The compound of claim any one of claims 41-58, wherein R^4 together with L^1 form a 5-8 membered carbocycle.

66. The compound of any one of claims 41-58, wherein R^4 together with L^1 form a 6-membered carbocycle.

67. The compound of any one of claims 41-58, wherein R^4 together with L^1 form a 6-membered carbocycle, and Q^2 is selected from $^*-NHC(=O)-C_{1-6}$ alkylene-O- and $^*-NHC(=S)-C_{1-6}$ alkylene-O-, wherein the asterisk (*) represents the point of attachment to L^1 .

68. The compound of any one of claims 41-58, wherein R^4 together with L^1 form a 6-membered carbocycle, and Q^2 is selected from $^*-NHC(=O)-CH_2-O-$ and $^*-NHC(=S)-CH_2-O-$, wherein the asterisk represents to point of attachment to L^1 .

69. The compound of claim 41, wherein the compound is a compound of Formula (IIa')



Formula (IIa')

or a pharmaceutically acceptable salt thereof.

70. The compound of claim 41, wherein:

R^1 is halo;

R^2 is selected from H, $-OH$, C_{1-6} alkyl, and C_{1-6} alkoxy;

Q^1 is S or O;

R^4 is H;

L^1 is C_{1-6} alkylene;

Q^2 is selected from -S-, and -O-;

E is a peptide comprising 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol;

the N terminal of the peptide is covalently attached to Z;

5 Z is $-C(=O)-L^2-Y$;

L^2 is selected from C_{1-6} alkylene, $-(CH_2CH_2-O)_n-C_{1-6}$ alkylene-*, and $-C_{1-6}$ alkylene- $(O-CH_2CH_2)_n-$;

n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

the asterisk (*) represents the point of attachment to Y; and

10 Y is an electrophilic group.

71. The compound of claim 41, wherein:

R^1 is halo;

R^2 is C_{1-6} alkoxy;

Q^1 is O;

15 R^4 is H;

L^1 is C_{1-6} alkylene;

Q^2 is -O-;

E is a peptide comprising 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol;

20 the N terminal of the peptide is covalently attached to Z;

Z is $-C(=O)-L^2-Y$;

L^2 is $-(CH_2CH_2-O)_n-C_{1-6}$ alkylene-*

n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

the asterisk (*) represents the point of attachment to Y; and

25 Y is a reactive group, preferably an electrophilic group.

72. The compound of any one of claims 41-71, wherein E is a peptide comprising 2 to 10 amino acids, and the N terminal of the peptide is covalently attached to Z.

73. The compound of any one of claims 41-71, wherein E is a peptide comprising 2 to 8 amino acids, and the N terminal of the peptide is covalently attached to Z.

74. The compound of any one of claims 41-71, wherein E is a peptide comprising 2 to 6 amino acids, and the N terminal of the peptide is covalently attached to Z.

75. The compound of any one of claims 41-71, wherein E is a peptide comprising 2 to 4 amino acids, and the N terminal of the peptide is covalently attached to Z.

76. The compound of any one of claims 41-71, wherein E is a peptide comprising 2 to 3 amino acids, and the N terminal of the peptide is covalently attached to Z.

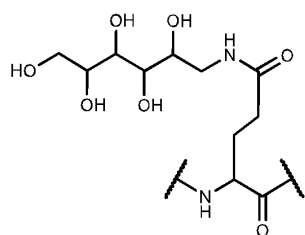
77. The compound of any one of claims 41-71, wherein each amino acid of E is an L amino acid, or at least one amino acid of E is a D amino acid.

78. The compound of any one of claims 41-71, wherein E comprises one or more amino acids selected from glycine, alanine, valine, glutamine, glutamic acid, phenylalanine, and leucine.

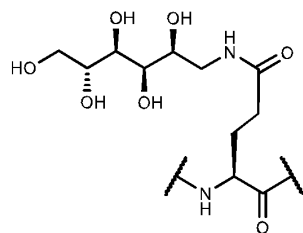
79. The compound of any one of claims 41-71, wherein one or more amino acid of E is substituted with one or more polyol.

80. The compound of any one of claims 41-71, wherein one or more of the glutamine or glutamic acid of E is substituted with one or more polyol.

81. The compound of any one of claims 41-71, wherein E comprises an amino acid having the following structure,



82. The compound of any one of claims 41-71, wherein E comprises an amino acid having the following structure,



83. The compound of any one of claims 41-71, wherein E is selected from -
 Ala-Val-*, -Val-Ala-*, -Gly-Gly-*, -Val-Cit-*, -Cit-Val-*, -Leu-Ala-*, -Ala-Leu-*, -Leu-
 Cit-*, -Cit-Leu-*, -Leu-Ala-*, -Ala-Leu-*, -Lys-Lys-*, -Ala-Lys-*, -Lys-Ala-*, -Val-
 5 Lys-*, -Lys-Val-*, -Tyr-Arg-*, -Arg-Tyr-*, -Arg-Arg-*, -Ala-Ala-*, -Phe-Lys-*, -Lys-
 Phe-*, -Thr-Thr-*, -Thr-Met-*, -Met-Thr-*, -Met-Tyr-*, -Tyr-Met-*, -Phe-Gln-*, -Gln-
 Phe-*, -Gly-Ser-*, -Leu-Gin-*, -Gin-Leu-*, -Ser-Ala-*, -Ser-Gly-*, -Val-Thr-*, -Thr-
 Val-*, -Val-Gln-*, -Ser-Vai-*, -Vai-Ser-*, -Ala-Met-*, -Met-Ala-*, -Val-Arg-*, -Arg-
 Val-*, -Phe-Ala-*, -Ala-Phe-*, -Cit-Val-*, -Gln-Val-*, -Phe-Arg-*, -Arg-Phe-*, -Ala-
 10 Val-Glu-*, -Ala-Ala-Ala-*, -Gly-Gly-Gly-*, -Ala-Val-Ala-*, -Gly-Val-Gly-*, -Ala-Val-
 Gly-*, -Gly-Phe-Lys-*, -Lys-Phe-Gly-*, -Leu-Ala-Leu-*, -Val-Ala-Leu-*, -Leu-Ala-Val-
 , -Val-Ala-Val-, -Ala-Val-Ala-Gly-*, -Gly-Phe-Gly-Gly-*, -Gly-Gly-Phe-Gly-*, -Ala-
 Val-Gly-Gly-*, -Ala-Ala-Ala-Ala-*, -Ala-Val-Ala-Ala-*, -Ala-Leu-Ala-Leu-*, -Leu-Ala-
 Leu-Ala-*, -Gly-Phe-Leu-Gly-*, and -Gly-Leu-Phe-Gly-*, wherein the Glu is optionally
 15 substituted with a polyol, and wherein the asterisk (*) represents the N-terminal of the
 peptides covalently attached to Z.

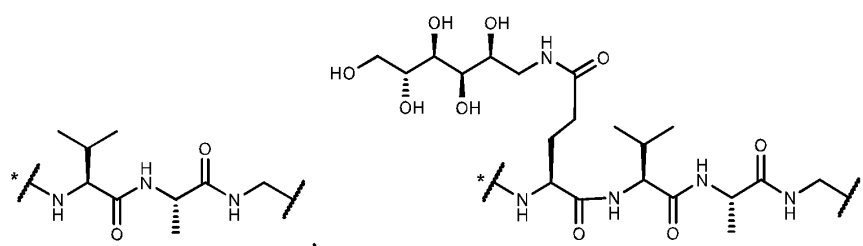
84. The compound of any one of claims 41-71, wherein E is selected from -
 Ala-Val-*, -Val-Ala-*, -Val-Lys-*, -Val-Arg-*, -Val-Cit-*, -Val-Arg-*, -Val-Cit-*, -Val-
 Lys-*, -Val-Arg-*, -Arg-Arg-*, -Ala-Ala-*, -Ala-Lys-*, -Ala-Arg-*, -Ala-Val-Glu-*, -
 20 Ala-Ala-Ala-*, -Ala-Val-Ala-*, -Ala-Ala-Gly-*, and -Ala-Val-Gly-*, wherein the Glu is
 optionally substituted with a polyol, and wherein the asterisk(*) represents the N-terminal
 of the peptides covalently attached to Z.

85. The compound of any one of claims 41-71, wherein E is selected from -
 Ala-Val-* and -Ala-Val-Glu-*, wherein the Glu is optionally substituted with a polyol,
 25 and wherein the asterisk(*) represents the N-terminal of the peptides covalently attached
 to Z.

86. The compound of any one of claims 41-71, wherein E is -Ala-Val-*, wherein the asterisk(*) represents the N-terminal of the peptides covalently attached to Z.

87. The compound of any one of claims 41-71, wherein E is -Ala-Val-Glu-*, wherein the Glu is substituted with a polyol, and wherein the asterisk(*) represents the N-terminal of the peptides covalently attached to Z.

88. The compound of any one of claims 41-71, wherein -E-NH-CH₂- has one of the following structures, wherein the asterisk(*) represents the N-terminal of the peptides covalently attached to Z:



wherein the asterisk(*) represents the N-terminal of the peptides covalently attached to Z.

89. The compound of any one of claims 41-88, wherein L² is C₁₋₆ alkylene.

90. The compound of any one of claims 41-88, wherein L² is C₃₋₆ alkylene.

91. The compound of any one of claims 41-88, wherein L² is -(CH₂)₅-.

92. The compound of any one of claims 41-88, wherein L² is selected from - (CH₂CH₂-O)_n-C₁₋₆ alkylene-*, and -C₁₋₆ alkylene-(O-CH₂CH₂)_n-, wherein n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and wherein the asterisk (*) represents the point of attachment to Y.

93. The compound of claim 92, wherein n is 2, 3, 4 or 5.

94. The compound of claim 92, wherein n is 2, 3 or 4.

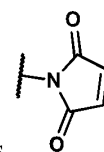
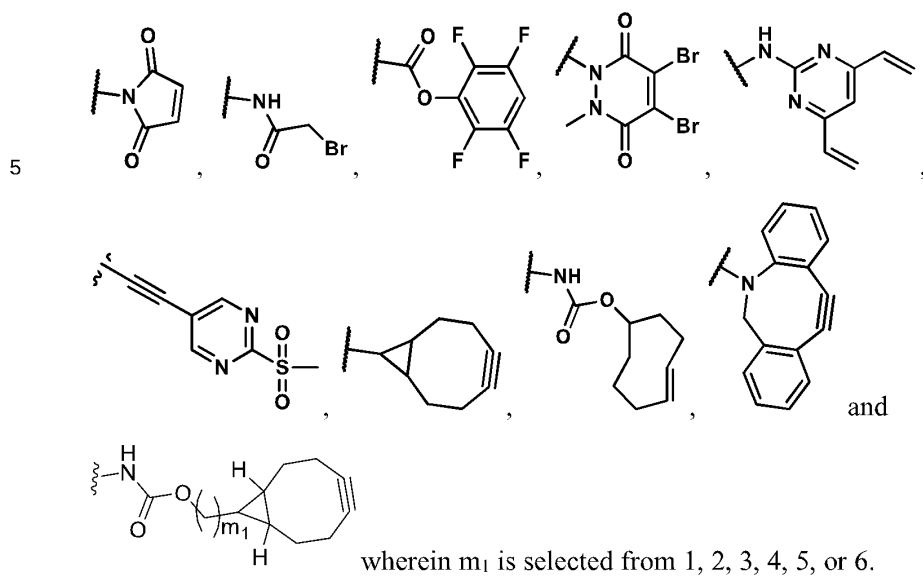
95. The compound of claim 92, wherein n is 3 or 4.

96. The compound of claim 92, wherein n is 4.

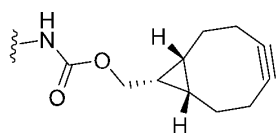
97. The compound of any one of claims 41-88, wherein L² is selected from - (CH₂CH₂-O)₄-C₁₋₄ alkylene-*, and -C₁₋₄ alkylene-(O-CH₂CH₂)₄-, wherein the asterisk (*) represents the point of attachment to Y.

98. The compound of any one of claims 41-88, wherein L^2 is selected from $-(CH_2CH_2-O)_4-CH_2CH_2-$ *, and $-CH_2CH_2-(O-CH_2CH_2)_4-$ *, and wherein the asterisk (*) represents the point of attachment to Y.

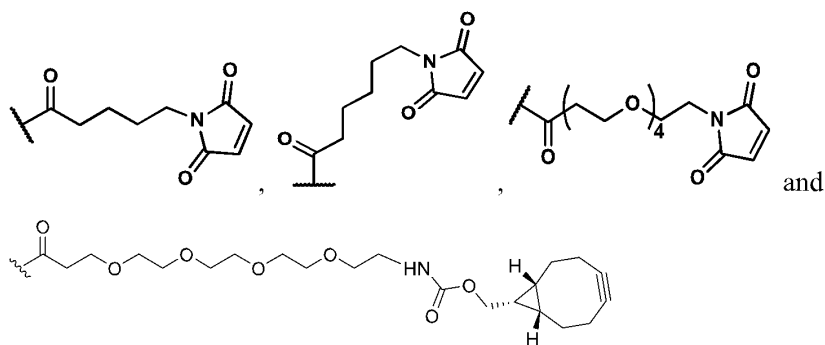
99. The compound of any one of claims 41-98, wherein Y is selected from



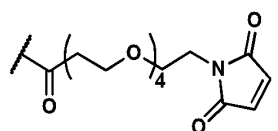
100. The compound of any one of claims 41-98, wherein Y is



101. The compound of any one of claims 41-88, wherein Z is selected from

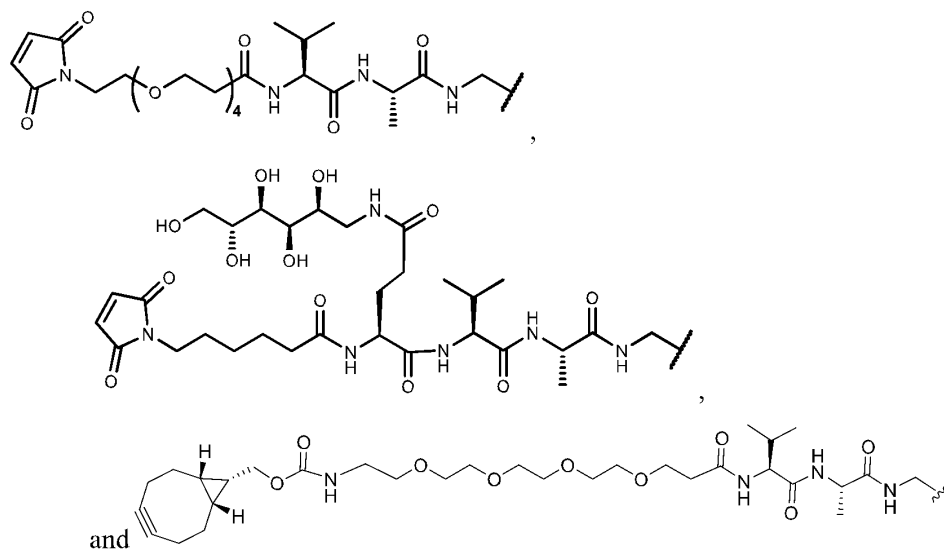


102. The compound of any one of claims 41-88, wherein Z is



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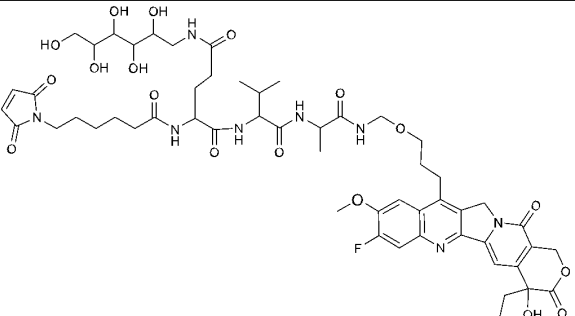
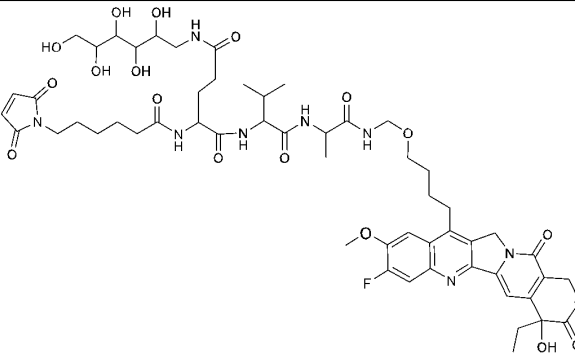
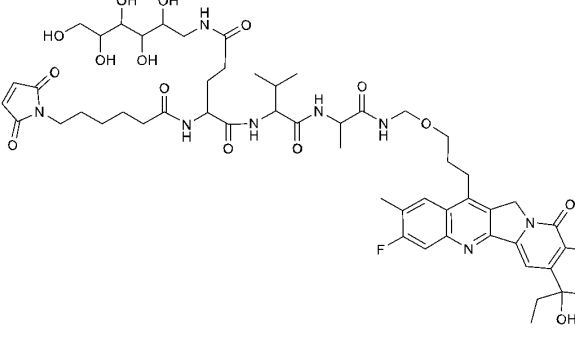
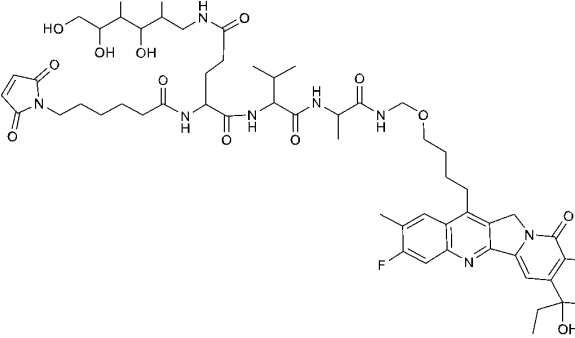
103. The compound of any one of claims 41-71, wherein $-\text{CH}_2\text{-NH-E-Z}$ has one of the following structures:



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104. The compound of claim 41, wherein the compound is:

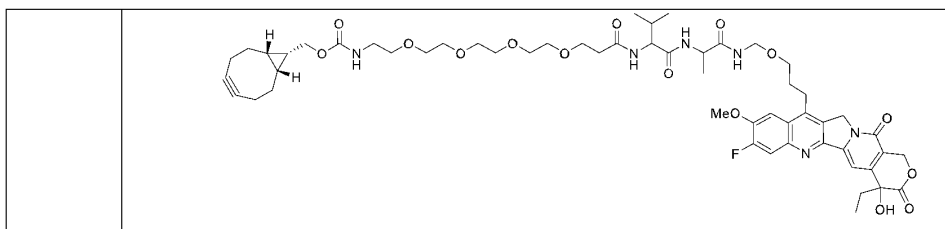
PL1'	Chemical structure of PL1' is a linear polymer. It features a maleimide end group connected via an ethylene spacer to a poly(ethylene glycol) (PEG) chain. The PEG chain is terminated by a diisobutyl succinate group, which is further linked to a diisobutyl succinate group. This diisobutyl succinate group is connected via an ethylene spacer to a 4-(4-methoxy-2-fluorophenyl)-1H-indole-3-carboxamide moiety. The indole moiety is further substituted with a 4-ethyl-2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl group.
PL2'	Chemical structure of PL2' is a linear polymer. It features a maleimide end group connected via an ethylene spacer to a poly(ethylene glycol) (PEG) chain. The PEG chain is terminated by a diisobutyl succinate group, which is further linked to a diisobutyl succinate group. This diisobutyl succinate group is connected via an ethylene spacer to a 4-(4-methoxy-2-fluorophenyl)-1H-indole-3-carboxamide moiety. The indole moiety is further substituted with a 4-ethyl-2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl group.
PL3'	Chemical structure of PL3' is a linear polymer. It features a maleimide end group connected via an ethylene spacer to a poly(ethylene glycol) (PEG) chain. The PEG chain is terminated by a diisobutyl succinate group, which is further linked to a diisobutyl succinate group. This diisobutyl succinate group is connected via an ethylene spacer to a 4-(4-methoxy-2-fluorophenyl)-1H-indole-3-carboxamide moiety. The indole moiety is further substituted with a 4-ethyl-2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl group.
PL4'	Chemical structure of PL4' is a linear polymer. It features a maleimide end group connected via an ethylene spacer to a poly(ethylene glycol) (PEG) chain. The PEG chain is terminated by a diisobutyl succinate group, which is further linked to a diisobutyl succinate group. This diisobutyl succinate group is connected via an ethylene spacer to a 4-(4-methoxy-2-fluorophenyl)-1H-indole-3-carboxamide moiety. The indole moiety is further substituted with a 4-ethyl-2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl group.

PL5'	 Chemical structure of PL5' derivative. It features a complex molecule with a central core containing a fluorine atom and a methoxy group. The core is linked to a side chain that includes a hydroxyl group, a carbonyl group, and a chain of hydroxyl groups. The side chain is further linked to a chain of carbonyl groups and a chain of hydroxyl groups.
PL6'	 Chemical structure of PL6' derivative. It features a complex molecule with a central core containing a fluorine atom and a methoxy group. The core is linked to a side chain that includes a hydroxyl group, a carbonyl group, and a chain of hydroxyl groups. The side chain is further linked to a chain of carbonyl groups and a chain of hydroxyl groups.
PL7'	 Chemical structure of PL7' derivative. It features a complex molecule with a central core containing a fluorine atom and a methoxy group. The core is linked to a side chain that includes a hydroxyl group, a carbonyl group, and a chain of hydroxyl groups. The side chain is further linked to a chain of carbonyl groups and a chain of hydroxyl groups.
PL8'	 Chemical structure of PL8' derivative. It features a complex molecule with a central core containing a fluorine atom and a methoxy group. The core is linked to a side chain that includes a hydroxyl group, a carbonyl group, and a chain of hydroxyl groups. The side chain is further linked to a chain of carbonyl groups and a chain of hydroxyl groups.

PL9'	Chemical structure of PL9' is a complex molecule. It features a 2,5-dioxo-3,4-dihydro-1H-pyridine-1-yl group connected via a polyether chain (containing a 4-unit repeat) to a dipeptide chain (NH-CH(CH₃)-C(=O)-NH-CH(CH₃)-C(=O)-NH-). This chain is further connected via an ether linkage to a 3,4-dihydro-2H-1,2,4-benzoxazin-6-yl group. The benzoxazin core is substituted with a 4-fluoro-2-methoxyphenyl group and a 4-ethyl-2-hydroxy-5-oxo-1,3-dioxol-2-yl group.
PL10'	Chemical structure of PL10' is similar to PL9', but the benzoxazin core is substituted with a 4-fluoro-2-methoxyphenyl group and a 4-ethyl-2-hydroxy-5-oxo-1,3-dioxol-2-yl group.
PL11'	Chemical structure of PL11' is similar to PL9', but the benzoxazin core is substituted with a 4-fluoro-2-methoxyphenyl group and a 4-ethyl-2-hydroxy-5-oxo-1,3-dioxol-2-yl group.
PL12'	Chemical structure of PL12' is similar to PL9', but the benzoxazin core is substituted with a 4-fluoro-2-methoxyphenyl group and a 4-ethyl-2-hydroxy-5-oxo-1,3-dioxol-2-yl group.

PL13'	Chemical structure of PL13' is a complex molecule. It features a pyridine ring substituted with a fluorine atom and a methyl group. This ring is part of a fused system with a thiophene ring. A side chain on the thiophene ring includes a methyl group, a hydroxyl group, and a carbonyl group. The molecule is linked via an ether bridge to a chain containing a methyl group, a carbonyl group, and a hydroxyl group. This chain is further linked to a pyridine ring substituted with a fluorine atom and a methyl group. The pyridine ring is part of a fused system with a thiophene ring. A side chain on the thiophene ring includes a methyl group, a hydroxyl group, and a carbonyl group. The molecule is linked via an ether bridge to a chain containing a methyl group, a carbonyl group, and a hydroxyl group. This chain is further linked to a pyridine ring substituted with a fluorine atom and a methyl group. The pyridine ring is part of a fused system with a thiophene ring. A side chain on the thiophene ring includes a methyl group, a hydroxyl group, and a carbonyl group.
PL14'	Chemical structure of PL14' is a complex molecule. It features a pyridine ring substituted with a fluorine atom and a methyl group. This ring is part of a fused system with a thiophene ring. A side chain on the thiophene ring includes a methyl group, a hydroxyl group, and a carbonyl group. The molecule is linked via an ether bridge to a chain containing a methyl group, a carbonyl group, and a hydroxyl group. This chain is further linked to a pyridine ring substituted with a fluorine atom and a methyl group. The pyridine ring is part of a fused system with a thiophene ring. A side chain on the thiophene ring includes a methyl group, a hydroxyl group, and a carbonyl group. The molecule is linked via an ether bridge to a chain containing a methyl group, a carbonyl group, and a hydroxyl group. This chain is further linked to a pyridine ring substituted with a fluorine atom and a methyl group. The pyridine ring is part of a fused system with a thiophene ring. A side chain on the thiophene ring includes a methyl group, a hydroxyl group, and a carbonyl group.
PL15'	Chemical structure of PL15' is a complex molecule. It features a pyridine ring substituted with a fluorine atom and a methyl group. This ring is part of a fused system with a thiophene ring. A side chain on the thiophene ring includes a methyl group, a hydroxyl group, and a carbonyl group. The molecule is linked via an ether bridge to a chain containing a methyl group, a carbonyl group, and a hydroxyl group. This chain is further linked to a pyridine ring substituted with a fluorine atom and a methyl group. The pyridine ring is part of a fused system with a thiophene ring. A side chain on the thiophene ring includes a methyl group, a hydroxyl group, and a carbonyl group. The molecule is linked via an ether bridge to a chain containing a methyl group, a carbonyl group, and a hydroxyl group. This chain is further linked to a pyridine ring substituted with a fluorine atom and a methyl group. The pyridine ring is part of a fused system with a thiophene ring. A side chain on the thiophene ring includes a methyl group, a hydroxyl group, and a carbonyl group.

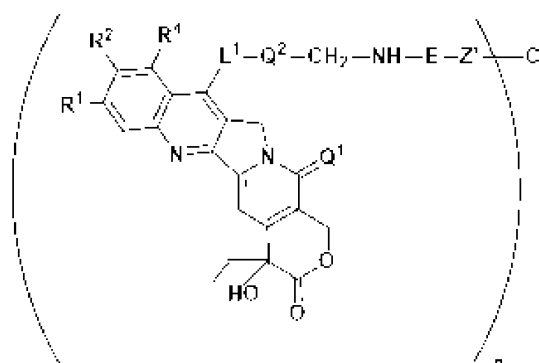
PL16'	Chemical structure of PL16' is a complex molecule. It features a pyridine ring substituted with a methoxy group and a fluorine atom. This ring is connected via a methylene bridge to a thiazolidine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group. The pyrazole ring is connected via a methylene bridge to a pyridine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group. The pyrazole ring is connected via a methylene bridge to a pyridine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group.
PL17'	Chemical structure of PL17' is a complex molecule. It features a pyridine ring substituted with a methoxy group and a fluorine atom. This ring is connected via a methylene bridge to a thiazolidine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group. The pyrazole ring is connected via a methylene bridge to a pyridine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group. The pyrazole ring is connected via a methylene bridge to a pyridine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group.
PL18'	Chemical structure of PL18' is a complex molecule. It features a pyridine ring substituted with a methoxy group and a fluorine atom. This ring is connected via a methylene bridge to a thiazolidine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group. The pyrazole ring is connected via a methylene bridge to a pyridine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group. The pyrazole ring is connected via a methylene bridge to a pyridine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group.
PL19'	Chemical structure of PL19' is a complex molecule. It features a pyridine ring substituted with a methoxy group and a fluorine atom. This ring is connected via a methylene bridge to a thiazolidine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group. The pyrazole ring is connected via a methylene bridge to a pyridine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group. The pyrazole ring is connected via a methylene bridge to a pyridine ring, which is further linked to a pyrazole ring. The pyrazole ring is substituted with a hydroxyl group and a methyl group. or
PL20'	



or a pharmaceutically acceptable salt thereof.

105. An antibody-drug conjugate comprising a drug and an antibody, wherein the drug comprises a compound of any one of claim 41-104, or a derivative thereof.

106. A compound of Formula (III'),



^p Formula (III'),

or a pharmaceutically acceptable salt thereof, wherein:

C is a cell binding agent;

R¹ is selected from halo, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R² is selected from H, -OH, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

Q¹ is S or O;

L¹ is C₁₋₆ alkylene;

Q² is selected from -S-, -O-, *-NHC(=O)-C₁₋₆ alkylene-O- and *-NHC(=S)-C₁₋₆ alkylene-O-*, wherein the asterisk represents to point of attachment to L¹;

E is a peptide comprising 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol;

the N terminal of the peptide is covalently attached to Z';

Z' is -C(=O)-L²-Y',

L^2 is selected from C_{1-6} alkylene, $-(CH_2CH_2-O)_n-C_{1-6}$ alkylene-*, and $-C_{1-6}$ alkylene- $(O-CH_2CH_2)_n$ *,

n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

the asterisk (*) represents the point of attachment to Y' ;

5 Y' is a group formed by a reaction of a reactive group such as an electrophilic group with another reactive group such as a reactive nucleophilic group present on the cell binding agent; and

p is the drug to antibody ratio (DAR) and p has a value between 1 to 18.

107. The compound of claim 106, wherein R^1 is halo.

108. The compound of claim 106, wherein R^1 is fluoro, chloro, or bromo.

109. The compound of claim 106, wherein R^1 is fluoro.

110. The compound of claim 106, wherein R^1 is C_{1-6} alkyl or C_{1-6} alkoxy.

111. The compound of claim 106, wherein R^1 is C_{1-6} alkyl.

112. The compound of claim 106, wherein R^1 is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl.

113. The compound of claim 106, wherein R^1 is methyl, ethyl, n-propyl, or isopropyl.

114. The compound of claim 106, wherein R^1 is C_{1-6} alkoxy.

115. The compound of claim 106, wherein R^1 is methoxy or ethoxy.

20 116. The compound of any one of claims 106-115, wherein R^2 is C_{1-6} alkyl or C_{1-6} alkoxy.

117. The compound of any one of claims 106-115, wherein R^2 is C_{1-6} alkyl.

118. The compound of any one of claims 106-115, wherein R^2 is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, or n-hexyl.

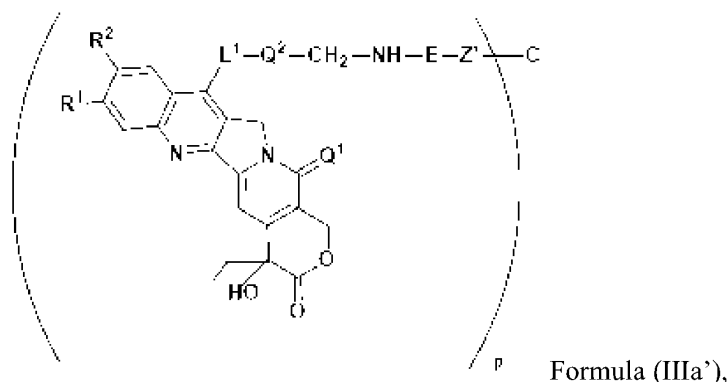
25 119. The compound of any one of claims 106-115, wherein R^2 is methyl, ethyl, n-propyl, or isopropyl.

120. The compound of any one of claims 106-115, wherein R^2 is C_{1-6} alkoxy.

121. The compound of any one of claims 106-115, wherein R^2 is methoxy or ethoxy.

30 122. The compound of any one of claims 106-121, wherein Q^1 is O.

123. The compound of any one of claims 106-121, wherein Q^1 is S.
124. The compound of any one of claims 106-123, wherein L^1 is C_{3-4} alkylene.
125. The compound of any one of claims 106-124, wherein Q^2 is O.
126. The compound of any one of claims 106-124, wherein Q^2 is S.
- 5 127. The compound of any one of claims 106-123, wherein $-L^1-Q^2$ is $^*-CH_2CH_2CH_2O-$, wherein the asterisk (*) represents the point of attachment to L^1 .
128. The compound of any one of claims 106-123, wherein $-L^1-Q^2$ is $^*-CH_2CH_2CH_2CH_2O-$, wherein the asterisk (*) represents the point of attachment to L^1 .
129. The compound of any one of claims 106-128, wherein R^4 is H.
- 10 130. The compound of any one of claims 106-123, wherein R^4 together with L^1 form a 5-8 membered carbocycle.
131. The compound of any one of claims 106-123, wherein R^4 together with L^1 form a 6-membered carbocycle.
132. The compound of any one of claims 106-123, wherein R^4 together with L^1 form a 6-membered carbocycle, and Q^2 is selected from $^*-NHC(=O)-C_{1-6}$ alkylene-O- and $^*-NHC(=S)-C_{1-6}$ alkylene-O-, wherein the asterisk (*) represents to point of attachment to L^1 .
- 15 133. The compound of any one of claims 106-123, wherein R^4 together with L^1 form a 6-membered carbocycle, and Q^2 is selected from $^*-NHC(=O)-CH_2-O-$ and $^*-NHC(=S)-CH_2-O-$, wherein the asterisk represents to point of attachment to L^1 .
- 20 134. The compound of claim 106, wherein the compound is a compound of Formula (IIIa'),



or a pharmaceutically acceptable salt thereof.

135. The compound of claim 106, wherein:

R^1 is fluoro;

5 R^2 is C_{1-4} alkyl or C_{1-4} alkoxy;

Q^1 is S or O;

R^4 is H;

L^1 is C_{1-6} alkylene;

Q^2 is -S- or -O-;

10 E is a peptide comprising 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol;

the N terminal of the peptide is covalently attached to Z' ;

Z' is $-C(=O)-L^2-Y'$,

15 L^2 is selected from C_{1-6} alkylene, $-(CH_2CH_2-O)_n-C_{1-6}$ alkylene-*, and $-C_{1-6}$ alkylene- $(O-CH_2CH_2)_n$ -*,

n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

the asterisk (*) represents the point of attachment to Y' ;

Y' is a group formed by a reaction of an electrophilic group with a reactive nucleophilic group present on the cell binding agent; and

20 p is the drug to antibody ratio (DAR) and p has a value between 1 to 18.

136. The compound of claim 105, wherein:

R^1 is fluoro;

R^2 is C_{1-4} alkoxy;

Q^1 is O;

R^4 is H;

L^1 is C_{1-6} alkylene;

Q^2 is -O-;

5 E is a peptide comprising 2 to 10 amino acids; wherein the amino acid is optionally substituted with one or more polyol;

the N terminal of the peptide is covalently attached to Z' ;

Z' is $-C(=O)-L^2-Y'$,

L^2 is $-(CH_2CH_2-O)_n-C_{1-6}$ alkylene-*,

10 n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

the asterisk (*) represents the point of attachment to Y' ;

Y' is a group formed by a reaction of an electrophilic group with a reactive nucleophilic group present on the cell binding agent; and

p is the drug to antibody ratio (DAR) and p has a value between 1 to 18.

15 137. The compound of any one of claims 106-136, wherein E is a peptide comprising 2 to 10 amino acids, and the N terminal of the peptide is covalently attached to Z' .

138. The compound of any one of claims 106-136, wherein E is a peptide comprising 2 to 8 amino acids, and the N terminal of the peptide is covalently attached to
20 Z' .

139. The compound of any one of claims 106-136, wherein E is a peptide comprising 2 to 6 amino acids, and the N terminal of the peptide is covalently attached to Z' .

140. The compound of any one of claims 106-136, wherein E is a peptide
25 comprising 2 to 4 amino acids, and the N terminal of the peptide is covalently attached to Z' .

141. The compound of any one of claims 106-136, wherein E is a peptide comprising 2 to 3 amino acids, and the N terminal of the peptide is covalently attached to Z' .

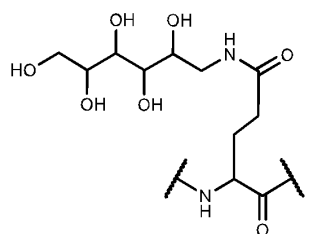
142. The compound of any one of claims 106-136, wherein each amino acid of E is an L amino acid, or at least one amino acid of E is a D amino acid.

143. The compound of any one of claims 106-136, wherein E comprises one or more amino acids selected from glycine, alanine, valine, glutamine, glutamic acid, phenylalanine, and leucine.

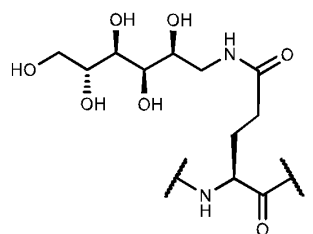
144. The compound of any one of claims 106-136, wherein one or more amino acid of E is substituted with one or more polyol.

145. The compound of any one of claims 106-136, wherein one or more of the glutamine or glutamic acid of E is substituted with one or more polyol.

146. The compound of any one of claims 106-136, wherein E comprises an amino acid having the following structure,



147. The compound of any one of claims 106-136, wherein E comprises an amino acid having the following structure,



148. The compound of any one of claims 106-136, wherein E is selected from -Ala-Val-*, -Val-Ala-*, -Gly-Gly-*, -Val-Cit-*, -Cit-Val-*, -Leu-Ala-*, -Ala-Leu-*, -Leu-Cit-*, -Cit-Leu-*, -Leu-Ala-*, -Ala-Leu-*, -Lys-Lys-*, -Ala-Lys-*, -Lys-Ala-*, -Val-Lys-*, -Lys-Val-*, -Tyr-Arg-*, -Arg-Tyr-*, -Arg-Arg-*, -Ala-Ala-*, -Phe-Lys-*, -Lys-Phe-*, -Thr-Thr-*, -Thr-Met-*, -Met-Thr-*, -Met-Tyr-*, -Tyr-Met-*, -Phe-Gln-*, -Gln-Phe-*, -Gly-Ser-*, -Leu-Gin-*, -Gin-Leu-*, -Ser-Ala-*, -Ser-Gly-*, -Val-Thr-*, -Thr-

Val-*, -Val-Gln-*, -Ser-Vai-*, -Vai-Ser-*, -Ala-Met-*, -Met-Ala-*, -Val-Arg-*, -Arg-Val-*, -Phe-Ala-*, -Ala-Phe-*, -Cit-Val-*, -Gln-Val-*, -Phe-Arg-*, -Arg-Phe-*, -Ala-Val-Glu-*, -Ala-Ala-Ala-*, -Gly-Gly-Gly-*, -Ala-Val-Ala-*, -Gly-Val-Gly-*, -Ala-Val-Gly-*, -Gly-Phe-Lys-*, -Lys-Phe-Gly-*, -Leu-Ala-Leu-*, -Val-Ala-Leu-*, -Leu-Ala-Val-*, -Val-Ala-Val-*, -Ala-Val-Ala-Gly-*, -Gly-Phe-Gly-Gly-*, -Gly-Gly-Phe-Gly-*, -Ala-Val-Gly-Gly-*, -Ala-Ala-Ala-Ala-*, -Ala-Val-Ala-Ala-*, -Ala-Leu-Ala-Leu-*, -Leu-Ala-Leu-Ala-*, -Gly-Phe-Leu-Gly-* and -Gly-Leu-Phe-Gly-*, wherein the Glu is optionally substituted with a polyol, and wherein * represents the N-terminal of the peptides covalently attached to Z'.

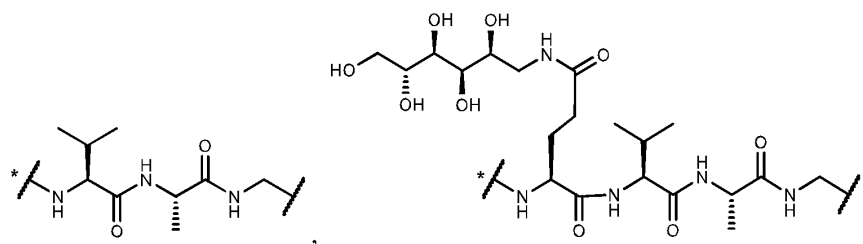
149. The compound of any one of claims 106-136, wherein E is selected from -Ala-Val-*, -Val-Ala-*, -Val-Lys-*, -Val-Arg-*, -Val-Cit-*, -Val-Arg-*, -Val-Cit-*, -Val-Lys-*, -Val-Arg-*, -Arg-Arg-*, -Ala-Ala-*, -Ala-Lys-*, -Ala-Arg-*, -Ala-Val-Glu-*, -Ala-Ala-Ala-*, -Ala-Val-Ala-*, -Ala-Ala-Gly-*, and -Ala-Val-Gly-*, wherein the Glu is optionally substituted with a polyol, and wherein * represents the N-terminal of the peptides covalently attached to Z'.

150. The compound of any one of claims 106-136, wherein E is selected from -Ala-Val-* and -Ala-Val-Glu-*, wherein the Glu is optionally substituted with a polyol, and wherein * represents the N-terminal of the peptides covalently attached to Z'.

151. The compound of any one of claims 106-136, wherein E is -Ala-Val-*, wherein * represents the N-terminal of the peptides covalently attached to Z'.

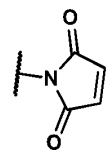
152. The compound of any one of claims 106-136, wherein E is -Ala-Val-Glu-*, wherein the Glu is substituted with a polyol, and wherein * represents the N-terminal of the peptides covalently attached to Z'.

153. The compound of any one of claims 106-136, wherein -E-NH-CH₂- has one of the following structures, wherein * represents the N-terminal of the peptides covalently attached to Z':

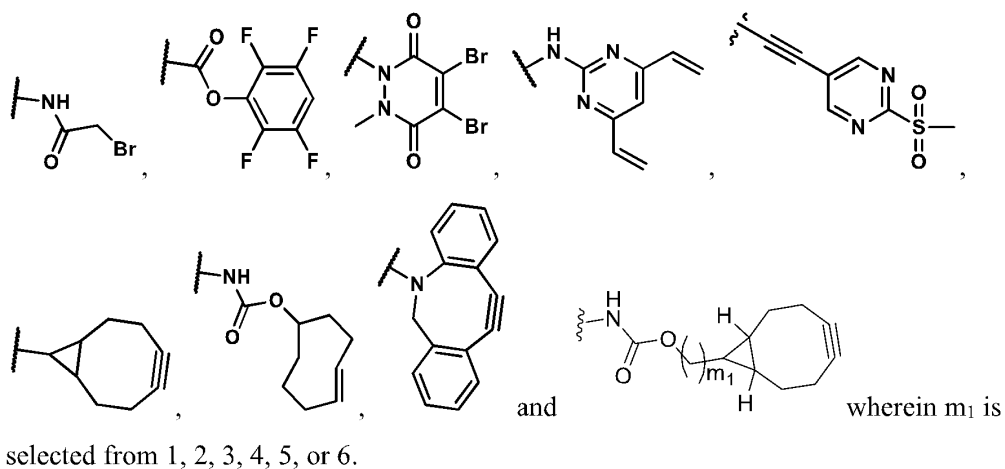


wherein * represents the N-terminal of the peptides covalently attached to Z'.

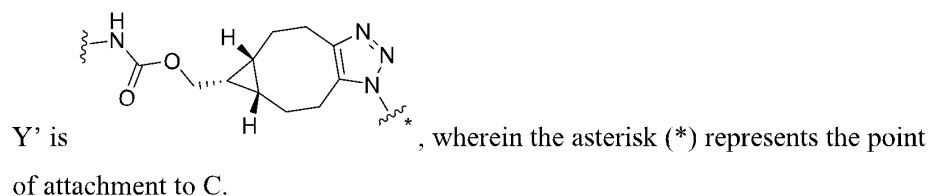
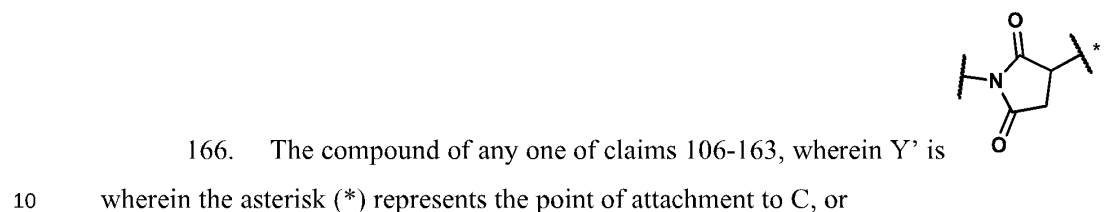
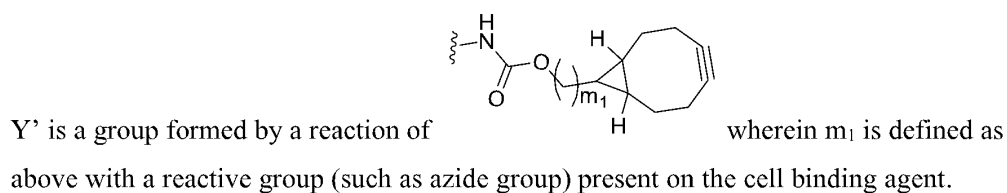
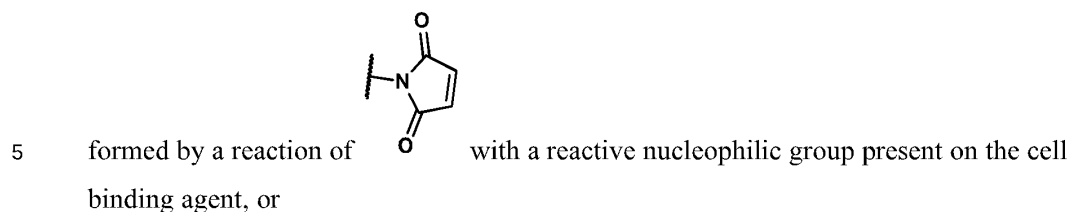
154. The compound of any one of claims 106-153, wherein L^2 is C_{1-6} alkylene.
155. The compound of any one of claims 106-153, wherein L^2 is C_{3-6} alkylene.
- 5 156. The compound of any one of claims 106-153, wherein L^2 is $-(CH_2)_5-$.
157. The compound of any one of claims 106-153, wherein L^2 is selected from $-(CH_2CH_2-O)_n-C_{1-6}$ alkylene-*, and $-C_{1-6}$ alkylene- $(O-CH_2CH_2)_n-$ *, wherein n is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and wherein the asterisk (*) represents the point of attachment to Y'.
- 10 158. The compound of claim 157, wherein n is 2, 3, 4 or 5.
159. The compound of claim 157, wherein n is 2, 3 or 4.
160. The compound of claim 157, wherein n is 3 or 4.
161. The compound of claim 157, wherein n is 4.
162. The compound of any one of claims 106-153, wherein L^2 is selected from $-(CH_2CH_2-O)_4-C_{1-4}$ alkylene-*, and $-C_{1-4}$ alkylene- $(O-CH_2CH_2)_4-$ *, wherein the asterisk (*) represents the point of attachment to Y'.
- 15 163. The compound of any one of claims 106-153, wherein L^2 is selected from $-(CH_2CH_2-O)_4-CH_2CH_2-$ *, and $-CH_2CH_2-(O-CH_2CH_2)_4-$ *, and wherein the asterisk (*) represents the point of attachment to Y'.
- 20 164. The compound of any one of claims 106-163, wherein Y' is a group formed by a reaction of an electrophilic group with a reactive nucleophilic group present



on the cell binding agent, wherein the electrophilic group is selected from



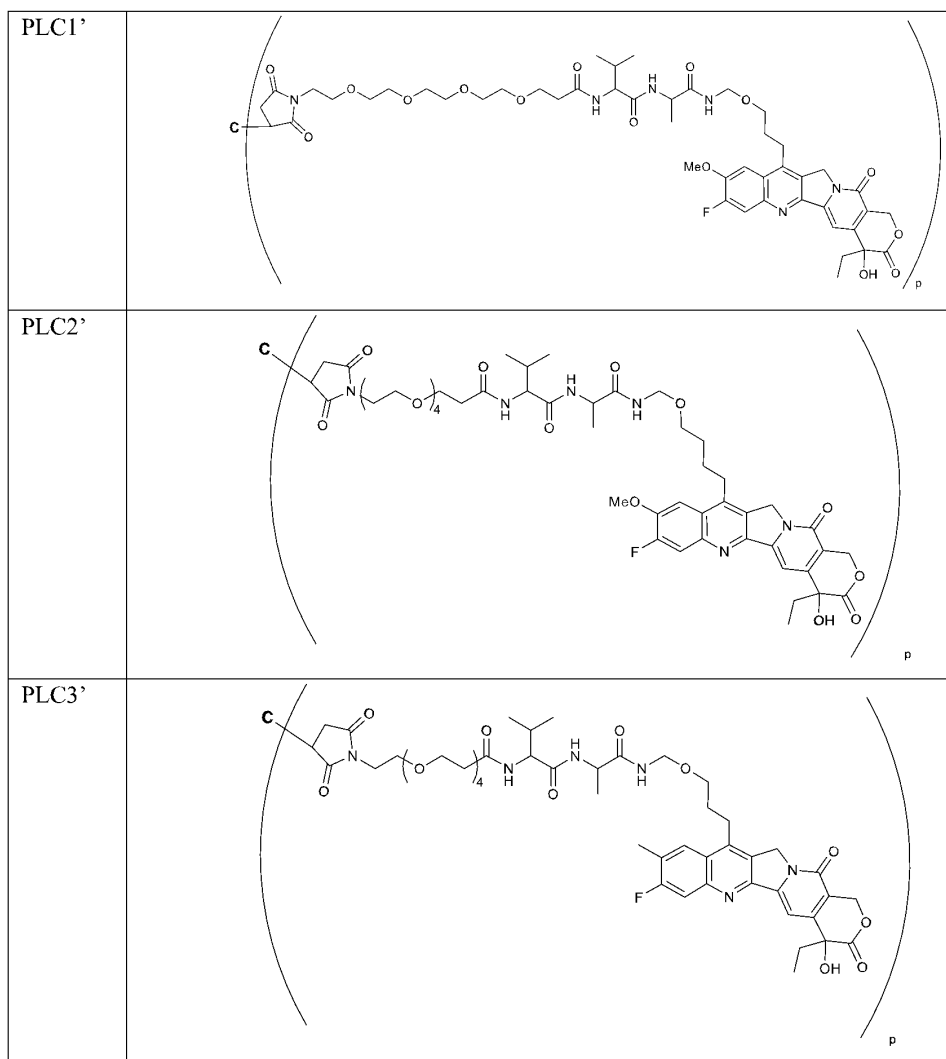
165. The compound of any one of claims 106-163, wherein Y' is a group

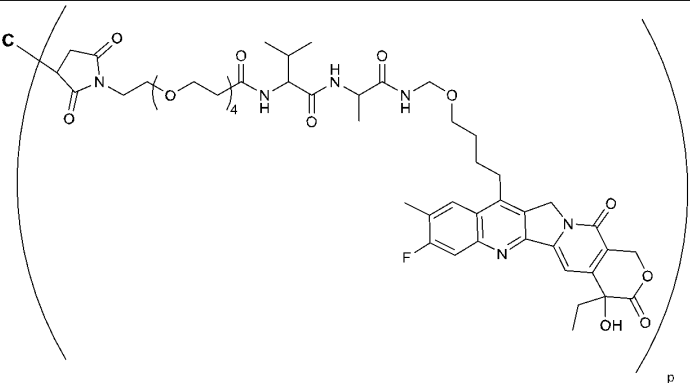
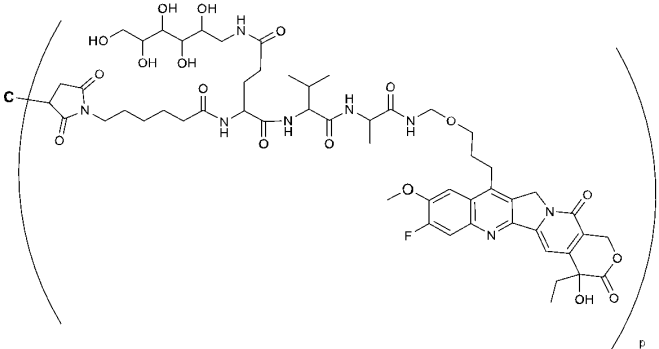
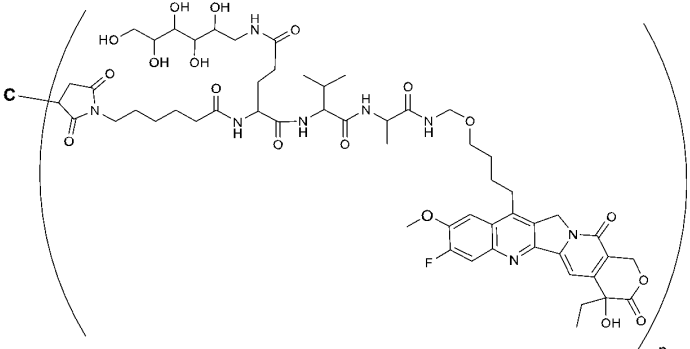


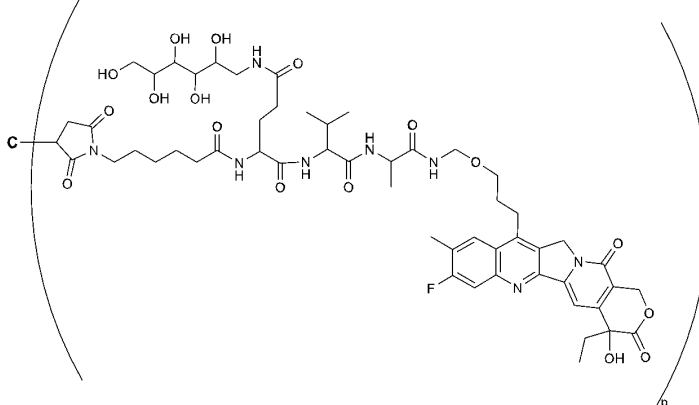
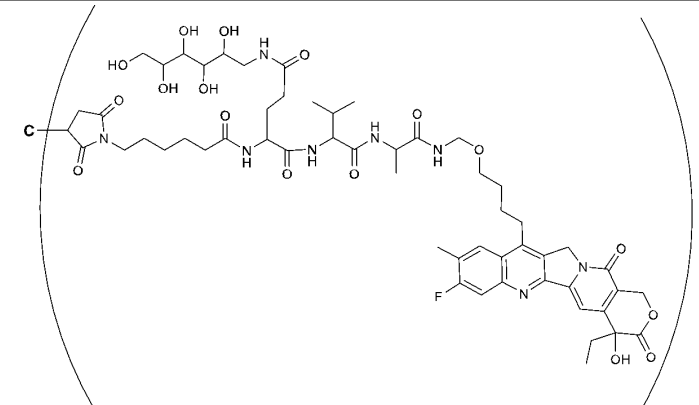
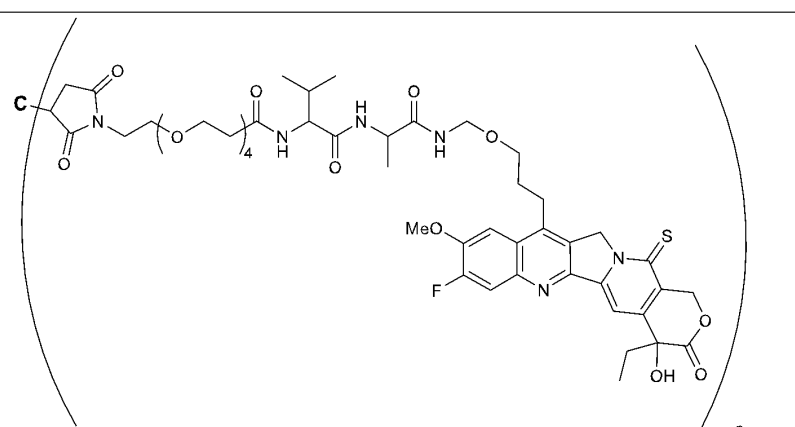
167. The compound of any one of claims 106-166, wherein the cell binding agent is an antibody or an antigen-binding fragment thereof.

168. The compound of any one of claims 106-167, wherein p has a value between 2-10, 4-8, 7-8, or 3.2 to 8.0.

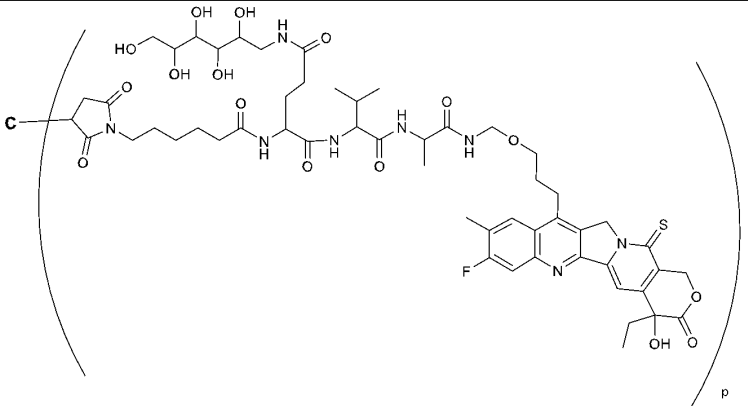
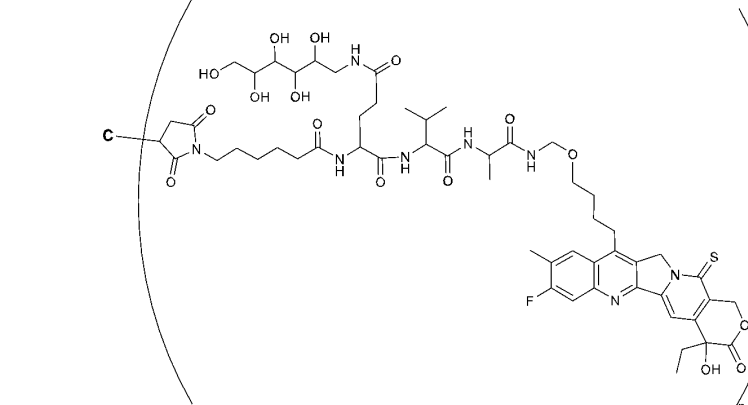
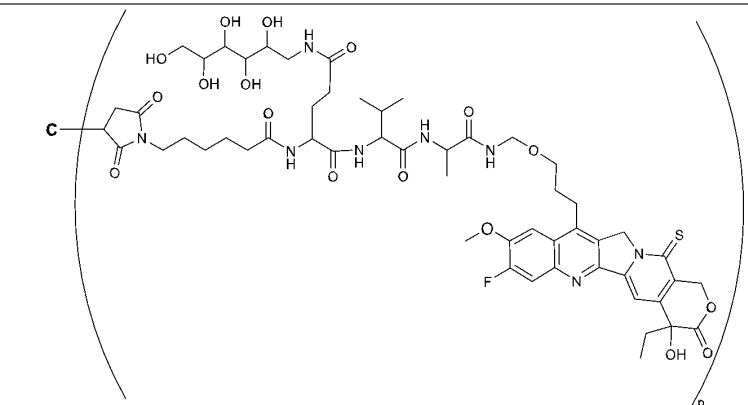
5 169. The compound of claim 106, wherein the compound of Formula (III') is:

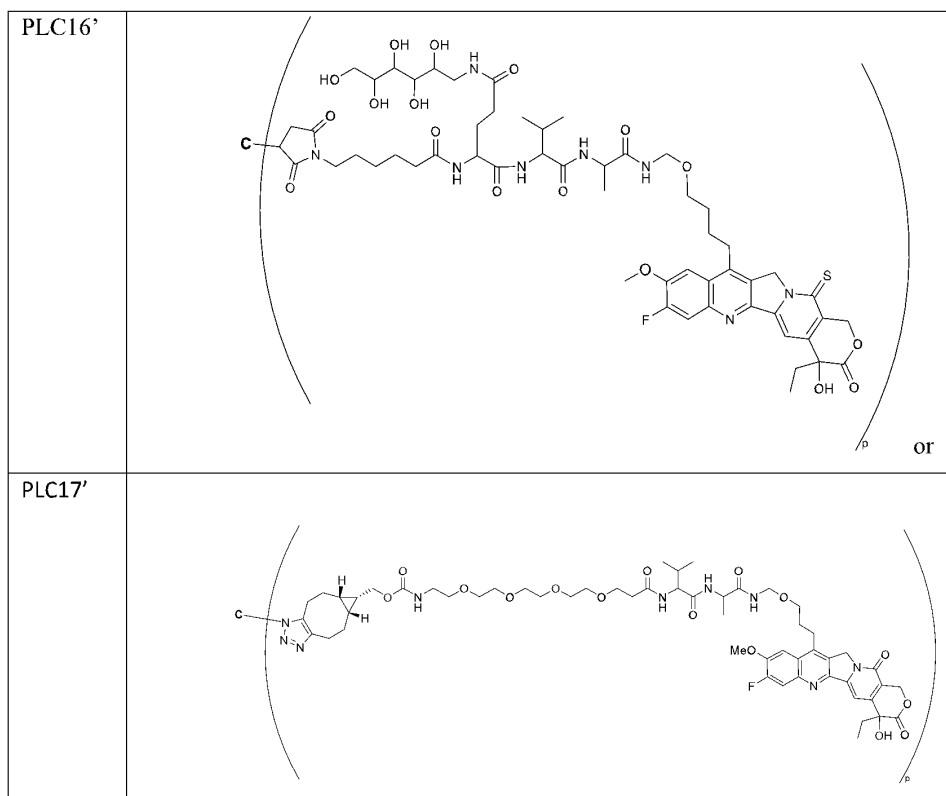


PLC4'	 Chemical structure of PLC4' monomer unit. The structure is enclosed in large parentheses. On the left, a carbon atom labeled 'C' is part of a five-membered ring containing a nitrogen atom and two carbonyl groups. This ring is connected to a chain: $-(OCH_2CH_2)_4-$, followed by an amide linkage $-NH-$ to a chiral center $-CH(CH_3)-$, another amide linkage $-NH-$ to another chiral center $-CH(CH_3)-$, and a final amide linkage $-NH-$ to a $-CH_2O-$ group. This $-CH_2O-$ group is connected to a complex polycyclic system. This system includes a benzene ring with a fluorine substituent, fused to a pyrazole ring, which is further fused to a six-membered ring containing a carbonyl group and a hydroxyl group. A $-CH_2-$ group connects the $-CH_2O-$ group to the pyrazole ring. The entire structure is labeled 'p' at the bottom right.
PLC5'	 Chemical structure of PLC5' monomer unit. The structure is enclosed in large parentheses. On the left, a carbon atom labeled 'C' is part of a five-membered ring containing a nitrogen atom and two carbonyl groups. This ring is connected to a chain: $-(OCH_2CH_2)_4-$, followed by an amide linkage $-NH-$ to a chiral center $-CH(CH_3)-$, another amide linkage $-NH-$ to another chiral center $-CH(CH_3)-$, and a final amide linkage $-NH-$ to a $-CH_2O-$ group. This $-CH_2O-$ group is connected to a complex polycyclic system. This system includes a benzene ring with a fluorine substituent and a methoxy group, fused to a pyrazole ring, which is further fused to a six-membered ring containing a carbonyl group and a hydroxyl group. A $-CH_2-$ group connects the $-CH_2O-$ group to the pyrazole ring. The entire structure is labeled 'p' at the bottom right.
PLC6'	 Chemical structure of PLC6' monomer unit. The structure is enclosed in large parentheses. On the left, a carbon atom labeled 'C' is part of a five-membered ring containing a nitrogen atom and two carbonyl groups. This ring is connected to a chain: $-(OCH_2CH_2)_4-$, followed by an amide linkage $-NH-$ to a chiral center $-CH(CH_3)-$, another amide linkage $-NH-$ to another chiral center $-CH(CH_3)-$, and a final amide linkage $-NH-$ to a $-CH_2O-$ group. This $-CH_2O-$ group is connected to a complex polycyclic system. This system includes a benzene ring with a fluorine substituent and a methoxy group, fused to a pyrazole ring, which is further fused to a six-membered ring containing a carbonyl group and a hydroxyl group. A $-CH_2-$ group connects the $-CH_2O-$ group to the pyrazole ring. The entire structure is labeled 'p' at the bottom right.

PLC7'	 Chemical structure of PLC7' is shown within a curved frame. The molecule features a fluorinated benzimidazole core. A side chain containing multiple hydroxyl groups and a carboxylic acid group is attached to the benzimidazole ring. The structure is labeled with 'C' at the carboxylic acid group and 'P' at the fluorine atom.
PLC8'	 Chemical structure of PLC8' is shown within a curved frame. The molecule features a fluorinated benzimidazole core. A side chain containing multiple hydroxyl groups and a carboxylic acid group is attached to the benzimidazole ring. The structure is labeled with 'C' at the carboxylic acid group and 'P' at the fluorine atom.
PLC9'	 Chemical structure of PLC9' is shown within a curved frame. The molecule features a fluorinated benzimidazole core. A side chain containing multiple hydroxyl groups and a carboxylic acid group is attached to the benzimidazole ring. The structure is labeled with 'C' at the carboxylic acid group and 'P' at the fluorine atom.

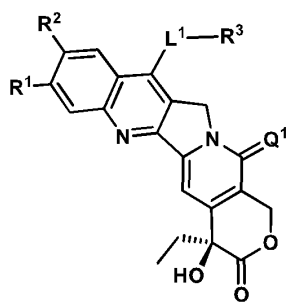
PLC10'	
PLC11'	
PLC12'	

PLC13'	 Chemical structure of PLC13' repeating unit. The structure is enclosed in large parentheses with a subscript 'p'. It features a central chain starting with a carbonyl group (C=O) attached to a five-membered ring containing a nitrogen atom. This is followed by a long chain of amide bonds (NH-CO) and hydroxyl groups (OH). The chain terminates with a complex heterocyclic system, including a benzene ring with a fluorine substituent, a pyridine ring, and a thiazine ring system with a sulfur atom and a hydroxyl group.
PLC14'	 Chemical structure of PLC14' repeating unit. The structure is enclosed in large parentheses with a subscript 'p'. It features a central chain starting with a carbonyl group (C=O) attached to a five-membered ring containing a nitrogen atom. This is followed by a long chain of amide bonds (NH-CO) and hydroxyl groups (OH). The chain terminates with a complex heterocyclic system, including a benzene ring with a fluorine substituent, a pyridine ring, and a thiazine ring system with a sulfur atom and a hydroxyl group.
PLC15'	 Chemical structure of PLC15' repeating unit. The structure is enclosed in large parentheses with a subscript 'p'. It features a central chain starting with a carbonyl group (C=O) attached to a five-membered ring containing a nitrogen atom. This is followed by a long chain of amide bonds (NH-CO) and hydroxyl groups (OH). The chain terminates with a complex heterocyclic system, including a benzene ring with a fluorine substituent, a pyridine ring, and a thiazine ring system with a sulfur atom and a hydroxyl group.



or a pharmaceutically acceptable salt thereof.

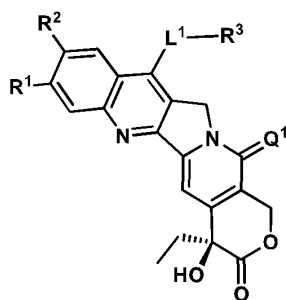
170. The compound of claim 1, wherein the compound is a compound of Formula (Ia)



Formula (Ia)

5 or a pharmaceutically acceptable salt thereof.

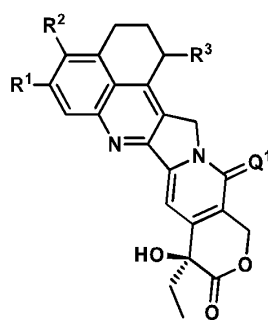
171. The compound of claim 1 or 170, wherein the compound is a compound of Formula (Ia)



Formula (Ia)

or a pharmaceutically acceptable salt thereof.

172. The compound of claim 1 or 170, wherein the compound is a compound of Formula (Ib)

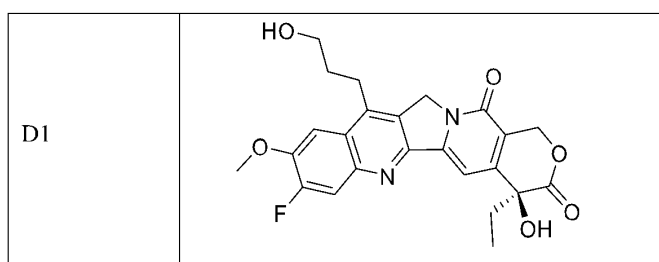


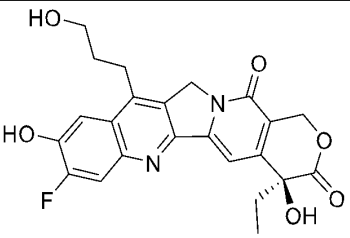
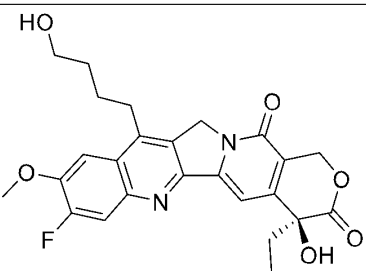
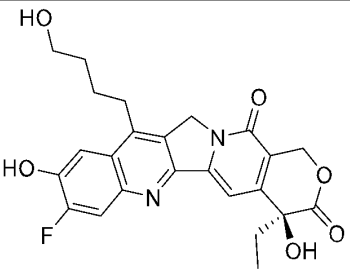
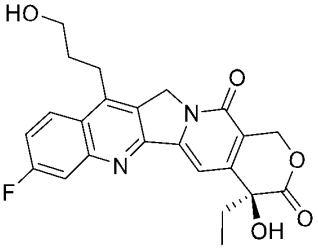
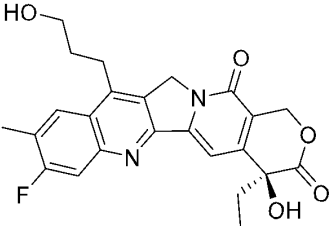
Formula (Ib)

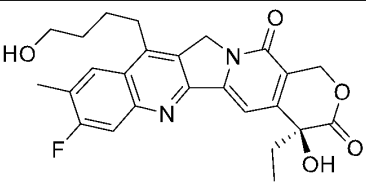
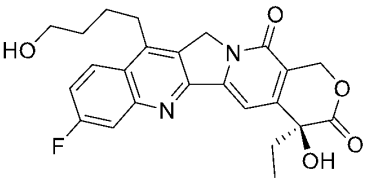
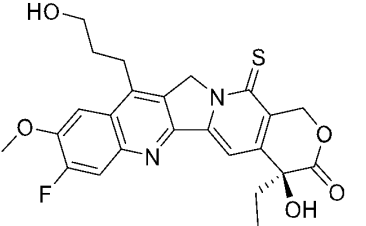
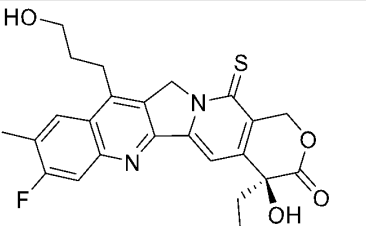
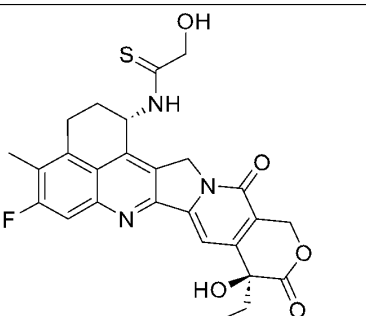
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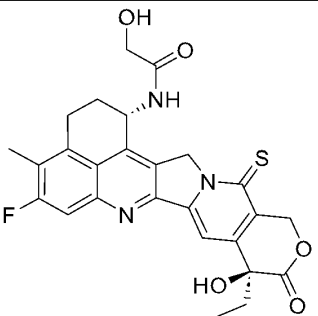
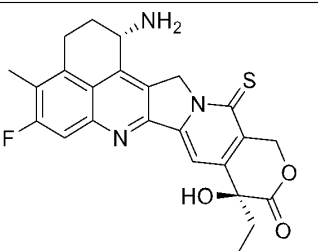
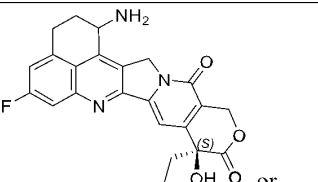
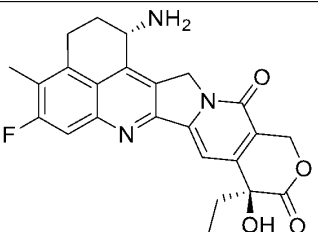
or a pharmaceutically acceptable salt thereof.

173. The compound of claim 1, wherein the compound is:



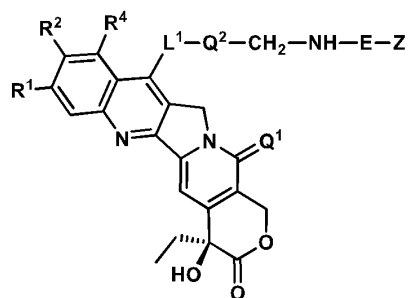
D2	
D3	
D4	
D5	
D6	

D7	
D8	
D9	
D10	
D11	

D12	
D13	
D14	
D15	

or a pharmaceutically acceptable salt thereof.

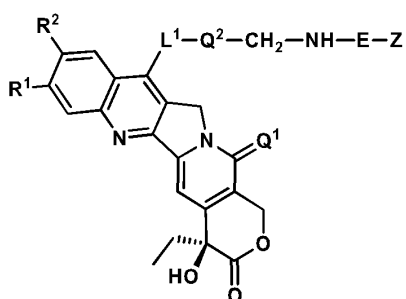
174. The compound of claim 41, wherein the compound is a compound of Formula (II)



Formula (II)

or a pharmaceutically acceptable salt thereof.

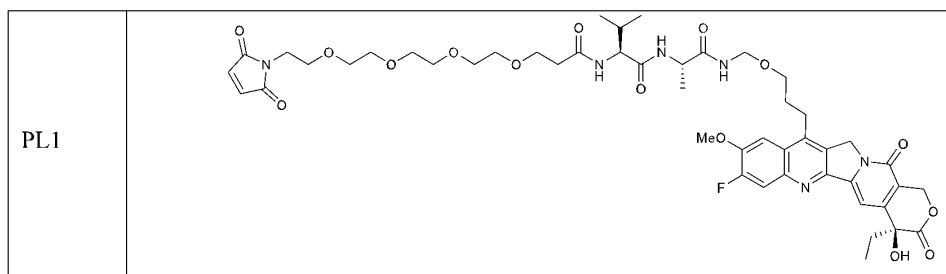
175. The compound of claim 41 or 174, wherein the compound is a compound of Formula (IIa)

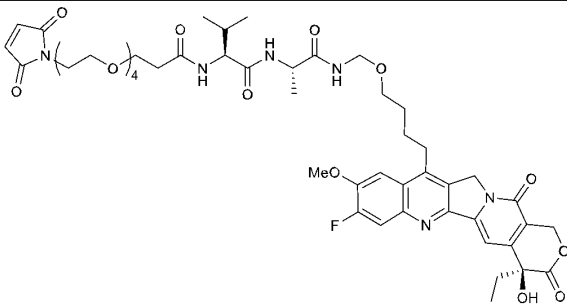
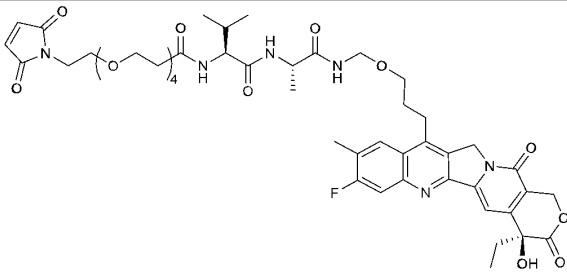
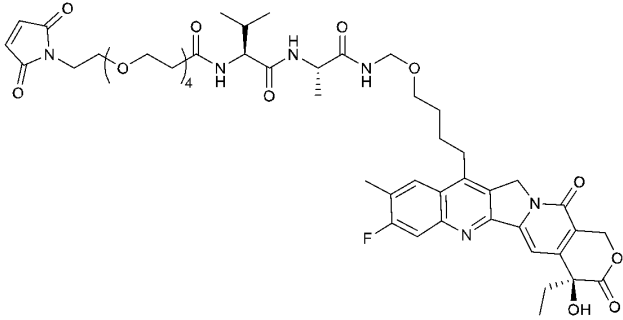
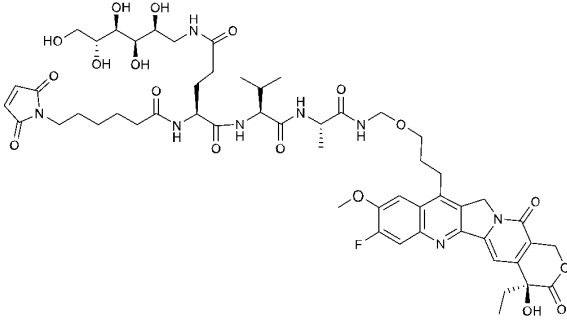


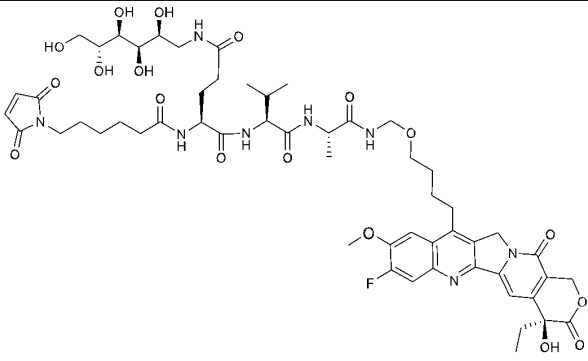
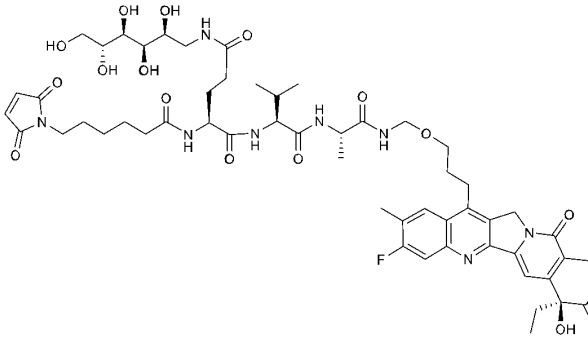
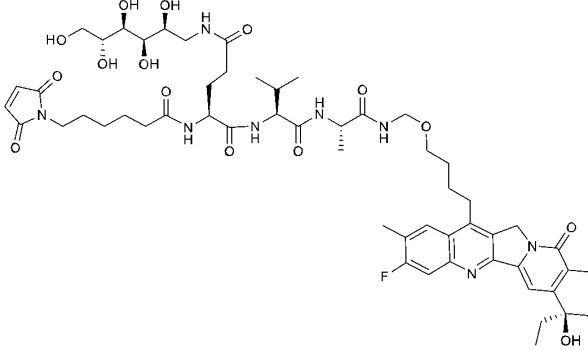
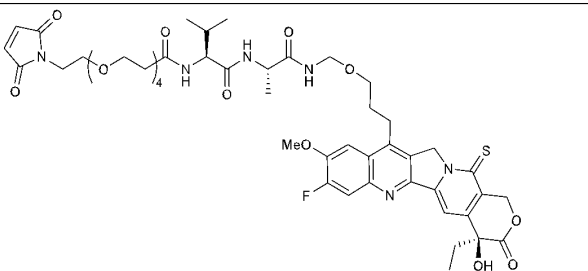
Formula (IIa)

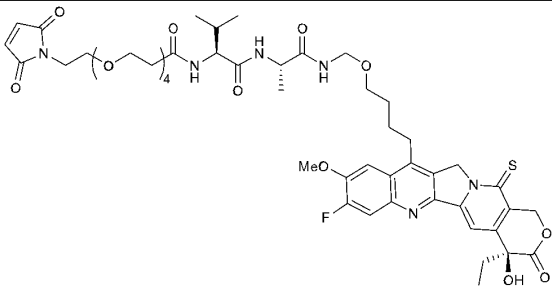
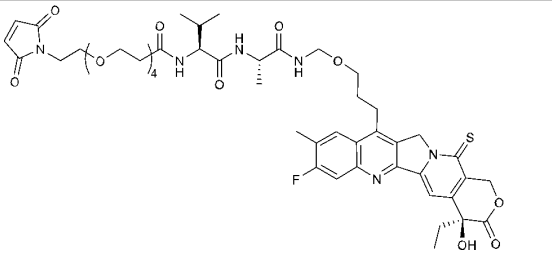
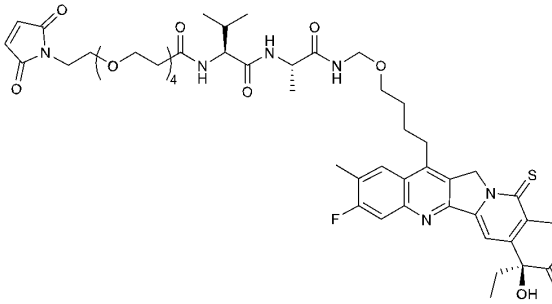
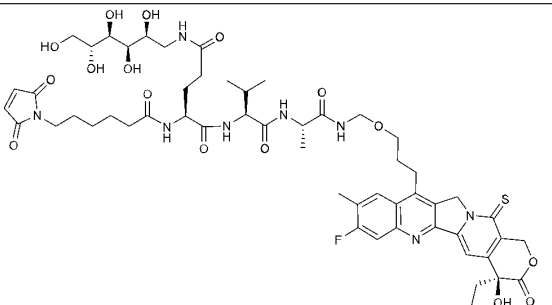
or a pharmaceutically acceptable salt thereof.

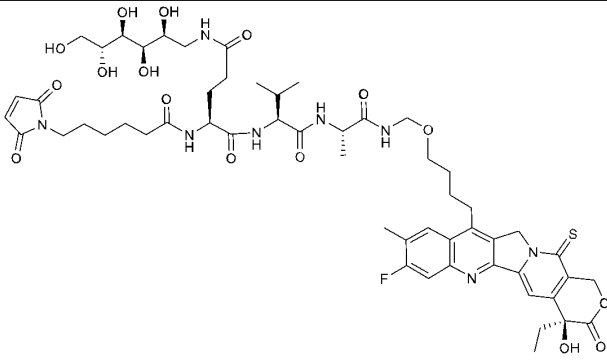
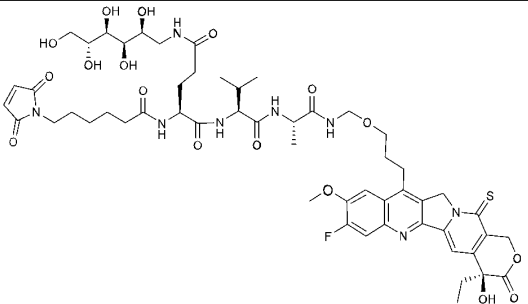
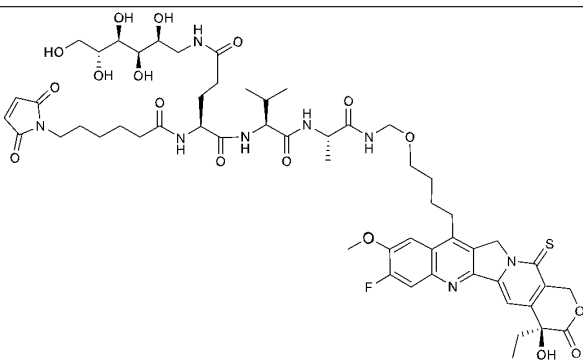
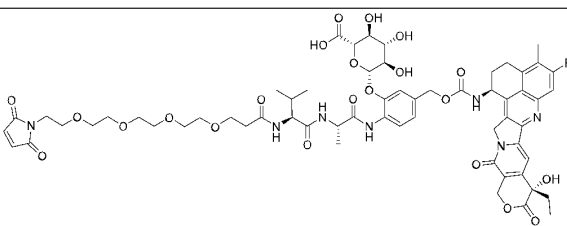
176. The compound of claim 41, wherein the compound is:

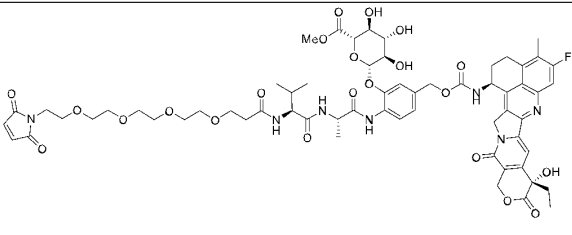
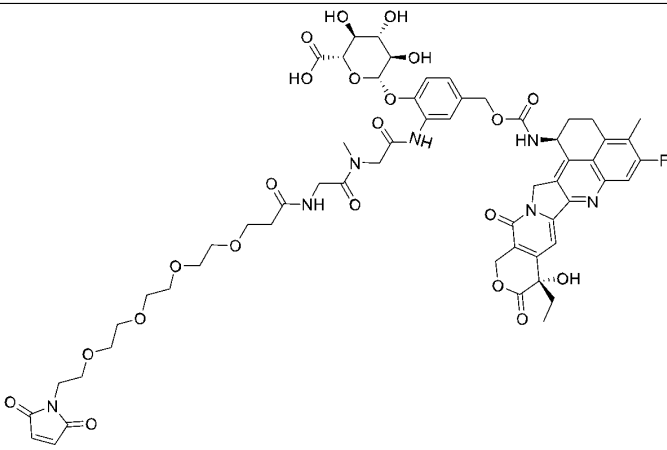
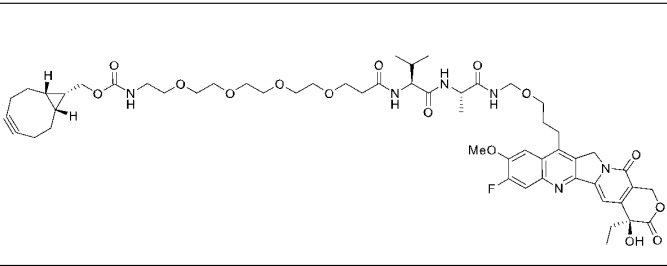


PL2	
PL3	
PL4	
PL5	

PL6	
PL7	
PL8	
PL9	

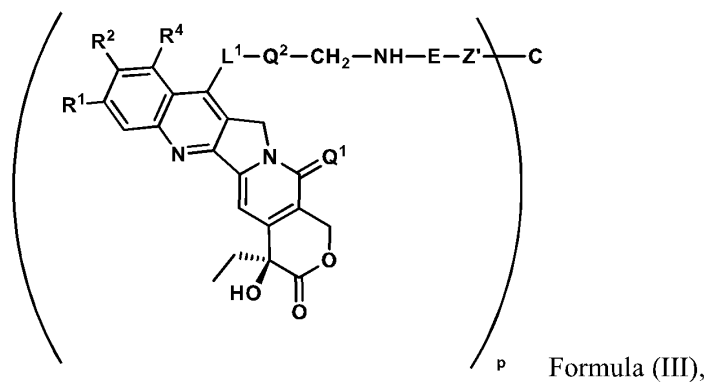
PL10	
PL11	
PL12	
PL13	

PL14	
PL15	
PL16	
PL17	

PL18	
PL19	 or
PL20	

or pharmaceutically acceptable salt thereof.

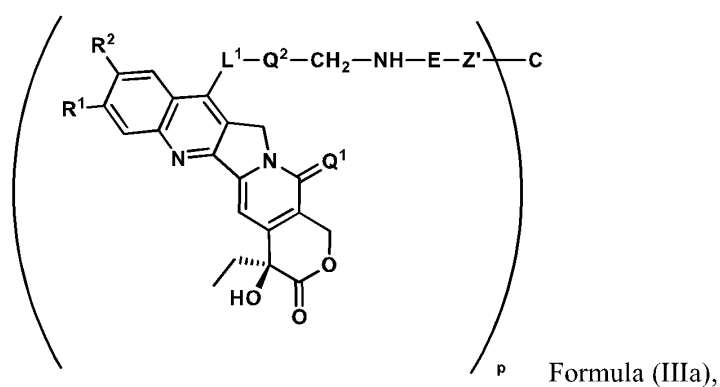
177. The compound of claim 106, wherein the compound is a compound of Formula (III),



or a pharmaceutically acceptable salt thereof.

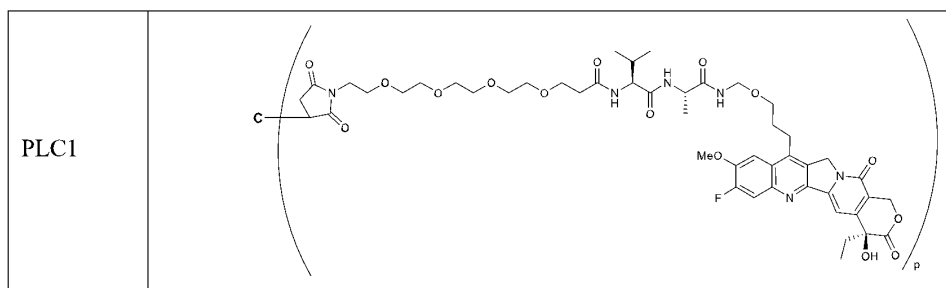
178. The compound of claim 106 or 177, wherein the compound is a compound of Formula (IIIa),

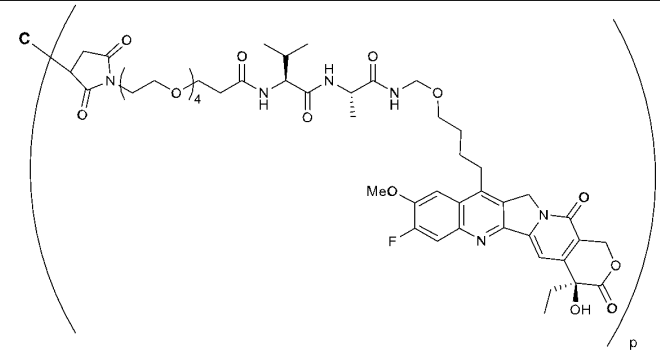
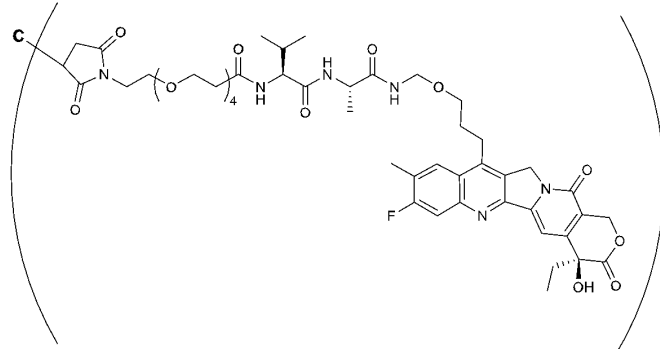
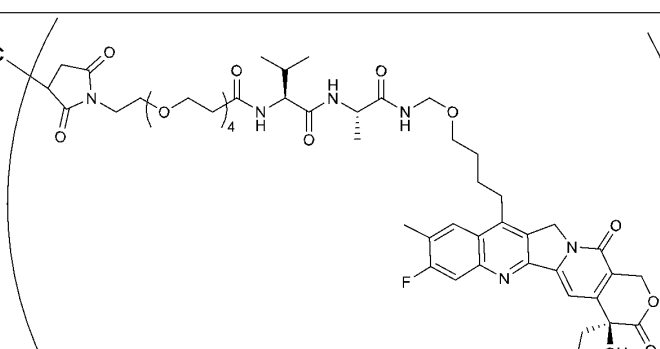
5

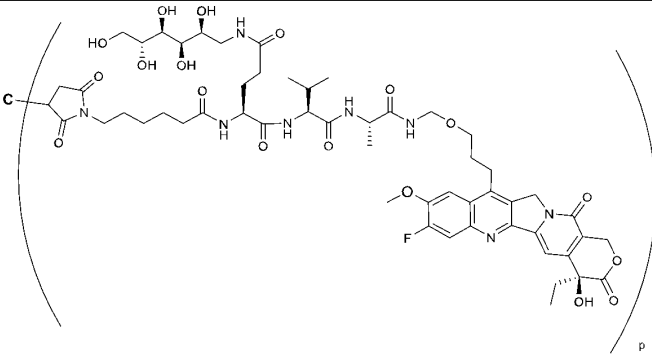
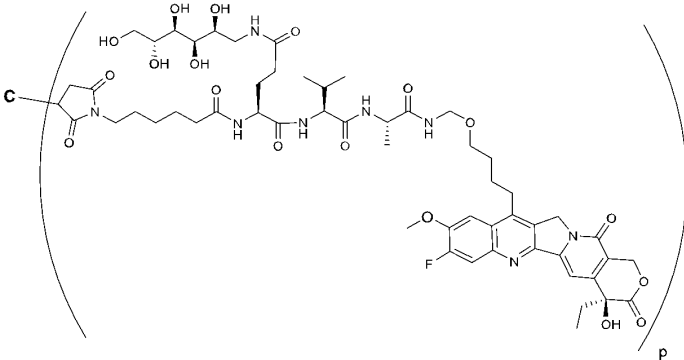
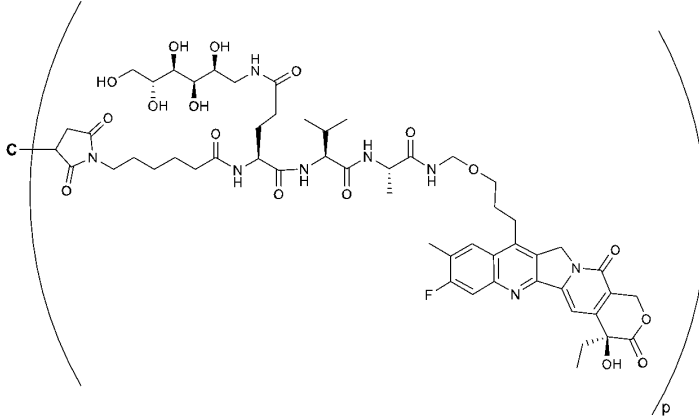


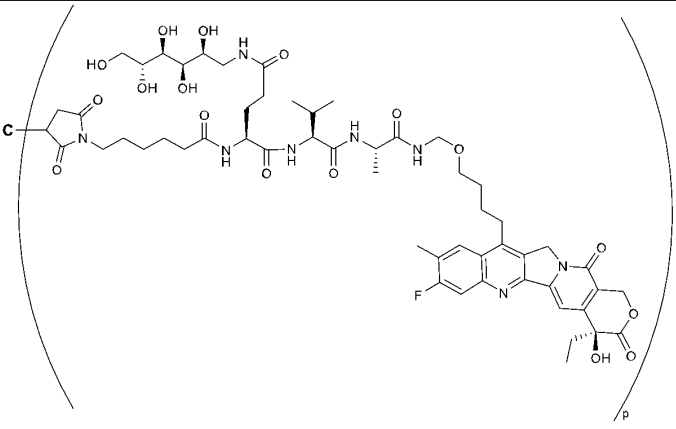
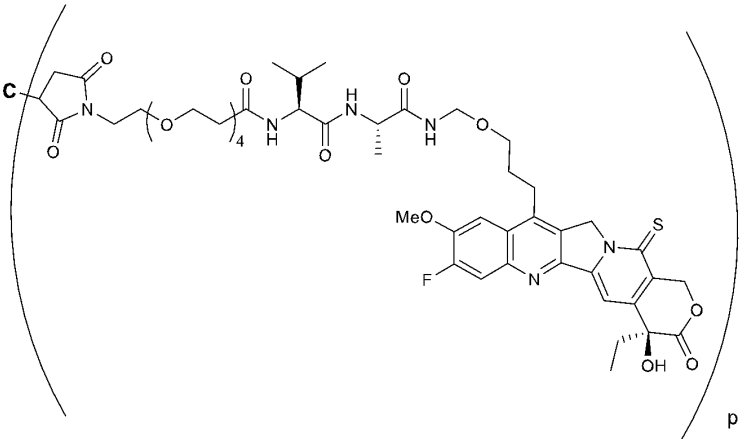
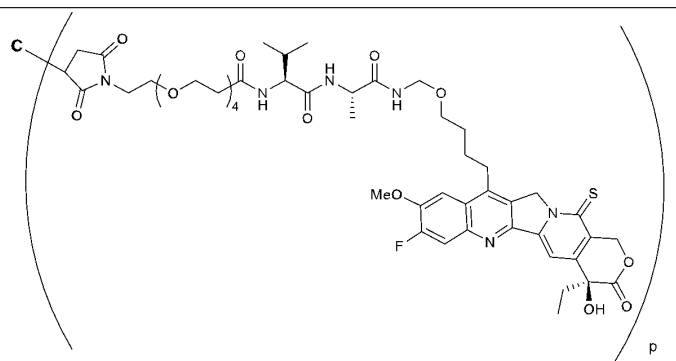
or a pharmaceutically acceptable salt thereof.

179. The compound of claim 106, wherein the compound is In some embodiments, the compound of Formula (III) is:

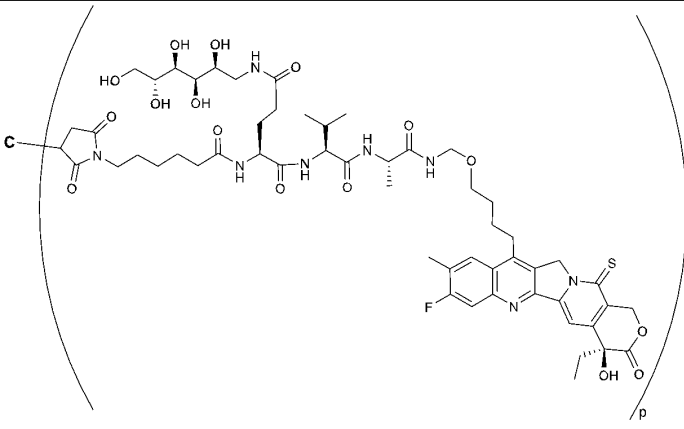
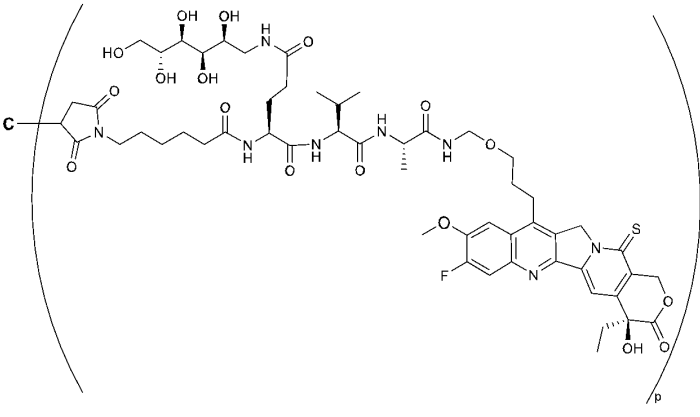
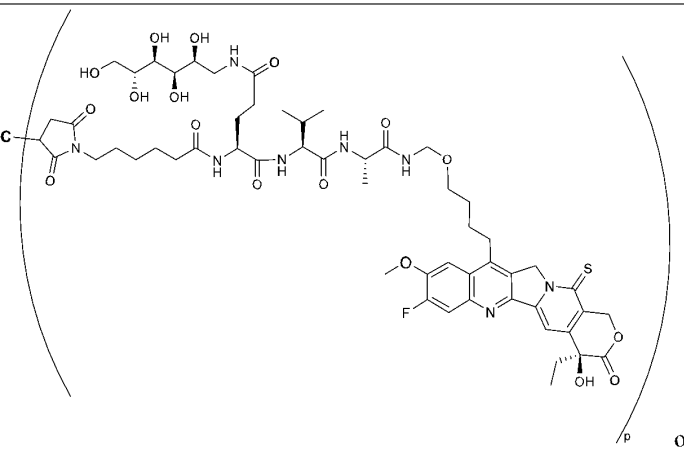


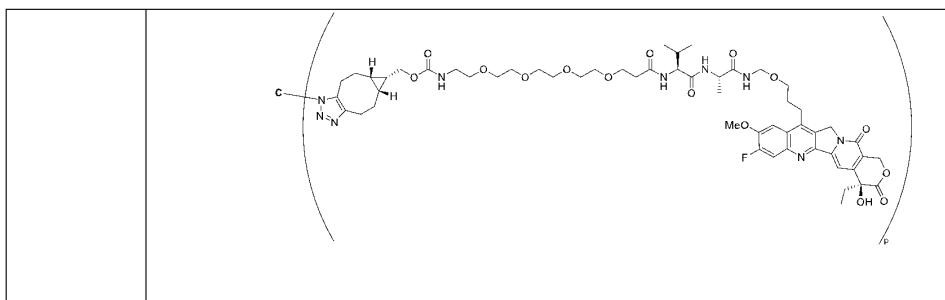
PLC2	 Chemical structure of PLC2, showing a polymer chain (C) with a repeating unit containing a carbonyl group and a methylene group, linked to a complex heterocyclic system (p) via a linker. The linker consists of a carbonyl group, a methylene group, and a carbonyl group, followed by a chain of four methylene groups, a carbonyl group, a methylene group, a carbonyl group, a methylene group, a carbonyl group, a methylene group, and a carbonyl group. The heterocyclic system (p) is a complex fused ring system containing a fluorine atom, a methoxy group, and a hydroxyl group.
PLC3	 Chemical structure of PLC3, showing a polymer chain (C) with a repeating unit containing a carbonyl group and a methylene group, linked to a complex heterocyclic system (p) via a linker. The linker consists of a carbonyl group, a methylene group, and a carbonyl group, followed by a chain of four methylene groups, a carbonyl group, a methylene group, a carbonyl group, a methylene group, a carbonyl group, a methylene group, and a carbonyl group. The heterocyclic system (p) is a complex fused ring system containing a fluorine atom, a methoxy group, and a hydroxyl group.
PLC4	 Chemical structure of PLC4, showing a polymer chain (C) with a repeating unit containing a carbonyl group and a methylene group, linked to a complex heterocyclic system (p) via a linker. The linker consists of a carbonyl group, a methylene group, and a carbonyl group, followed by a chain of four methylene groups, a carbonyl group, a methylene group, a carbonyl group, a methylene group, a carbonyl group, a methylene group, and a carbonyl group. The heterocyclic system (p) is a complex fused ring system containing a fluorine atom, a methoxy group, and a hydroxyl group.

PLC5	 Chemical structure of PLC5, a complex molecule featuring a central chain with multiple amide and ester linkages, a terminal hydroxyl group, and a side chain containing a fluorinated benzene ring and a pyridine ring. The structure is enclosed in large parentheses with a 'C' label on the left and a 'p' label on the right.
PLC6	 Chemical structure of PLC6, a complex molecule featuring a central chain with multiple amide and ester linkages, a terminal hydroxyl group, and a side chain containing a fluorinated benzene ring and a pyridine ring. The structure is enclosed in large parentheses with a 'C' label on the left and a 'p' label on the right.
PLC7	 Chemical structure of PLC7, a complex molecule featuring a central chain with multiple amide and ester linkages, a terminal hydroxyl group, and a side chain containing a fluorinated benzene ring and a pyridine ring. The structure is enclosed in large parentheses with a 'C' label on the left and a 'p' label on the right.

PLC8	 Chemical structure of PLC8, a polymer-drug conjugate. The polymer chain (C) is a poly(ε-caprolactone) derivative with a terminal hydroxyl group. The drug moiety (P) is a complex molecule featuring a fluorinated benzene ring, a pyridine ring, and a lactone ring, connected by an amide linkage. The polymer chain is attached to the drug moiety via an amide bond.
PLC9	 Chemical structure of PLC9, a polymer-drug conjugate. The polymer chain (C) is a poly(ε-caprolactone) derivative with a terminal hydroxyl group. The drug moiety (P) is a complex molecule featuring a fluorinated benzene ring, a pyridine ring, and a lactone ring, connected by an amide linkage. The polymer chain is attached to the drug moiety via an amide bond.
PLC10	 Chemical structure of PLC10, a polymer-drug conjugate. The polymer chain (C) is a poly(ε-caprolactone) derivative with a terminal hydroxyl group. The drug moiety (P) is a complex molecule featuring a fluorinated benzene ring, a pyridine ring, and a lactone ring, connected by an amide linkage. The polymer chain is attached to the drug moiety via an amide bond.
PLC11	

PLC12	
PLC13	

PLC14	 Chemical structure of PLC14, showing a complex molecule with a central chain containing multiple amide and ester linkages, and a side chain with a fluorinated benzene ring and a thiazolidine ring system. The structure is enclosed in a large curved line, with a 'C' label at the top left and a 'P' label at the bottom right.
PLC15	 Chemical structure of PLC15, showing a complex molecule with a central chain containing multiple amide and ester linkages, and a side chain with a fluorinated benzene ring and a thiazolidine ring system. The structure is enclosed in a large curved line, with a 'C' label at the top left and a 'P' label at the bottom right.
PLC16	 Chemical structure of PLC16, showing a complex molecule with a central chain containing multiple amide and ester linkages, and a side chain with a fluorinated benzene ring and a thiazolidine ring system. The structure is enclosed in a large curved line, with a 'C' label at the top left and a 'P' label at the bottom right.
PLC17	



or a pharmaceutically acceptable salt thereof.

180. A pharmaceutical composition comprising the compound of any one of claims 1-38, 41-104 or 106-179.

181. A pharmaceutical composition comprising the compound of any one of claims 1-38, 41-104 or 106-179, and a second therapeutic agent.

182. A method of preparing a conjugate comprising a cell binding agent and a drug, the method comprising contacting a cell binding agent with the compound of any one of claims 1-38, 41-104 or 170-176 such that a covalent bond forms between the cell binding agent and the compound.

183. The method of claim 182, wherein the cell binding agent is an antibody or an antigen-binding fragment thereof.

184. The method of claim 182, wherein the cell binding agent is a monoclonal antibody or an antigen-binding fragment thereof.

185. A conjugate comprising a cell binding agent and a drug, wherein the conjugate is prepared according to the method of any one of claims 182-184.

186. The conjugate of claim 185, comprising a cell binding agent that is an antibody or an antigen binding fragment thereof.

187. The conjugate of claim 185, comprising a cell binding agent that is a monoclonal antibody or an antigen-binding fragment thereof.

188. A method of treating a cell proliferative disease or disorder or inhibiting abnormal cell growth, the method comprising administering the compound of any one of claims 1-38, 41-104 or 106-179 or the pharmaceutical composition of claim 170 or 171 to a subject in need thereof.

189. The method of claim 188, wherein the method is for treating cancer.

190. The method of claim 189, wherein the cancer is adenocarcinoma, brain cancer, bladder cancer, breast cancer, cervical cancer, choriocarcinoma, a CNS tumor, colon or colorectal cancer, diffuse intrinsic pontine glioma (DIPG), endometrial cancer, esophageal cancer, Ewing's sarcoma, fallopian tube cancer, gall bladder cancer, gastric
5 cancer, glioblastoma, head and neck cancer, hematological cancer, Hodgkin's lymphoma, kidney cancer, laryngeal cancer, leukemia, liver cancer, lung cancer, lymphoma, melanoma, Merkel cell carcinoma, mesothelioma, multiple myeloma, myelodysplastic syndrome (MDS), neuroblastoma, non-Hodgkin's lymphoma, osteosarcoma, pancreatic cancer, peritoneal cancer, prostate cancer, ovarian cancer, renal cancer,
10 rhabdomyosarcoma salivary gland cancer, sarcoma, skin cancer, small intestine cancer, squamous cell carcinoma, testicular cancer, thyroid cancer, uterine cancer, or Wilms tumor.

191. The method of claim 189, wherein the cancer is breast cancer, lung cancer, gastric cancer, prostate cancer, pancreatic cancer, or colon cancer.

15 192. The method of claim 189, wherein the cancer is breast cancer.