

β -GLUCURONIDE LINKER-PAYLOADS, PROTEIN CONJUGATES THEREOF, AND METHODS THEREOF

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119 of U.S. provisional application no. 63/355,975, filed June 27, 2022, the content of which is hereby incorporated by reference in its entirety.

FIELD

[0002] Provided herein are β -glucuronide linker-payload compounds, and macromolecule conjugates thereof; pharmaceutical compositions comprising the β -glucuronide linker-payload compounds and/or conjugates; methods of producing the β -glucuronide linker-payload compounds and/or conjugates; and methods of using the β -glucuronide linker-payload compounds, conjugates, and compositions for therapy. The β -glucuronide linker-payload compounds, conjugates, and compositions are useful, for instance, in methods of treatment and prevention of cell proliferation and cancer, methods of detection of cell proliferation and cancer, and methods of diagnosis of cell proliferation and cancer.

BACKGROUND

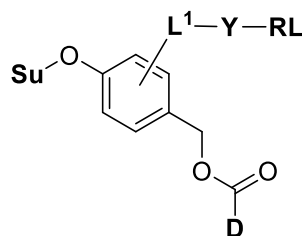
[0003] Biotherapeutics provide a wealth of treatment and diagnostic potential for patients worldwide. However, many drugs based on macromolecules, such as proteins, peptides, and antibodies, present limitations on their effective use, including limitations on bioavailability, absorption, distribution, metabolism, and excretion (ADME). Some of these limitations can affect drug dosage, half-life, side effects, and toxicities. Strategies for improving the effectiveness of biotherapeutics remain needed.

SUMMARY

[0004] Provided herein are compounds of Formulae (I), (IA), (IB), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), (IVB), and sub-formulas thereof, compositions comprising such compounds, methods of producing such compounds, and methods of using such compounds, conjugates, and compositions in treatment and diagnosis. The compounds of the present disclosure, including compounds of Formulae (I), (IA), (IB), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), (IVB), and sub-formulas, embodiments and examples thereof, are useful for modulating the bioavailability and ADME of macromolecular compounds. In certain examples, the compounds can be used to prepare prodrug conjugates of macromolecular

compounds for use *in vivo* or elsewhere. In certain examples, the compounds and conjugates feature functionality amenable to enzymatic cleavage to release a payload compound for use *in vivo* or elsewhere. These compounds can be varied to tune the physiochemical properties and plasma stability of the conjugates. This provides a platform for modulating the bioavailability and ADME of a macromolecule *in vivo*.

[0005] In an aspect, provided is a compound of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

L¹ is -C₁₋₆ alkylene-;

Y is -**X¹**-C₁₋₆ alkylene-[**X¹**-C₁₋₆ alkylene]_n-[**X¹**]_p-,
-**X¹**-C₂₋₆ alkenylene-[**X¹**-C₂₋₆ alkenylene]_n-[**X¹**]_p-, or
-**X¹**-C₂₋₆ alkynylene-[**X¹**-C₂₋₆ alkynylene]_n-[**X¹**]_p-, wherein at least one alkylene, alkenylene,
or alkynylene in **Y** is substituted with one or more substituents selected from **R⁵⁰**, and

wherein the alkylene, alkenylene, or alkynylene in **Y** is optionally substituted with one or more substituents selected from **R⁵¹**;

R⁵⁰ is -C₁₋₆ alkylene-**X²**-[C₁₋₆ alkylene]_m-**POLY**,
-C₂₋₆ alkenylene-**X²**-[C₂₋₆ alkenylene]_m-**POLY**, or
-C₂₋₆ alkynylene-**X²**-[C₂₋₆ alkynylene]_m-**POLY**, wherein each alkylene, alkenylene, or
alkynylene of **R⁵⁰** is optionally substituted with one or more substituents selected from
halogen, -CN, -NO₂, -OH, -N(**R¹⁰**)₂, -C(O)N(**R¹⁰**)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅,
-NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-
membered heterocycle, and C₁₋₁₀ haloalkyl;

R⁵¹ is independently selected from halogen, -CN, -NO₂, -OH, -N(**R¹⁰**)₂,
-C(O)N(**R¹⁰**)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅, -NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl, C₂₋₁₀
alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and C₁₋₁₀ haloalkyl;

X¹ and **X²** are independently selected from -N(**R¹⁰**)-, -C(O)-, and -N(**R¹⁰**)C(O)-;

R¹⁰ is independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and C₁₋₁₀ haloalkyl;

POLY is a water-soluble polymer;

n is an integer selected from zero, one, two, and three;

m is an integer selected from zero and one;

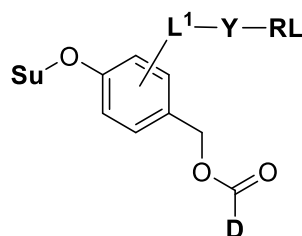
p is an integer selected from zero and one;

Su is a hexose form of a monosaccharide;

D is a drug moiety; and

RL is a reactive linker group residue.

[0006] In some examples, provided is a compound of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

L¹ is -C₁₋₆ alkylene-;

Y is -**X¹**-C₁₋₆ alkylene-[**X¹**-C₁₋₆ alkylene]_n-**X¹**-,
 -**X¹**-C₂₋₆ alkenylene-[**X¹**-C₂₋₆ alkenylene]_n-**X¹**-, or
 -**X¹**-C₂₋₆ alkynylene-[**X¹**-C₂₋₆ alkynylene]_n-**X¹**-, wherein at least one alkylene, alkenylene, or alkynylene in **Y** is substituted with one or more substituents selected from **R⁵⁰**;

R⁵⁰ is -C₁₋₆ alkylene-**X²**-[C₁₋₆ alkylene]_m-**POLY**,
 -C₂₋₆ alkenylene-**X²**-[C₂₋₆ alkenylene]_m-**POLY**, or
 -C₂₋₆ alkynylene-**X²**-[C₂₋₆ alkynylene]_m-**POLY**, wherein each alkylene, alkenylene or alkynylene of **R⁵⁰** is optionally substituted with one or more substituents selected from halogen, -CN, -NO₂, -OH, -N(**R¹⁰**)₂, -C(O)N(**R¹⁰**)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅, -NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and C₁₋₁₀ haloalkyl;

X¹ and **X²** are independently selected from -C(O)- and -N(**R¹⁰**)C(O)-;

R¹⁰ is independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and C₁₋₁₀ haloalkyl;

POLY is a water-soluble polymer;

n is an integer selected from zero, one, two, and three;

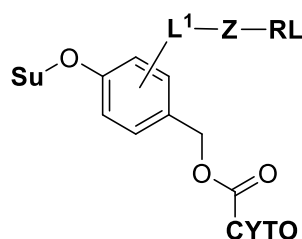
m is an integer selected from zero and one;

Su is a hexose form of a monosaccharide;

D is a drug moiety; and

RL is a reactive linker group residue.

[0007] In some examples, the present disclosure provides a compound according to the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

L¹ is -C₁₋₆ alkylene-;

Z is -**X¹**-C₁₋₆ alkylene-[**X¹**-C₁₋₆ alkylene]_{**n**}-**X¹**-, -**X¹**-C₂₋₆ alkenylene-[**X¹**-C₂₋₆ alkenylene]_{**n**}-**X¹**-, -**X¹**-C₂₋₆ alkynylene-[**X¹**-C₂₋₆ alkynylene]_{**n**}-**X¹**-, wherein alkylene, alkenylene, or alkynylene in **Z** is optionally substituted with one or more substituents selected from halogen, -CN, -NO₂, -OH, -N(**R¹⁰**)₂, -C(O)N(**R¹⁰**)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅, -NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and C₁₋₁₀ haloalkyl;

X¹ and **X²** are independently selected from -C(O)- and -N(**R¹⁰**)C(O)-;

R¹⁰ is independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and C₁₋₁₀ haloalkyl;

POLY is a water-soluble polymer;

n is an integer selected from zero, one, two, and three;

m is an integer selected from zero and one;

Su is a hexose form of a monosaccharide;

RL is a reactive linker group residue.

[illegible]

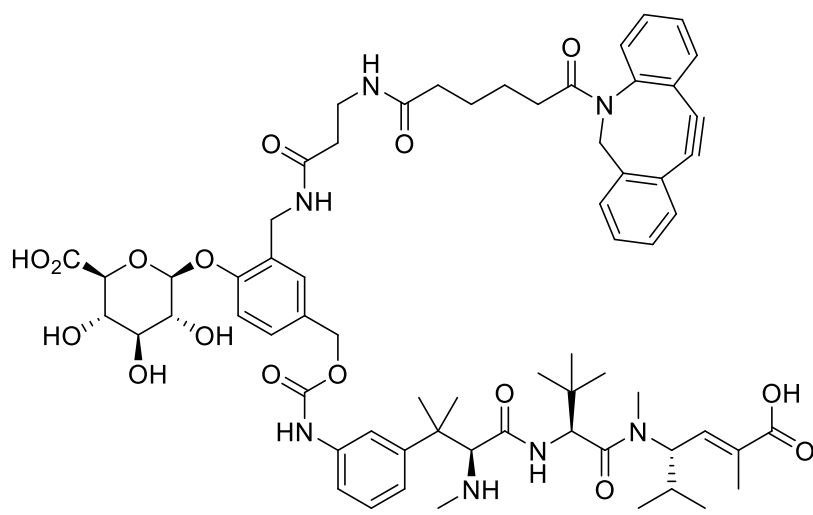
, and a salt thereof.

C=C1C=CC(=O)N(C1Cc2ccccc2)c3c(ccccc3)N(C(=O)CCCCC(=O)NC(=O)CCNC(=O)Cc4ccc(OC(=O)Nc5ccccc5)cc4Oc6oc7c(O)c(O)c(C(=O)O)oc7o6

113, or a pharmaceutically

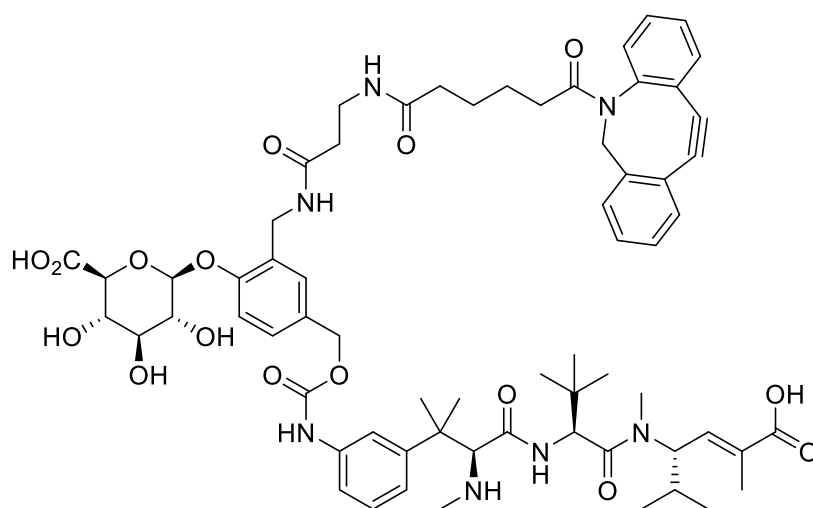
acceptable salt thereof.

[0009] Provided is a compound selected from



, and a salt thereof.

[0009a] In another aspect, provided is a compound having the following chemical structure

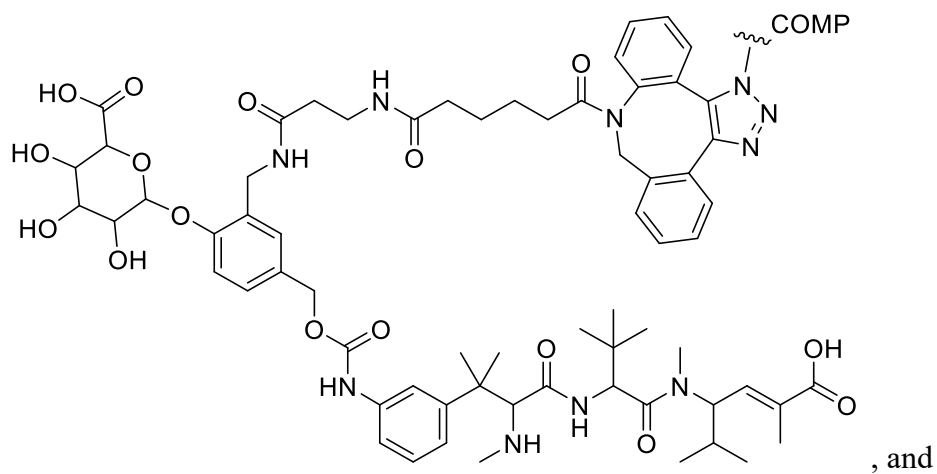


114, or a pharmaceutically

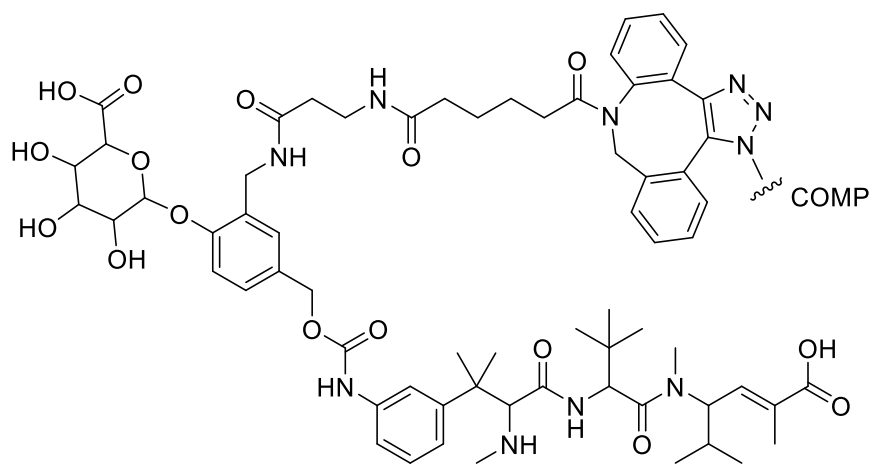
acceptable salt thereof.

[0010] Provided are conjugates comprising residues of the compounds of, for example, Formula (I), (IA), (IB), (III), (IIIA), (IIIB), or a pharmaceutically acceptable salt thereof, linked to a second compound. In another aspect, provided herein is a conjugate comprising the compound as provided herein, or a pharmaceutically acceptable salt thereof, linked to a second compound.

[0011] In another aspect, provided is a conjugate having the following chemical structure



, and

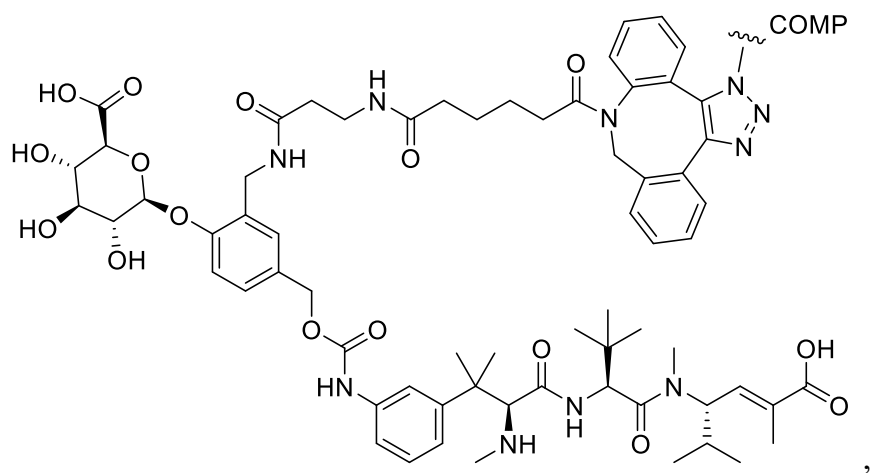


, and a pharmaceutically

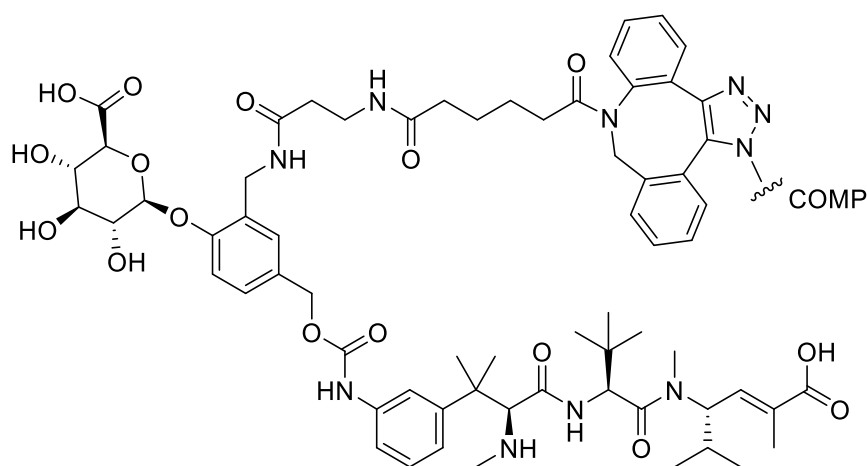
acceptable salt of any one thereof,

wherein  is the residue of the second compound.

[0012] In another aspect, provided is a conjugate having the following chemical structure



,



, and a pharmaceutically

acceptable salt of any one thereof,

wherein  COMP is the residue of the second compound.

[0013] Provided are pharmaceutical compositions comprising the compounds of Formulae (I), (IA), (IB), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), and (IVB), and a pharmaceutically acceptable excipient, carrier, or diluent. In another aspect, provided herein is a pharmaceutical composition comprising the compound as provided herein or conjugate as provided herein; and a pharmaceutically acceptable excipient, carrier, or diluent. Any suitable pharmaceutical composition may be used.

[0014] Provided are compounds of Formulae (I), (IA), (IB), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), and (IVB), or pharmaceutical compositions thereof, are useful for therapy. In another aspect, provided herein is the compound as provided herein, the conjugate as provided herein, or the pharmaceutical composition as provided herein for use in therapy. Provided are compounds of Formulae (I), (IA), (IB), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), and (IVB), or pharmaceutical compositions thereof, are useful for the treatment of cancer. In another aspect, provided herein is the compound as provided herein, the conjugate as provided herein, or the pharmaceutical composition as provided herein for use in the treatment of cancer. Provided are compounds of Formulae (I), (IA), (IB), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), and (IVB), or pharmaceutical compositions thereof, are useful for a medicament. In another aspect, provided herein is the compound as provided herein, the conjugate as provided herein, or the pharmaceutical composition as provided herein for use as a medicament.

[0015] Provided are methods for inhibiting tubulin polymerization in a subject in need thereof comprising administering an effective amount of the compounds of Formulae (I), (IA), (IB), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), and (IVB), or pharmaceutical compositions thereof, to the subject. In another aspect, provided is the compound as provided herein, the conjugate as provided herein, or the pharmaceutical composition as provided herein for use in inhibiting tubulin polymerization. Provided are methods for reducing cell proliferation in a subject in need thereof comprising administering an effective amount of the compounds of Formulae (I), (IA), (IB), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), and (IVB), or pharmaceutical compositions thereof, to the subject. In another aspect, provided is the compound as provided herein, the conjugate as provided herein, or the pharmaceutical composition as provided herein for use in reducing cell proliferation. Provided are methods for treating cell proliferation or cancer in a subject in need thereof comprising administering an effective amount of the compounds of Formulae

(I), (IA), (IB), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), and (IVB), or pharmaceutical compositions thereof, to the subject. In another aspect, provided is use of the compound as provided herein, the conjugate as provided herein, or the pharmaceutical composition as provided herein in the manufacture of a medicament for the treatment of cancer.

[0016] Provided are methods for producing a conjugate, comprising contacting the compounds of Formula (I), (IA), (IB), (III), (IIIA), or (IIIB), with a second compound under conditions suitable for conjugating Formula (I), (IA), (IB), (III), (IIIA), or (IIIB), with the second compound; wherein the second compound comprises an alkyne, cyclooctyne, strained alkene, tetrazine, methylcyclopropene, thiol, maleimide, carbonyl, amine, oxyamine, or azide. In another aspect, provided is a method of producing a conjugate, comprising contacting the compound as provided herein with a second compound under conditions suitable for conjugating the compound as provided herein with the second compound; wherein the second compound comprises an alkyne, cyclooctyne, strained alkene, tetrazine, methylcyclopropene, thiol, maleimide, carbonyl, amine, oxyamine, or azide.

BRIEF DESCRIPTION OF THE FIGURES

[0017] FIG. 1 shows MALDI-ToF data for drug to antibody ratios (DAR) following conjugation to an antibody.

[0018] FIG. 2A-FIG. 2F shows cell killing activity of certain β -Glu linker-payloads conjugated as ADCs having a DAR = 8, and certain free payloads.

[0019] FIG. 3A-FIG. 3D shows the susceptibility of the β -glucuronide linker-payloads to enzymatic cleavage after treatment with β -glucuronidase.

DETAILED DESCRIPTION

[0020] Described herein are compounds of Formulae (I), (IA), (IB), (III), (IIIA), and (IIIB), and conjugates of Formulae (II), (IIA), (IIB), (IV), (IVA), and (IVB) useful for modulating the bioavailability and ADME of such macromolecular conjugate compounds. In some instances, the compounds described herein are useful for preparing conjugates, for instance prodrugs, of macromolecules for *in vivo* use.

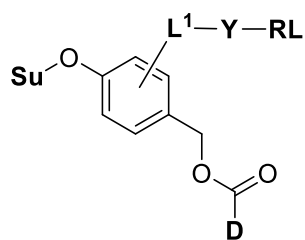
Definitions

[0021] Unless otherwise defined, all terms of art, notations, and other scientific terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this disclosure pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or ready reference. The techniques and procedures described

or referenced herein are generally well understood and are commonly employed using conventional methodologies by those skilled in the art, for example, the widely utilized molecular cloning methodologies described in Green & Sambrook, *Molecular Cloning: A Laboratory Manual* 4th ed. (2012), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; and Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons. As

WHAT IS CLAIMED IS:

1. A compound according to the structure of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

L¹ is -C₁₋₆ alkylene-;

Y is -**X¹**-C₁₋₆ alkylene-[**X¹**-C₁₋₆ alkylene]_n-[**X¹**]_p-,
 -**X¹**-C₂₋₆ alkenylene-[**X¹**-C₂₋₆ alkenylene]_n-[**X¹**]_p-, or
 -**X¹**-C₂₋₆ alkynylene-[**X¹**-C₂₋₆ alkynylene]_n-[**X¹**]_p-, wherein at least one alkylene, alkenylene,
 or alkynylene in **Y** is substituted with one or more substituents selected from **R⁵⁰**, and

wherein the alkylene, alkenylene, or alkynylene in **Y** is optionally substituted with
 one or more substituents selected from **R⁵¹**;

R⁵⁰ is -C₁₋₆ alkylene-**X²**-[C₁₋₆ alkylene]_m-**POLY**,
 -C₂₋₆ alkenylene-**X²**-[C₂₋₆ alkenylene]_m-**POLY**, or
 -C₂₋₆ alkynylene-**X²**-[C₂₋₆ alkynylene]_m-**POLY**, wherein each alkylene, alkenylene, or
 alkynylene of **R⁵⁰** is optionally substituted with one or more substituents selected from
 halogen, -CN, -NO₂, -OH, -N(**R¹⁰**)₂, -C(O)N(**R¹⁰**)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅,
 -NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-
 membered heterocycle, and C₁₋₁₀ haloalkyl;

R⁵¹ is independently selected from halogen, -CN, -NO₂, -OH, -N(**R¹⁰**)₂,
 -C(O)N(**R¹⁰**)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅, -NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl, C₂₋₁₀
 alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and C₁₋₁₀ haloalkyl;

X¹ and **X²** are independently selected from -N(**R¹⁰**)-, -C(O)-, and -N(**R¹⁰**)C(O)-;

R¹⁰ is independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl,
 C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and
 C₁₋₁₀ haloalkyl;

POLY is a water-soluble polymer;

n is an integer selected from zero, one, two, and three;

m is an integer selected from zero and one;

p is an integer selected from zero and one;

Su is a hexose form of a monosaccharide;

D is a drug moiety; and

RL is a reactive linker group residue.

2. The compound of claim 1, wherein

L¹ is -C₁₋₆ alkylene-;

Y is -**X¹**-C₁₋₆ alkylene-[**X¹**-C₁₋₆ alkylene]_{**n**}-**X¹**-,
-**X¹**-C₂₋₆ alkenylene-[**X¹**-C₂₋₆ alkenylene]_{**n**}-**X¹**-, or
-**X¹**-C₂₋₆ alkynylene-[**X¹**-C₂₋₆ alkynylene]_{**n**}-**X¹**-, wherein at least one alkylene, alkenylene, or
alkynylene in **Y** is substituted with one or more substituents selected from **R⁵⁰**;

R⁵⁰ is -C₁₋₆ alkylene-**X²**-[C₁₋₆ alkylene]_{**m**}-**POLY**,
-C₂₋₆ alkenylene-**X²**-[C₂₋₆ alkenylene]_{**m**}-**POLY**, or
-C₂₋₆ alkynylene-**X²**-[C₂₋₆ alkynylene]_{**m**}-**POLY**, wherein each alkylene, alkenylene or
alkynylene of **R⁵⁰** is optionally substituted with one or more substituents selected from
halogen, -CN, -NO₂, -OH, -N(**R¹⁰**)₂, -C(O)N(**R¹⁰**)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅,
-NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-
membered heterocycle, and C₁₋₁₀ haloalkyl;

X¹ and **X²** are independently selected from -C(O)- and -N(**R¹⁰**)C(O)-;

R¹⁰ is independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀
alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and C₁₋₁₀ haloalkyl;

POLY is a water-soluble polymer;

n is an integer selected from zero, one, two, and three;

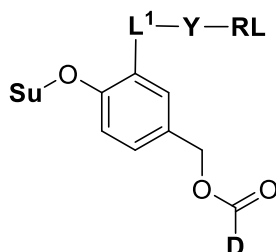
m is an integer selected from zero and one;

Su is a hexose form of a monosaccharide;

D is a drug moiety; and

RL is a reactive linker group residue.

3. The compound or salt of claim 1 or 2, wherein the compound of Formula (I) is according to Formula (IA)



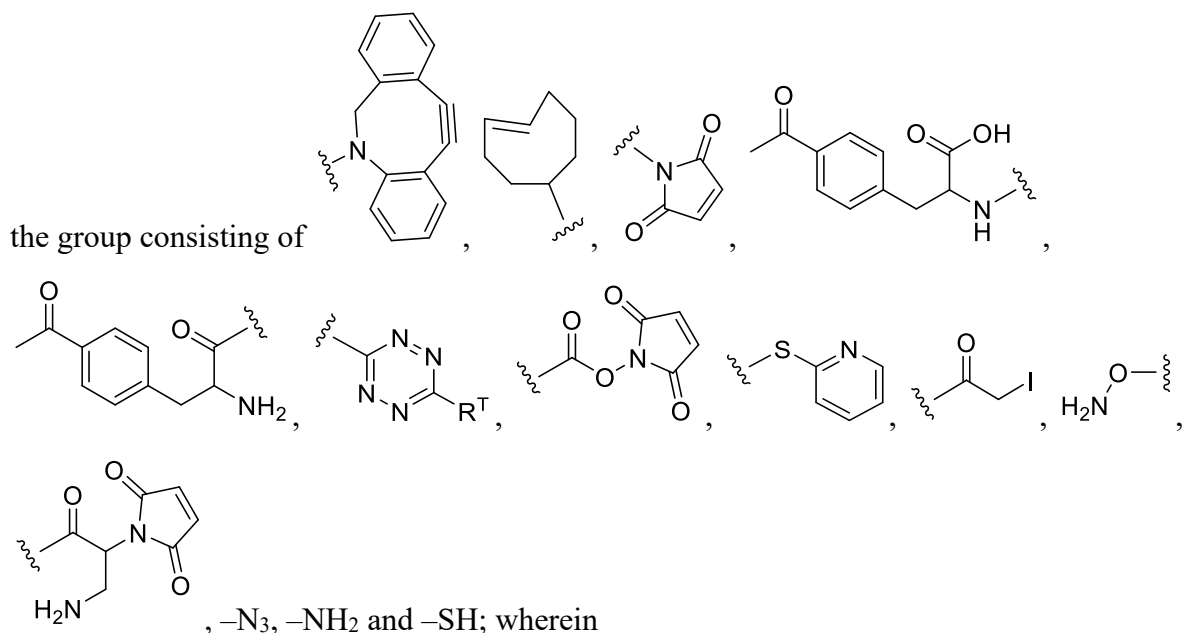
(IA)

or a pharmaceutically acceptable salt thereof.

4. The compound or salt of any one of the previous claims, wherein **L¹** is -C₁₋₃ alkylene-.
5. The compound or salt of claim 1 or 3, wherein **p** is one.
6. The compound or salt of any one of the previous claims, wherein **Y** is -**X¹**-C₁₋₆ alkylene-[**X¹**-C₁₋₆ alkylene]_{**n**}-**X¹**-, wherein at least one alkylene in **Y** is substituted with one or more substituents selected from **R**⁵⁰.
7. The compound or salt of any one of the previous claims, wherein **Y** is -**X¹**-C₁₋₄ alkylene-[**X¹**-C₁₋₄ alkylene]_{**n**}-**X¹**-, wherein at least one alkylene in **Y** is substituted with one or more substituents selected from **R**⁵⁰.
8. The compound or salt of claim 7, wherein **Y** is -**X¹**-C₁₋₄ alkylene-**X¹**-C₁₋₄ alkylene-**X¹**-C₁₋₄ alkylene-**X¹**-, wherein at least one alkylene in **Y** is substituted with one or more substituents selected from **R**⁵⁰.
9. The compound or salt of claim 7, wherein **Y** is -**X¹**-C₁₋₄ alkylene-**X¹**-C₁₋₄ alkylene-**X¹**-, wherein at least one alkylene in **Y** is substituted with one or more substituents selected from **R**⁵⁰.
10. The compound or salt of any one of claims 1, 3, or 4, wherein **p** is zero.
11. The compound or salt of any one of claims 1, 3, or 4, wherein **Y** is -**X¹**-C₁₋₆ alkylene-[**X¹**-C₁₋₆ alkylene]_{**n**}-, wherein at least one alkylene in **Y** is substituted with one or more substituents selected from **R**⁵⁰, and wherein the alkylene in **Y** is optionally substituted with one or more substituents selected from **R**⁵¹.

12. The compound or salt of any one of claims 1, 3, or 4, wherein **Y** is $-\text{X}^1\text{-C}_{1-4}\text{ alkylene-}[\text{X}^1\text{-C}_{1-4}\text{ alkylene}]_n-$, wherein at least one alkylene in **Y** is substituted with one or more substituents selected from **R**⁵⁰, and wherein the alkylene in **Y** is optionally substituted with one or more substituents selected from **R**⁵¹.
13. The compound or salt of claim 12, wherein **Y** is $-\text{X}^1\text{-C}_{1-4}\text{ alkylene-X}^1\text{-C}_{1-4}\text{ alkylene-X}^1\text{-C}_{1-4}\text{ alkylene-}$, wherein at least one alkylene in **Y** is substituted with one or more substituents selected from **R**⁵⁰, and wherein the alkylene in **Y** is optionally substituted with one or more substituents selected from **R**⁵¹.
14. The compound or salt of any one of the previous claims, wherein **R**⁵¹ is independently selected from halogen, -CN, -NO₂, -OH, -NH₂, -C(O)NH₂, and -C(O)-.
15. The compound or salt of any one of the previous claims, wherein **R**⁵⁰ is $-\text{C}_{1-6}\text{ alkylene-X}^2\text{-}[\text{C}_{1-6}\text{ alkylene}]_m\text{-POLY}$, wherein each alkylene of **R**⁵⁰ is optionally substituted with one or more substituents selected from halogen, -CN, -NO₂, -OH, -N(**R**¹⁰)₂, -C(O)N(**R**¹⁰)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅, -NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and C₁₋₁₀ haloalkyl.
16. The compound or salt of any one of the previous claims, wherein **m** is one.
17. The compound or salt of any one of the previous claims, wherein **POLY** is polyethylene glycol (PEG), methoxypolyethylene glycol (mPEG), poly(propylene glycol) (PPG), copolymers of ethylene glycol and propylene glycol, poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharides), poly(α -hydroxy acid), poly(vinyl alcohol), polyphosphazene, polyoxazolines (POZ), poly(*N*-acryloylmorpholine), polysarcosine, or a combination thereof.
18. The compound or salt of claim 17, wherein **POLY** comprises a polyethylene glycol (PEG) or methoxypolyethylene glycol (mPEG).
19. The compound or salt of any one of the previous claims, wherein **POLY** is
- $$\begin{array}{c} \text{---} \left[\text{O} \text{---} \text{CH}_2 \text{---} \text{CH}_2 \right]_{n1} \text{OMe} \end{array}$$
- , wherein --- represents attachment to the remainder of the compound, and wherein **n1** is an integer from one to twenty.
20. The compound or salt of claim 19, wherein **n1** is an integer between five to fifteen.

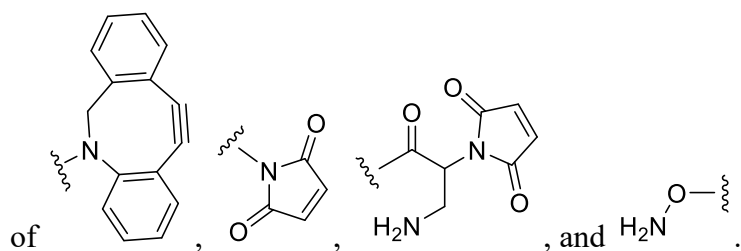
21. The compound or salt of any one of the previous claims, wherein **RL** comprises an alkyne, cyclooctyne, a strained alkene, a tetrazine, methylcyclopropene, a thiol, a *para*-acetyl-phenylalanine residue, an oxyamine, a maleimide, or an azide.
22. The compound or salt of any one of the previous claims, wherein **RL** is selected from



R^T is C₁₋₆ alkyl; and

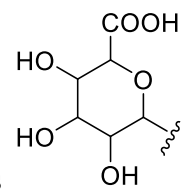
~ represents attachment to the remainder of the compound.

23. The compound or salt of claim 22, wherein **R^T** is methyl, ethyl, or propyl.
24. The compound or salt of claim 23, wherein **R^T** is methyl.
25. The compound or salt of claim 22, wherein **RL** is selected from the group consisting



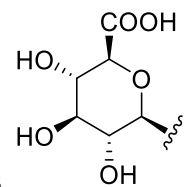
26. The compound or salt of claim 22, wherein **RL** is
-

27. The compound or salt of any one of the previous claims, wherein **Su** is



wherein  represents attachment to the remainder of the compound.

28. The compound or salt of any one of the previous claims, wherein **Su** is



wherein  represents attachment to the remainder of the compound.

29. The compound or salt of any one of the previous claims, wherein **D** is an immunomodulatory payload.

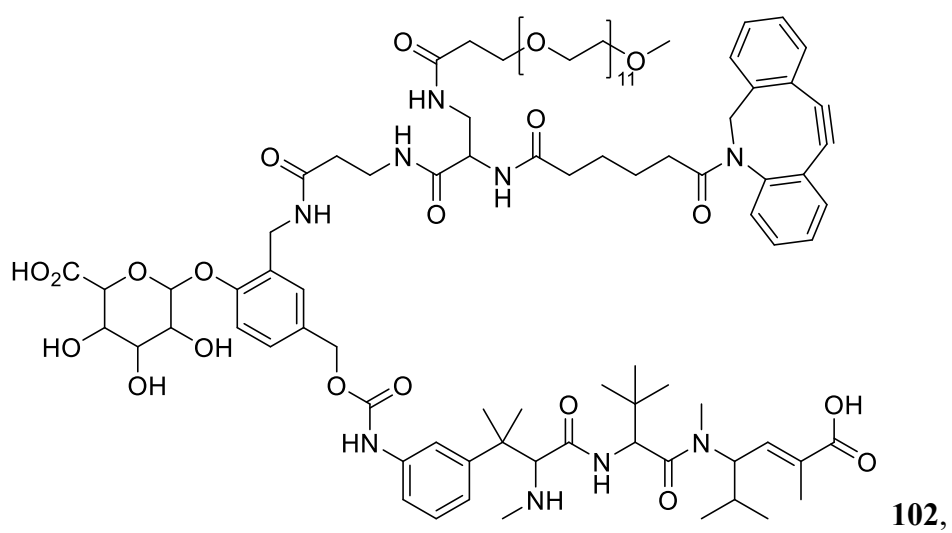
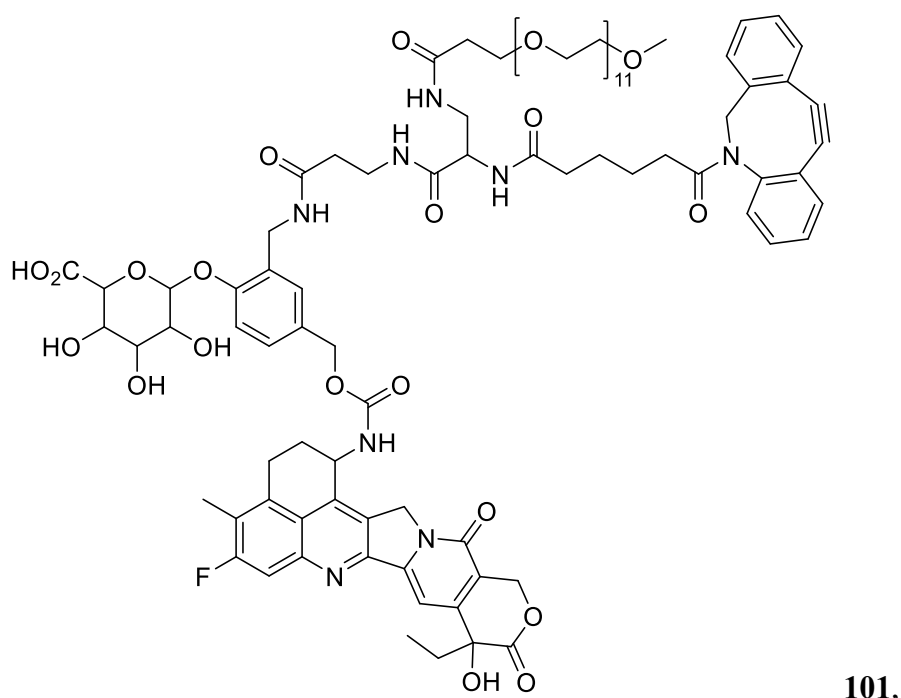
30. The compound or salt of claim 29, wherein the immunomodulatory payload is an agonist of stimulator of interferon gene (STING), Toll-like receptor 7 (TLR7), Toll-like receptor 7/8 (TLR7/8), or Toll-like receptor 8 (TLR8).

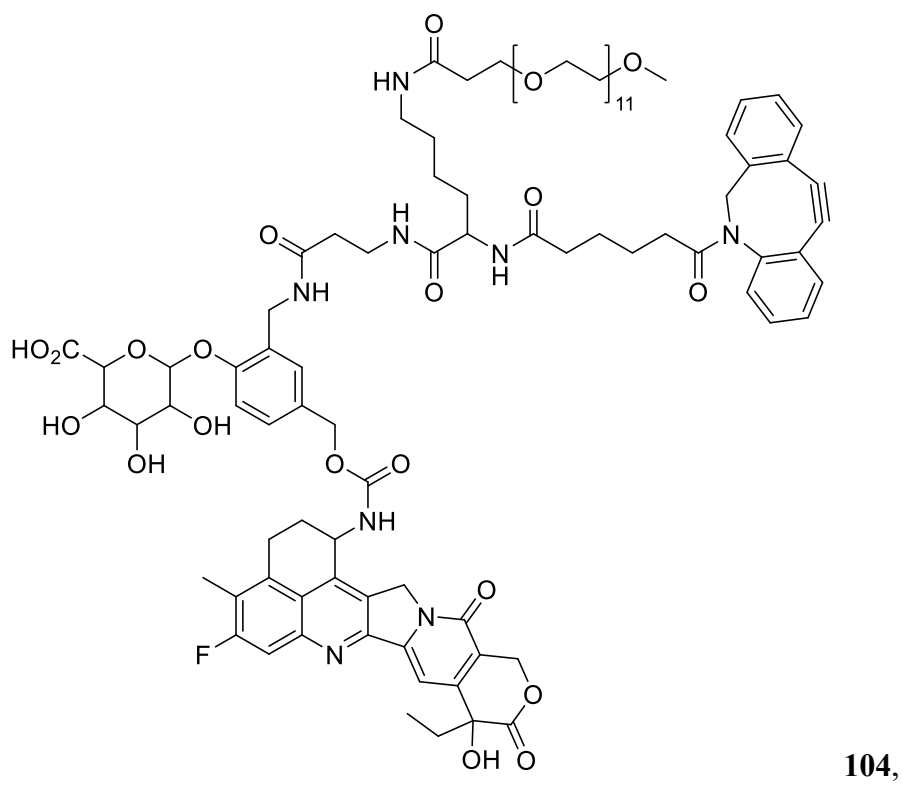
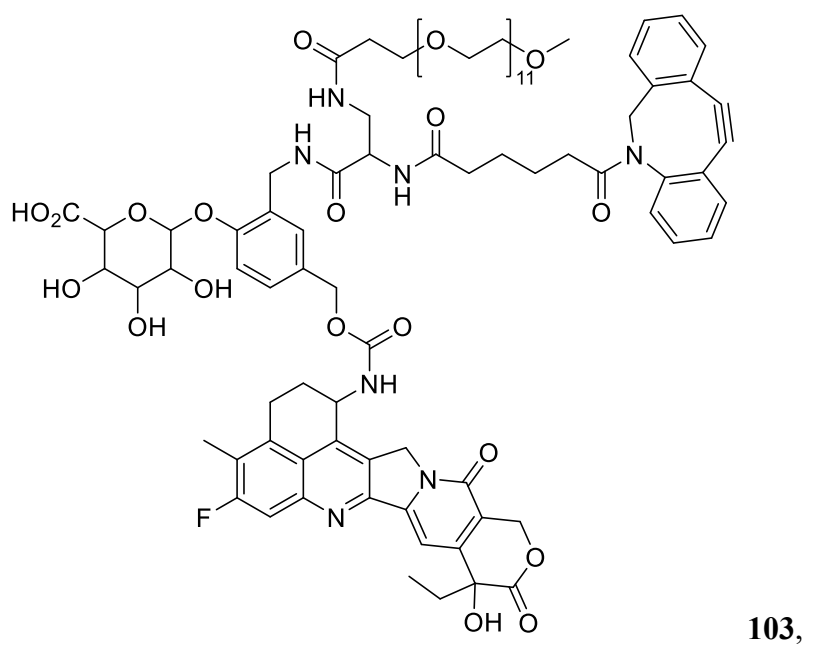
31. The compound or salt of claim 30, wherein the agonist of STING is selected from the group consisting of a small molecule agonist of the STING pathway, an antibody that activates STING activity, a recombinant protein that activates the STING pathway, TTI-10001, DMXAA (ASA404), CDNs, c-di-GMP, 2'3'-cGAMP, MK-1454, ADU-S100 (MIW815), SB11285, ADU-V19, IACS-8779, IACS-8803, IMSA101, non-CDNs, E7766, MK-2118, diABZI, MSA-2, JNJ-‘6196, bacterial vectors, SYNBI891, and STACT.

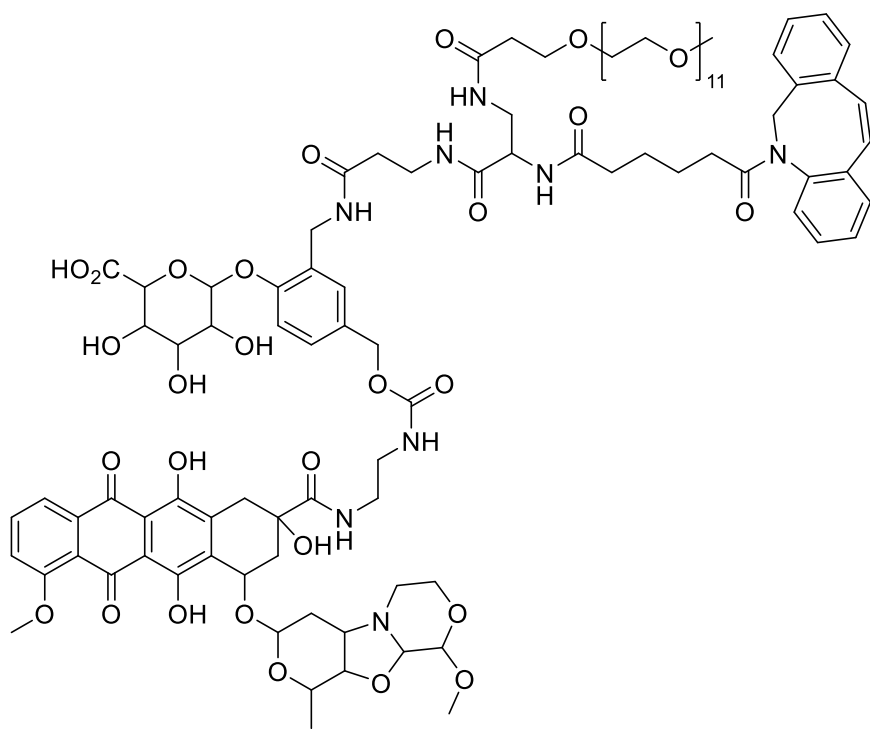
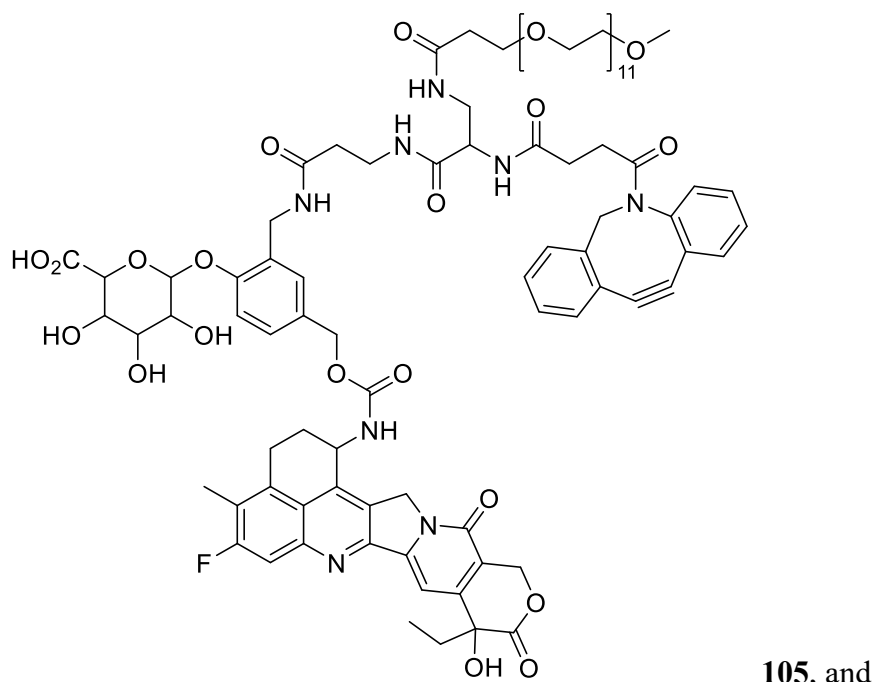
32. The compound or salt of claim 30, wherein the agonist of Toll-like receptor 7 (TLR7) is selected from the group consisting of GS-986, PRTX-007, PRX-034, S-34240, MBS-8, and APR-002.

33. The compound or salt of claim 30, wherein the agonist of Toll-like receptor 7/8 (TLR7/8) is selected from the group consisting of imiquimod (R837), resiquimod (R848), 852-A (PF-4878691), vesatolimod (GS-9620), AZD8848, motolimod (VTX-2337), selgantolimod (GS-9688), NKTR-262, RG-7854 (RO 7020531), DSP-0509, BDB-001, BDC-1001, LHC-165, SHR-2150, JNJ-4964 (TQ-73334), RO-7119929, DN-1508052, VTX-1463, BNT-411 (SC1), APR-003, ALT-702, TRANSCON, VX-001, SNAPvax, R848-HA, SM360320, and GSK2245035.

34. The compound or salt of claim 30, wherein the agonist of Toll-like receptor 8 (TLR8) is selected from the group consisting of SBT-6050, SBT-6290, and ZM-TLR8 agonist.
35. The compound or salt of any one of the previous claims, wherein **D** is a cytotoxic payload.
36. The compound or salt of claim 35, wherein the cytotoxic payload is a tubulin inhibitor, a DNA topoisomerase I inhibitor, or a DNA topoisomerase II inhibitor.
37. The compound or salt of any one of the previous claims, wherein **D** is selected from the group consisting of hemiasterlins, camptothecins, anthracyclines, PNU-159682, and EDA PNU-159682 derivatives.
38. The compound or salt of any one of the previous claims, wherein **D** is hemiasterlin, exatecan, PNU-159682, or EDA PNU-159682 derivatives.
39. The compound or salt of any one of the previous claims, wherein the compound is selected from

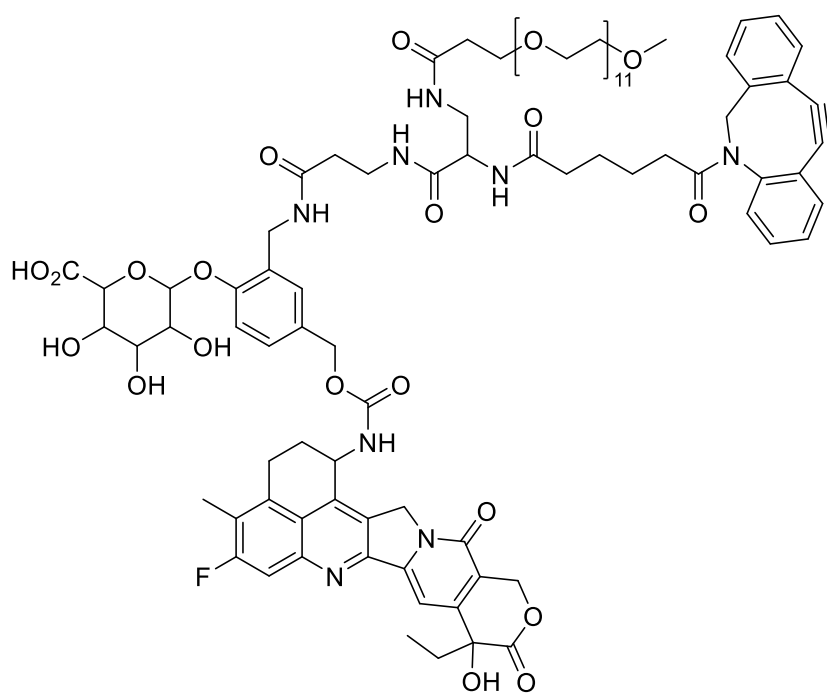




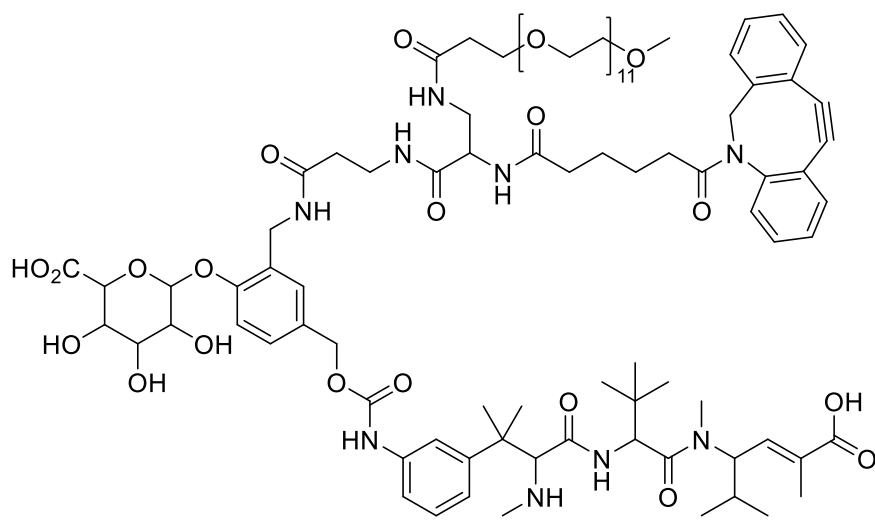


a pharmaceutically acceptable salt of any one thereof.

40. The compound or salt of any one of the previous claims, wherein the compound is selected from



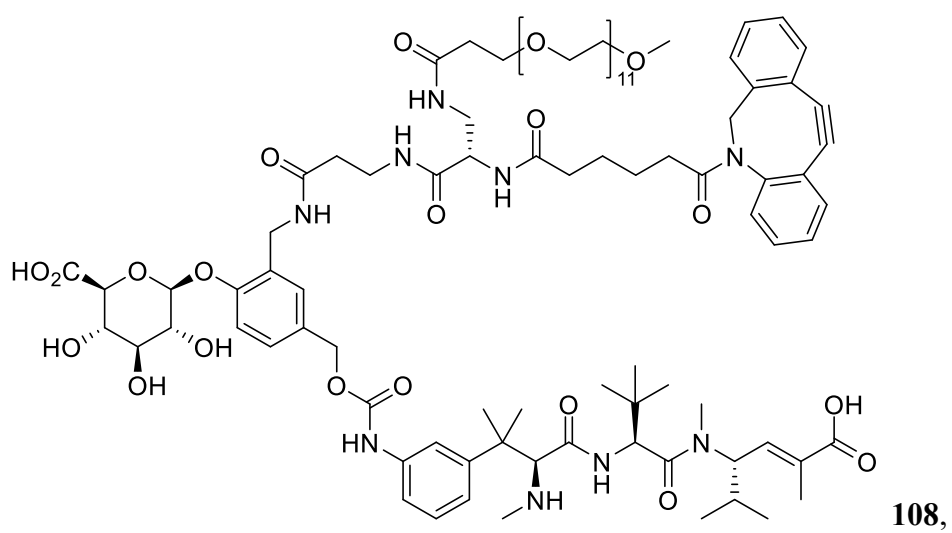
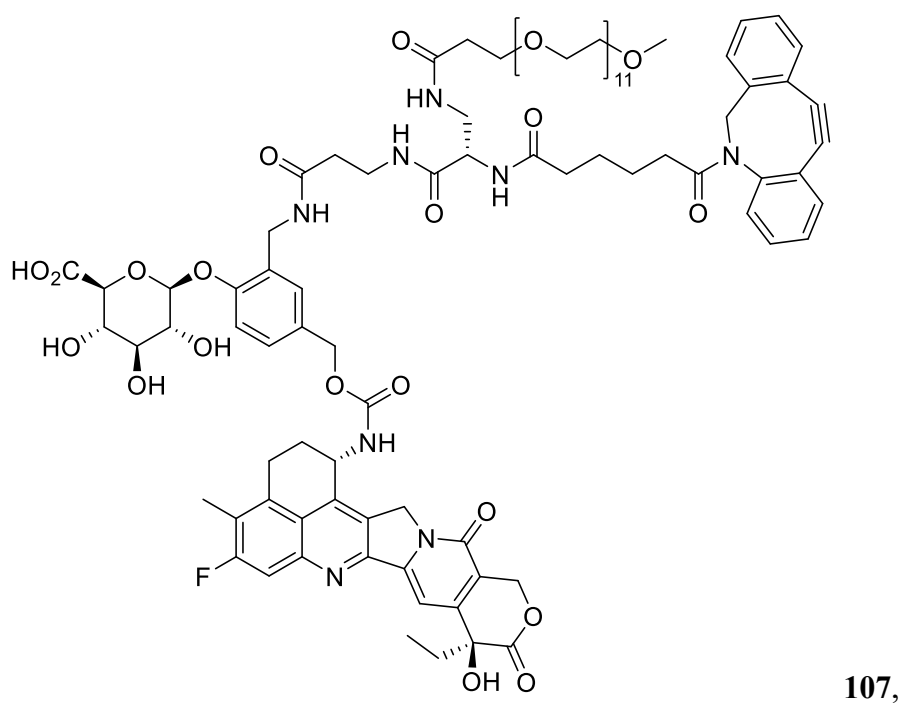
101, and

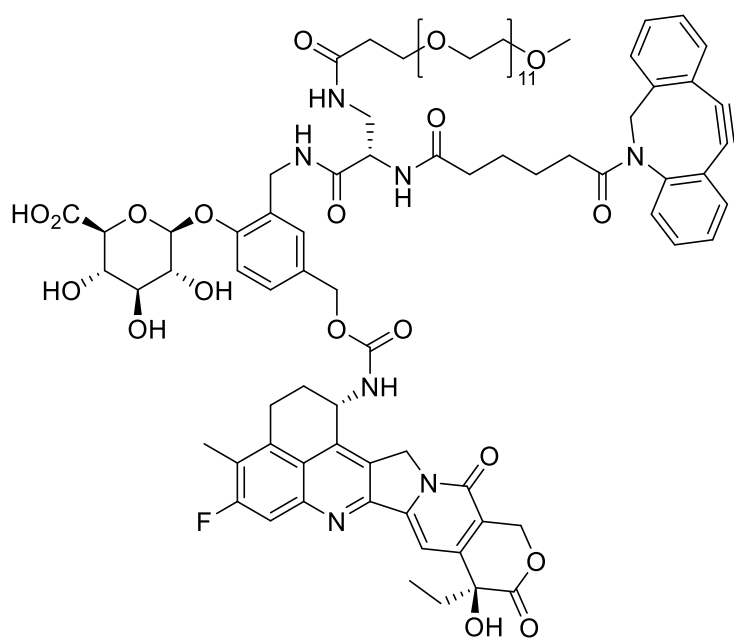


102, or

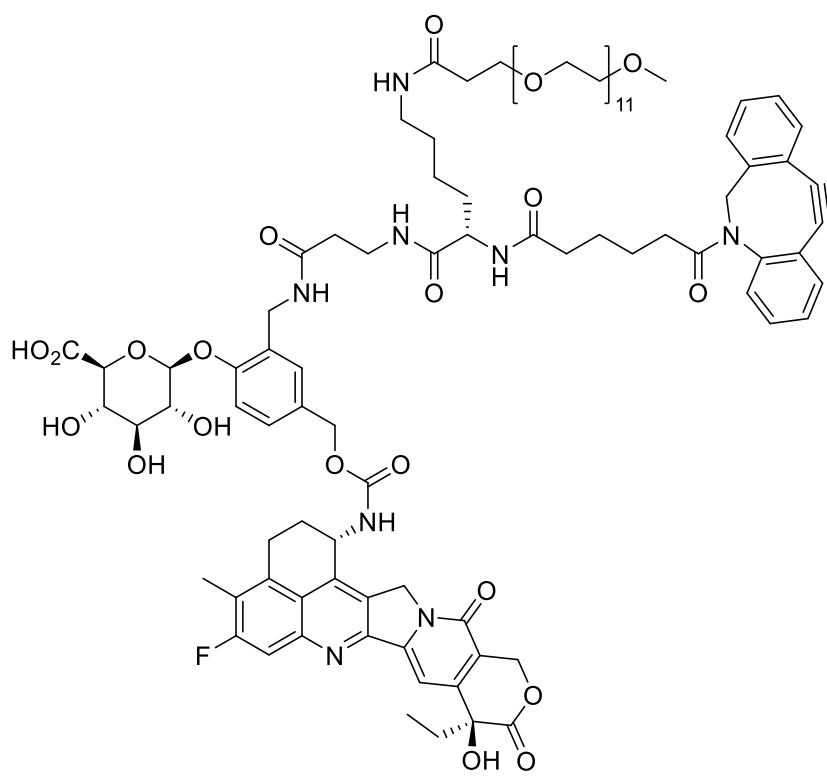
a pharmaceutically acceptable salt of any one thereof.

41. The compound or salt of any one of the previous claims, wherein the compound is selected from

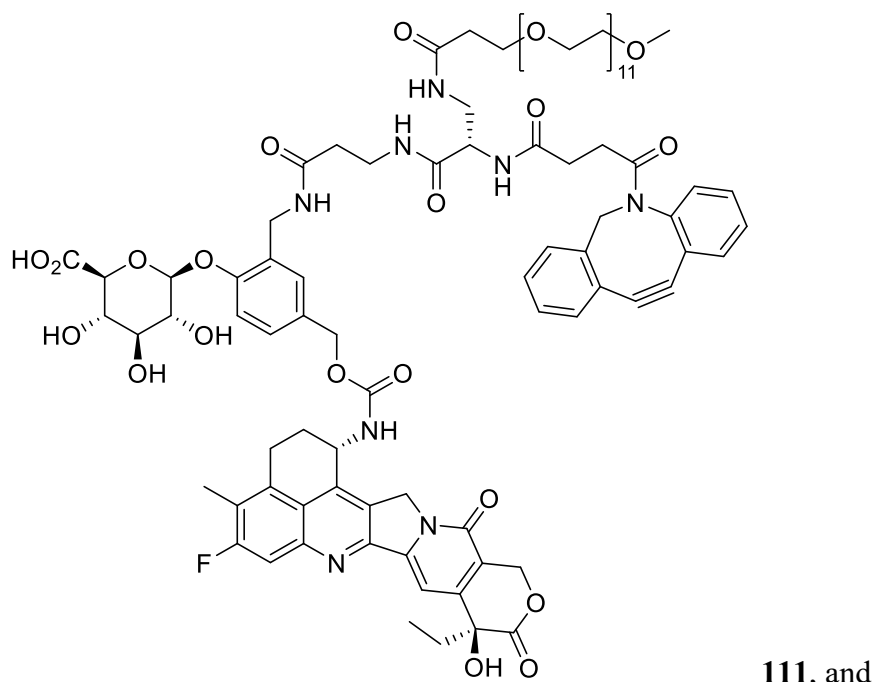




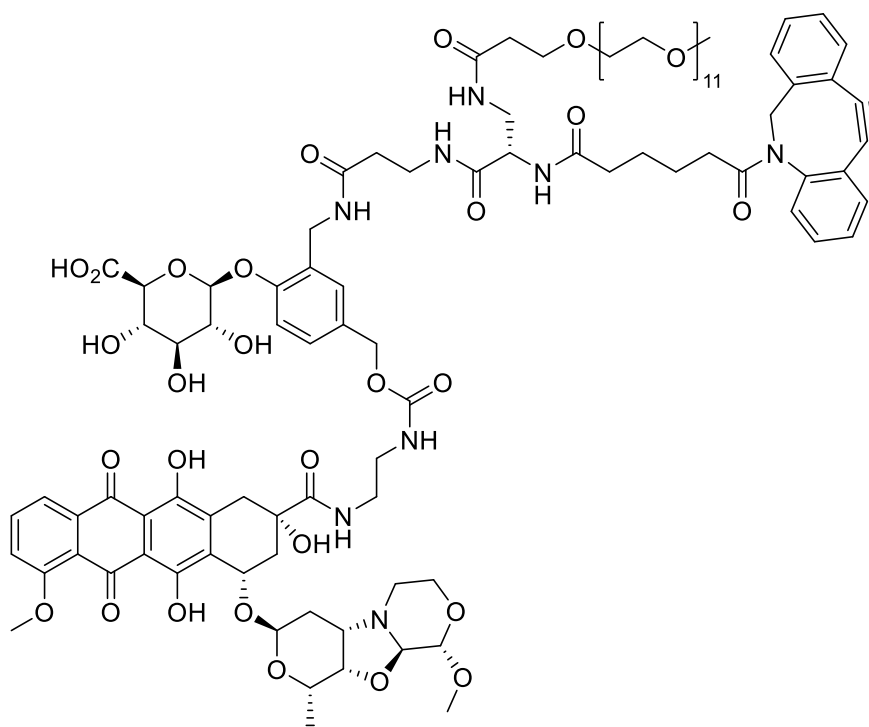
109,



110,



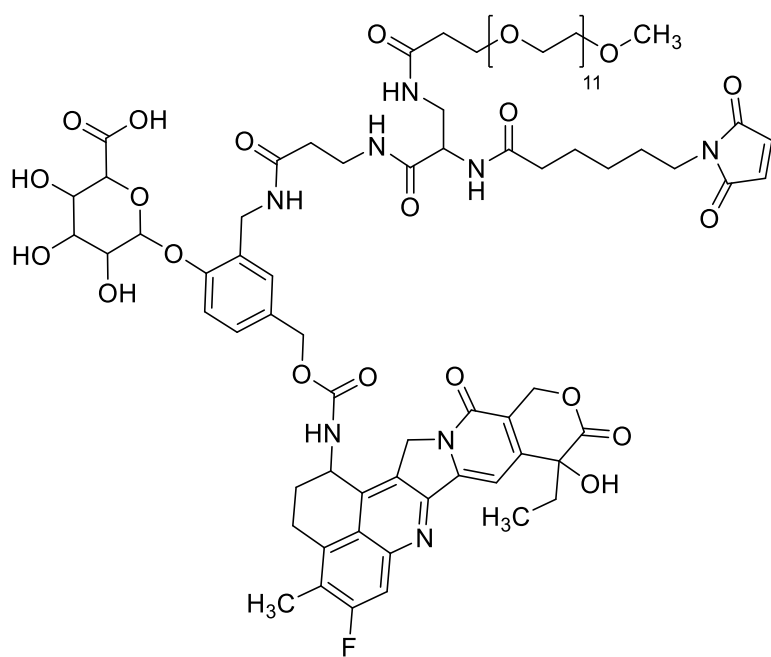
111, and



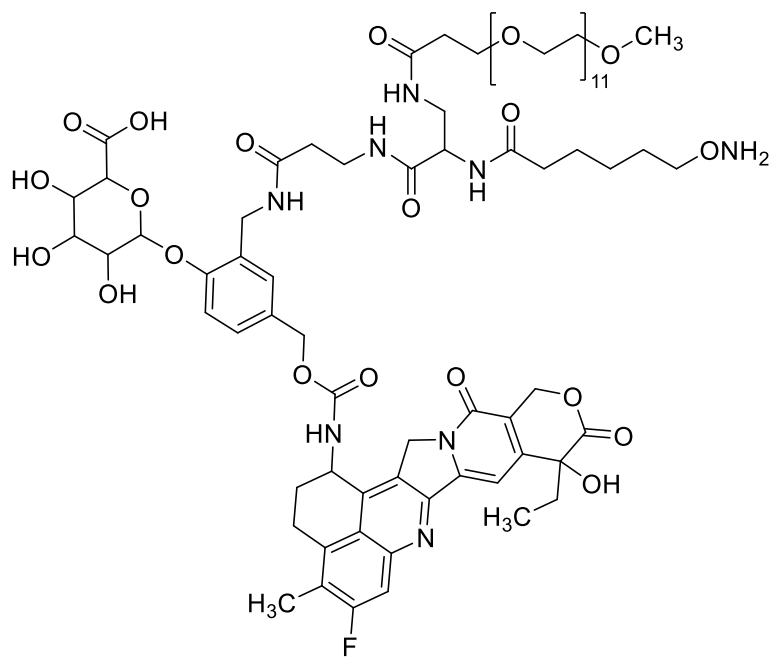
112, or

a pharmaceutically acceptable salt of any one thereof.

42. The compound or salt of any one of claims 1, 3, 4, or 10-38, wherein the compound is selected from



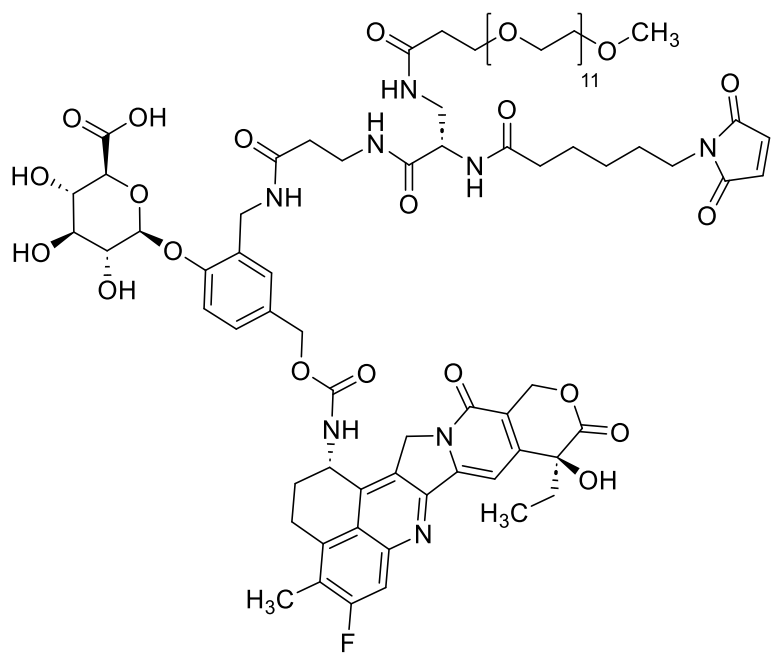
111aa,



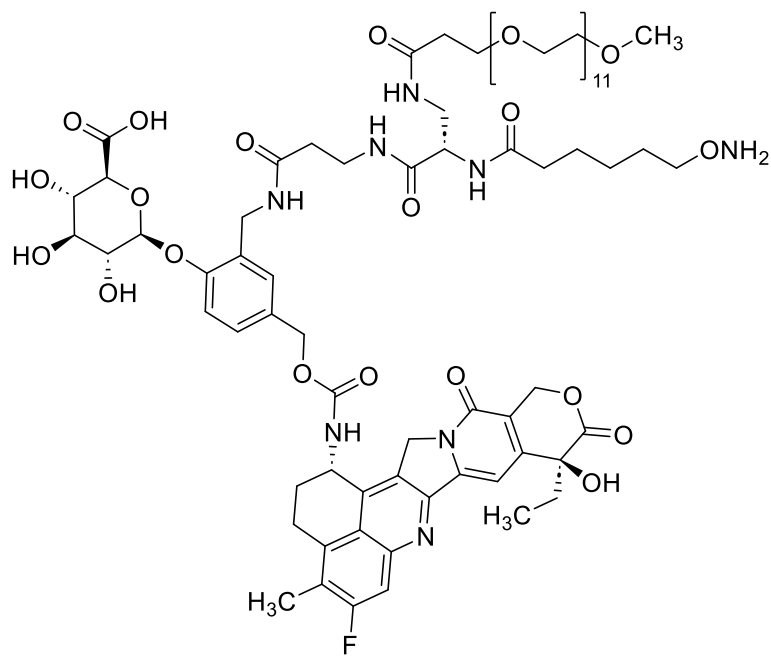
111cc,



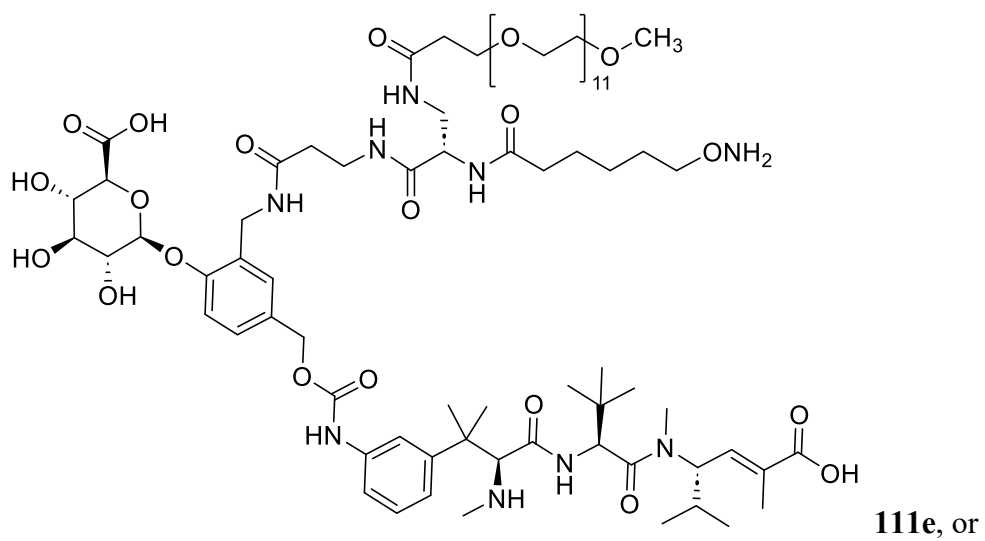
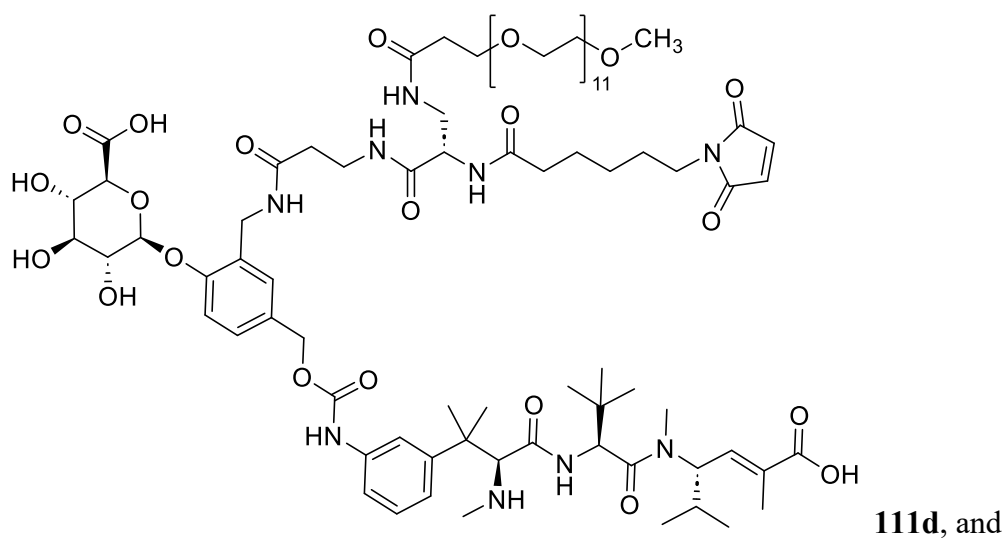
43. The compound or salt of any one of claims 1, 3, 4, or 10-38, wherein the compound is selected from



111a,

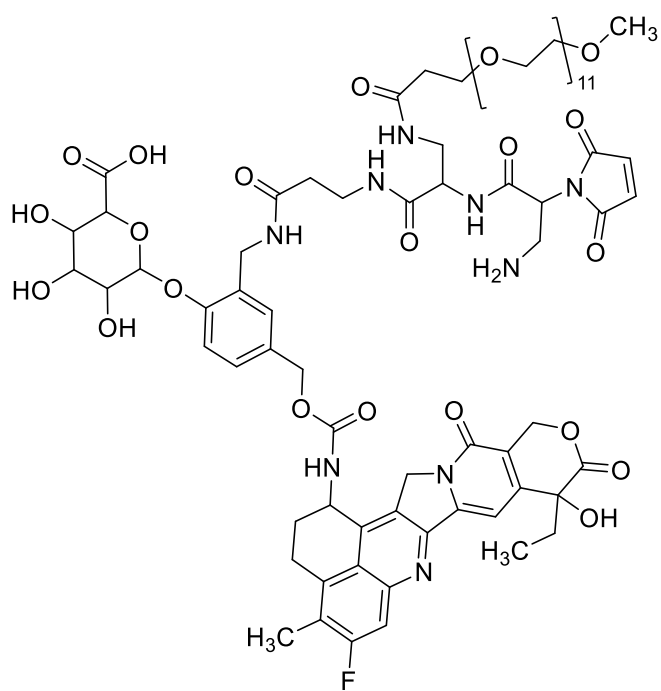


111c,

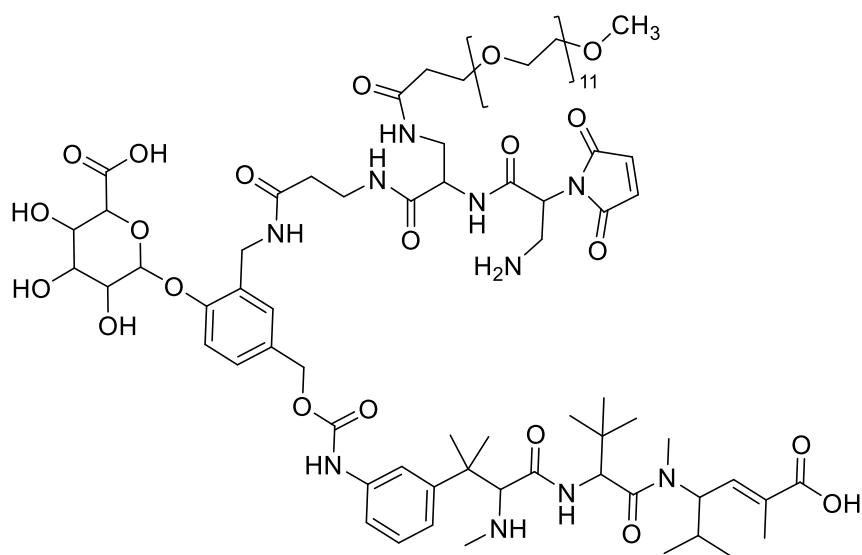


a pharmaceutically acceptable salt of any one thereof.

44. The compound or salt of any one of claims 1-9 or 15-38, wherein the compound is selected from



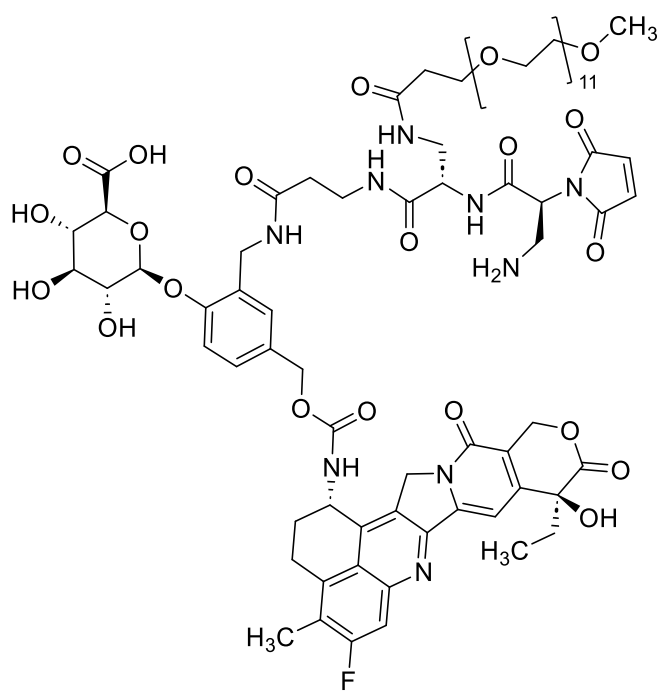
111bb, and



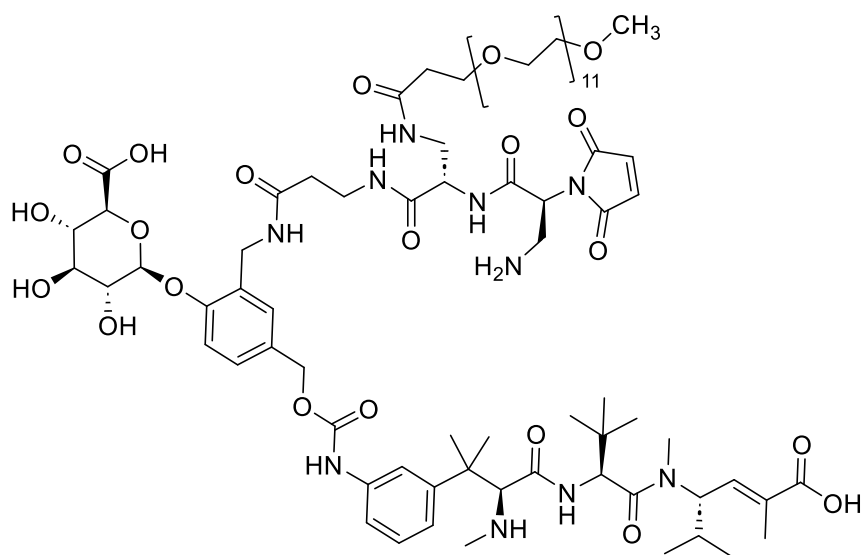
111ff, or

a pharmaceutically acceptable salt of any one thereof.

45. The compound or salt of any one of claims 1-9 or 15-38, wherein the compound is selected from



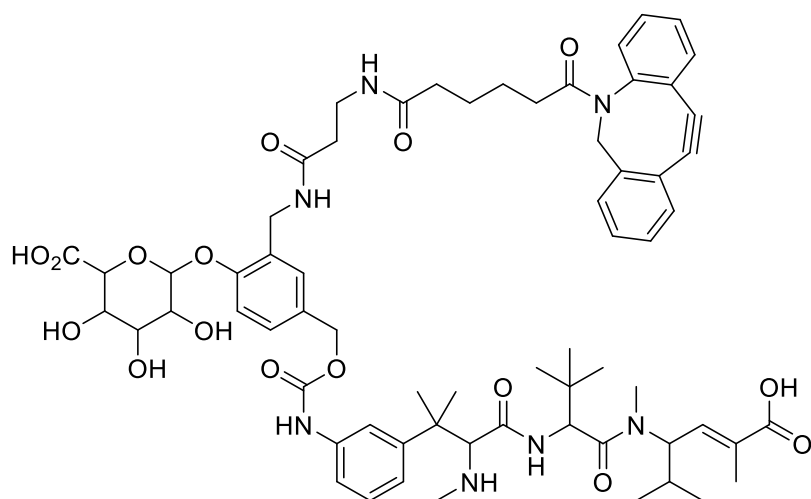
111b, and



111f, or

a pharmaceutically acceptable salt of any one thereof.

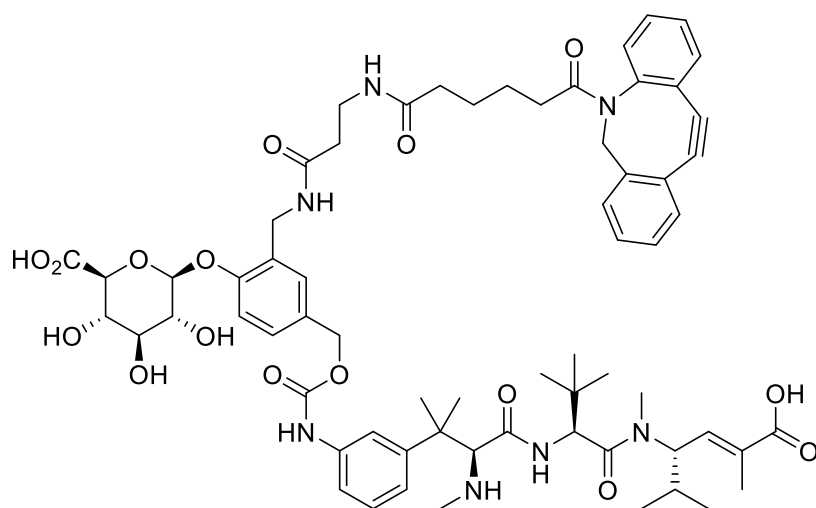
46. A compound having the following chemical structure



113, or a pharmaceutically

acceptable salt thereof.

47. A compound having the following chemical structure

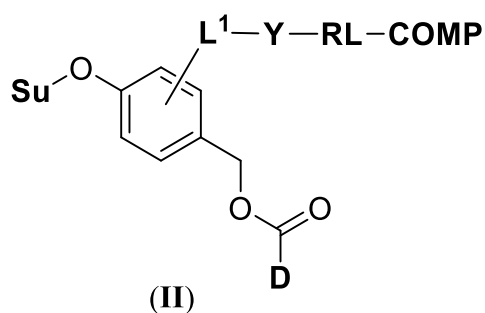


114, or a pharmaceutically

acceptable salt thereof.

48. A conjugate comprising the compound of any one of the previous claims, or a pharmaceutically acceptable salt thereof, linked to a second compound.

49. The conjugate of claim 48, according to the structure of Formula II



wherein

COMP is a residue of a second compound;

L¹ is -C₁₋₆ alkylene-;

Y is -**X¹**-C₁₋₆ alkylene-[**X¹**-C₁₋₆ alkylene]_n-[**X¹**]_p-,
-**X¹**-C₂₋₆ alkenylene-[**X¹**-C₂₋₆ alkenylene]_n-[**X¹**]_p-, or
-**X¹**-C₂₋₆ alkynylene-[**X¹**-C₂₋₆ alkynylene]_n-[**X¹**]_p-, wherein at least one alkylene, alkenylene
or alkynylene in **Y** is substituted with one or more substituents selected from **R⁵⁰**, and

wherein the alkylene, alkenylene, or alkynylene in **Y** is optionally substituted with
one or more substituents selected from **R⁵¹**;

R⁵⁰ is -C₁₋₆ alkylene-**X²**-[C₁₋₆ alkylene]_m-**POLY**,
-C₂₋₆ alkenylene-**X²**-[C₂₋₆ alkenylene]_m-**POLY**, or
-C₂₋₆ alkynylene-**X²**-[C₂₋₆ alkynylene]_m-**POLY**, wherein each alkylene, alkenylene, or
alkynylene of **R⁵⁰** is optionally substituted with one or more substituents selected from
halogen, -CN, -NO₂, -OH, -N(**R¹⁰**)₂, -C(O)N(**R¹⁰**)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅,
-NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-
membered heterocycle, and C₁₋₁₀ haloalkyl;

R⁵¹ is independently selected from halogen, -CN, -NO₂, -OH, -N(**R¹⁰**)₂,
-C(O)N(**R¹⁰**)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅, -NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl,
C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and C₁₋₁₀
haloalkyl;

X¹ and **X²** are independently selected from -N(**R¹⁰**)-, -C(O)-, and -N(**R¹⁰**)C(O)-;

R¹⁰ is independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl,
C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and
C₁₋₁₀ haloalkyl;

POLY is a water-soluble polymer;

n is an integer selected from zero, one, two, and three;

m is an integer selected from zero and one;

p is an integer selected from zero and one;

Su is a hexose form of a monosaccharide;

D is a drug moiety; and

RL is a reactive linker group residue.

50. The conjugate of claim 49, wherein

COMP is a residue of a second compound;

L¹ is -C₁₋₆ alkylene-;

Y is -**X¹**-C₁₋₆ alkylene-[**X¹**-C₁₋₆ alkylene]_{**n**}-**X¹**-,
-**X¹**-C₂₋₆ alkenylene-[**X¹**-C₂₋₆ alkenylene]_{**n**}-**X¹**-, or
-**X¹**-C₂₋₆ alkynylene-[**X¹**-C₂₋₆ alkynylene]_{**n**}-**X¹**-, wherein at least one alkylene, alkenylene or
alkynylene in **Y** is substituted with one or more substituents selected from **R⁵⁰**;

R⁵⁰ is -C₁₋₆ alkylene-**X²**-[C₁₋₆ alkylene]_{**m**}-**POLY**,
-C₂₋₆ alkenylene-**X²**-[C₂₋₆ alkenylene]_{**m**}-**POLY**, or
-C₂₋₆ alkynylene-**X²**-[C₂₋₆ alkynylene]_{**m**}-**POLY**, wherein each alkylene, alkenylene or
alkynylene of **R⁵⁰** is optionally substituted with one or more substituents selected from
halogen, -CN, -NO₂, -OH, -N(**R¹⁰**)₂, -C(O)N(**R¹⁰**)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅,
-NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-
membered heterocycle, and C₁₋₁₀ haloalkyl;

X¹ and **X²** are independently selected from -C(O)- and -N(**R¹⁰**)C(O)-;

R¹⁰ is independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl,
C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and
C₁₋₁₀ haloalkyl;

POLY is a water-soluble polymer;

n is an integer selected from zero, one, two, and three;

m is an integer selected from zero and one;

Su is a hexose form of a monosaccharide;

D is a drug moiety; and

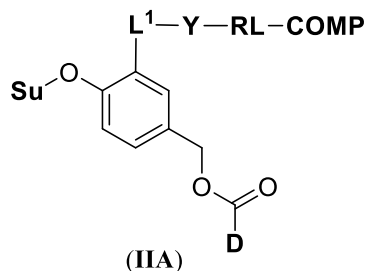
RL is a reactive linker group residue.

51. The conjugate of claim 49 or 50, wherein **COMP** is a residue of a polypeptide.

52. The conjugate of claim 49 or 50, wherein **COMP** is a residue of an antibody.

53. The conjugate of claim 49 or 50, wherein **COMP** is a residue of an antibody chain.

54. The conjugate of claim 49 or 50, wherein the conjugate of Formula (II) is according to Formula (IIA)



55. The conjugate of any one of claims 49-54, wherein L^1 is $-C_{1-3}$ alkylene-.

56. The conjugate of claim 49 or 54, wherein p is one.

57. The conjugate of any one of claims 50-56, wherein Y is $-X^1-C_{1-6}$ alkylene- $[X^1-C_{1-6}$ alkylene] $_n-X^1-$, wherein at least one alkylene in Y is substituted with one or more substituents selected from R^{50} .

58. The conjugate of any one of claims 50-57, wherein Y is $-X^1-C_{1-4}$ alkylene- $[X^1-C_{1-4}$ alkylene] $_n-X^1-$, wherein at least one alkylene in Y is substituted with one or more substituents selected from R^{50} .

59. The conjugate of claim 58, wherein Y is $-X^1-C_{1-4}$ alkylene- X^1-C_{1-4} alkylene- X^1-C_{1-4} alkylene- X^1- , wherein at least one alkylene in Y is substituted with one or more substituents selected from R^{50} .

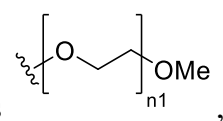
60. The conjugate of claim 58, wherein Y is $-X^1-C_{1-4}$ alkylene- X^1-C_{1-4} alkylene- X^1- , wherein at least one alkylene in Y is substituted with one or more substituents selected from R^{50} .

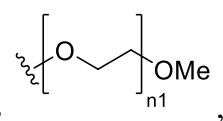
61. The conjugate of any one of claims 49, 54, or 55, wherein p is zero.

62. The conjugate of any one of claims 49, 54, or 55, wherein Y is $-X^1-C_{1-6}$ alkylene- $[X^1-C_{1-6}$ alkylene] $_n-$, wherein at least one alkylene in Y is substituted with one or more substituents selected from R^{50} , and wherein the alkylene in Y is optionally substituted with one or more substituents selected from R^{51} .

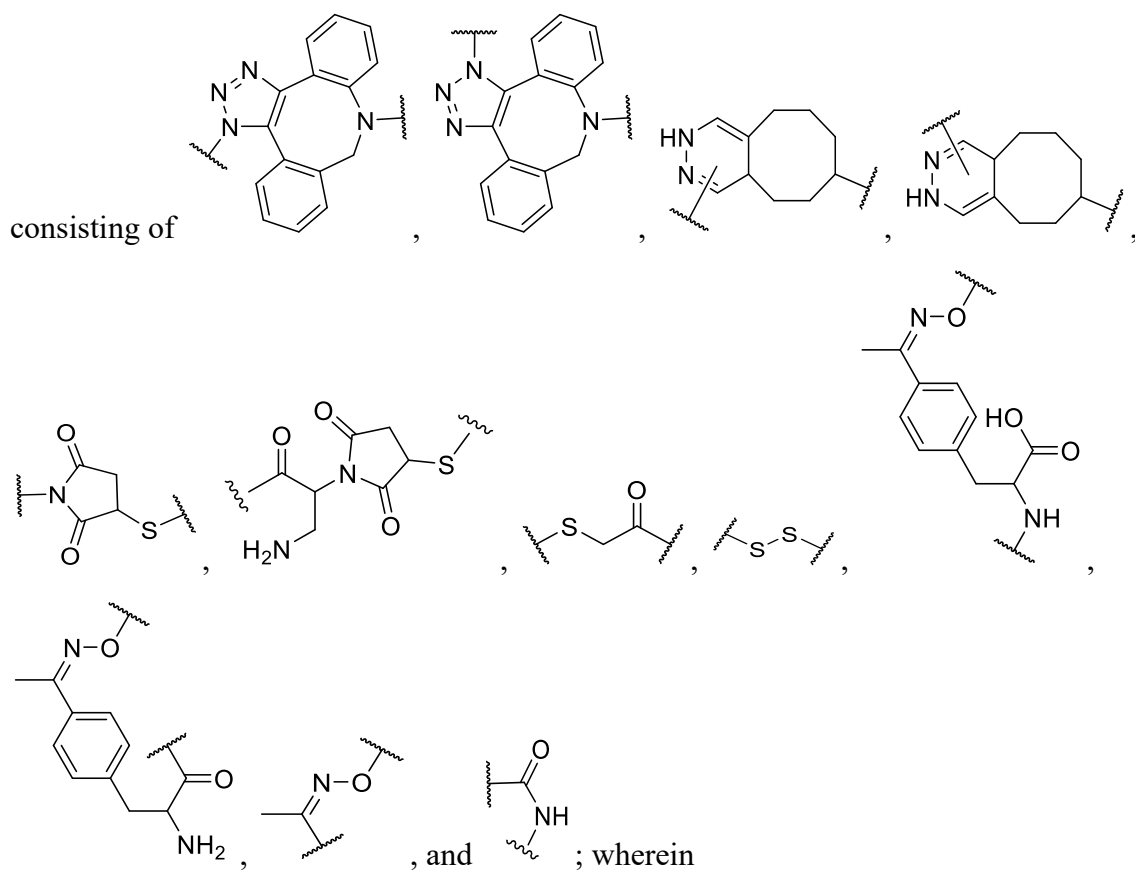
63. The conjugate of any one of claims 49, 54, or 55, wherein Y is $-X^1-C_{1-4}$ alkylene- $[X^1-C_{1-4}$ alkylene] $_n-$, wherein at least one alkylene in Y is substituted with one or more substituents selected from R^{50} , and wherein the alkylene in Y is optionally substituted with one or more substituents selected from R^{51} .

64. The conjugate of claim 63, wherein **Y** is $-\text{X}^1\text{-C}_{1-4}\text{ alkylene-}\text{X}^1\text{-C}_{1-4}\text{ alkylene-}\text{X}^1\text{-C}_{1-4}\text{ alkylene-}$, wherein at least one alkylene in **Y** is substituted with one or more substituents selected from **R**⁵⁰, and wherein the alkylene in **Y** is optionally substituted with one or more substituents selected from **R**⁵¹.
65. The conjugate of any one of the previous claims, wherein **R**⁵¹ is independently selected from halogen, -CN, -NO₂, -OH, -NH₂, -C(O)NH₂, and -C(O)-.
66. The conjugate of any one of claims 49-60, wherein **R**⁵⁰ is $-\text{C}_{1-6}\text{ alkylene-}\text{X}^2\text{-}[\text{C}_{1-6}\text{ alkylene}]_m\text{-POLY}$, wherein each alkylene of **R**⁵⁰ is optionally substituted with one or more substituents selected from halogen, -CN, -NO₂, -OH, -N(**R**¹⁰)₂, -C(O)N(**R**¹⁰)₂, -C(O)-, -C(S)-, -C(O)OCH₂C₆H₅, -NHC(O)OCH₂C₆H₅, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, 3- to 12-membered heterocycle, and C₁₋₁₀ haloalkyl.
67. The conjugate of any one of claims 49-66, wherein **m** is one.
68. The conjugate of any one of claims 49-67, wherein **POLY** is polyethylene glycol (PEG), methoxypolyethylene glycol (mPEG), poly(propylene glycol) (PPG), copolymers of ethylene glycol and propylene glycol, poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharides), poly(α -hydroxy acid), poly(vinyl alcohol), polyphosphazene, polyoxazolines (POZ), poly(*N*-acryloylmorpholine), polysarcosine, or a combination thereof.
69. The conjugate of claim 66, wherein **POLY** comprises a polyethylene glycol (PEG) or methoxypolyethylene glycol (mPEG).



70. The conjugate of any one of claims 49-69, wherein **POLY** is , wherein $\sim_2$ represents attachment to the remainder of the compound, and wherein **n1** is an integer from one to twenty.
71. The conjugate of claim 70, wherein **n1** is an integer between five to fifteen.
72. The conjugate of any one of claims 49-71, wherein **RL** comprises an alkyne, cyclooctyne, a strained alkene, a tetrazine, a thiol, a *para*-acetyl-phenylalanine residue, an oxyamine, amine, a maleimide, or an azide.

73. The conjugate of any one of claims 49-72, wherein **RL** is selected from the group



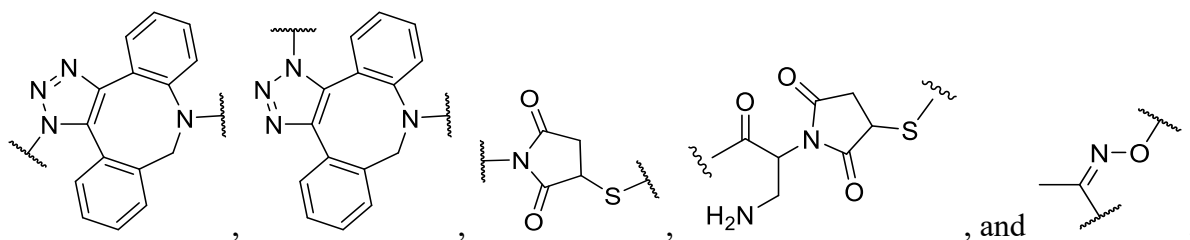
R^T is C₁₋₆ alkyl; and

wavy line represents attachment to the remainder of the compound.

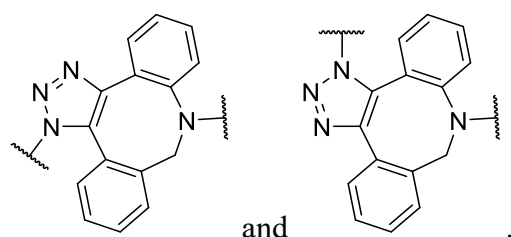
74. The conjugate of any one of claims 49-73, wherein **R^T** is methyl, ethyl, or propyl.

75. The conjugate of any one of claims 49-73, wherein **R^T** is methyl.

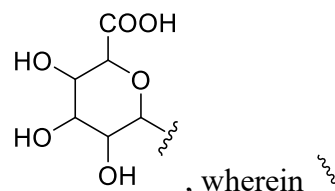
76. The conjugate of claim 73, wherein **RL** is selected from the group consisting of



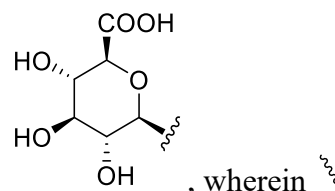
77. The conjugate of claim 76, wherein **RL** is selected from the group consisting of



78. The conjugate of any one of claims 49-76, wherein **Su** is
represents attachment to the remainder of the compound.



79. The conjugate of any one of claims 49-78, wherein **Su** is
represents attachment to the remainder of the compound.



80. The conjugate of any one of the previous claims, wherein **D** is an immunomodulatory payload.

81. The conjugate of claim 80, wherein the immunomodulatory payload is an agonist of stimulator of interferon gene (STING), Toll-like receptor 7 (TLR7), Toll-like receptor 7/8 (TLR7/8), or Toll-like receptor 8 (TLR8).

82. The conjugate of claim 81, wherein the agonist of STING is selected from the group consisting of a small molecule agonist of the STING pathway, an antibody that activates STING activity, a recombinant protein that activates the STING pathway, TTI-10001, DMXAA (ASA404), CDNs, c-di-GMP, 2'3'-cGAMP, MK-1454, ADU-S100 (MIW815), SB11285, ADU-V19, IACS-8779, IACS-8803, IMSA101, non-CDNs, E7766, MK-2118, diABZI, MSA-2, JNJ-6196, bacterial vectors, SYNBI891, and STACT.

83. The conjugate of claim 81, wherein the agonist of Toll-like receptor 7 (TLR7) is selected from the group consisting of GS-986, PRTX-007, PRX-034, S-34240, MBS-8, and APR-002.

84. The conjugate of claim 81, wherein the agonist of Toll-like receptor 7/8 (TLR7/8) is selected from the group consisting of imiquimod (R837), resiquimod (R848), 852-A (PF-4878691), vesatolimod (GS-9620), AZD8848, motolimod (VTX-2337), selgantolimod (GS-9688), NKTR-262, RG-7854 (RO 7020531), DSP-0509, BDB-001, BDC-1001, LHC-165,

SHR-2150, JNJ-4964 (TQ-73334), RO-7119929, DN-1508052, VTX-1463, BNT-411 (SC1), APR-003, ALT-702, TRANSCON, VX-001, SNAPvax, R848-HA, SM360320, and GSK2245035.

85. The conjugate of claim 81, wherein the agonist of Toll-like receptor 8 (TLR8) is selected from the group consisting of SBT-6050, SBT-6290, and ZM-TLR8 agonist.

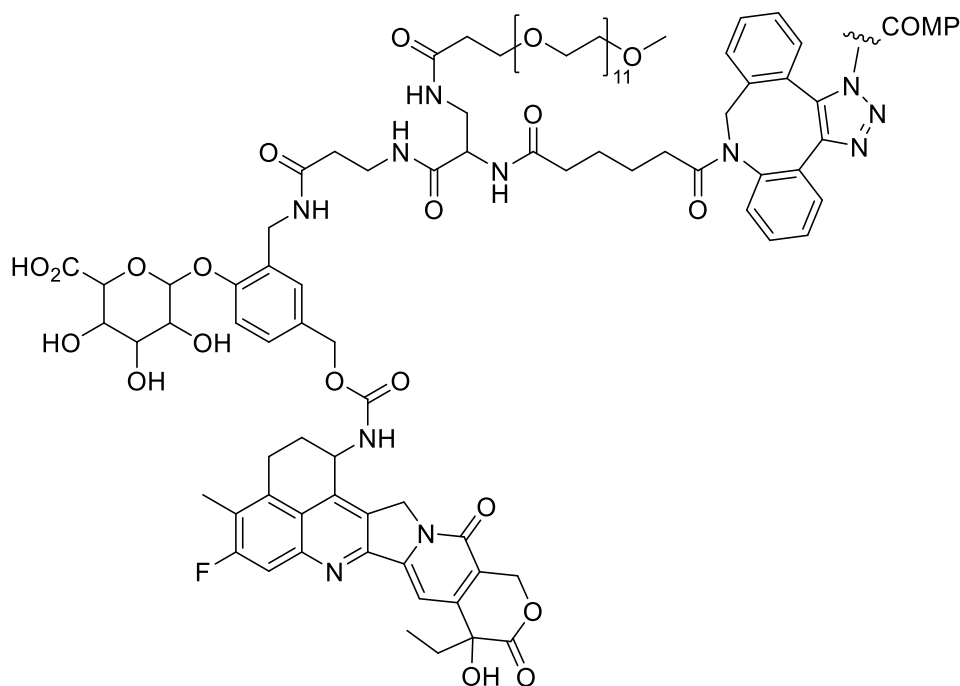
86. The conjugate of any one of claims 49-79, wherein **D** is a cytotoxic payload.

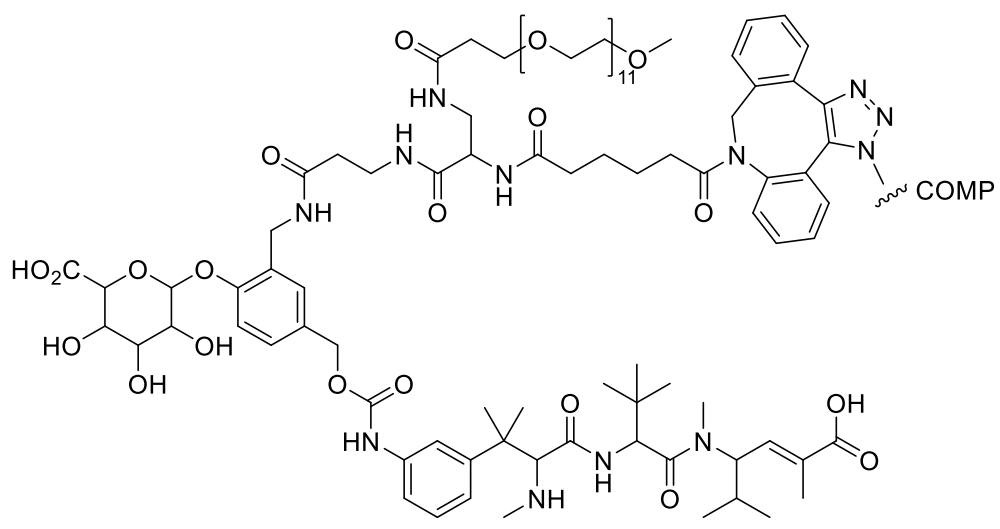
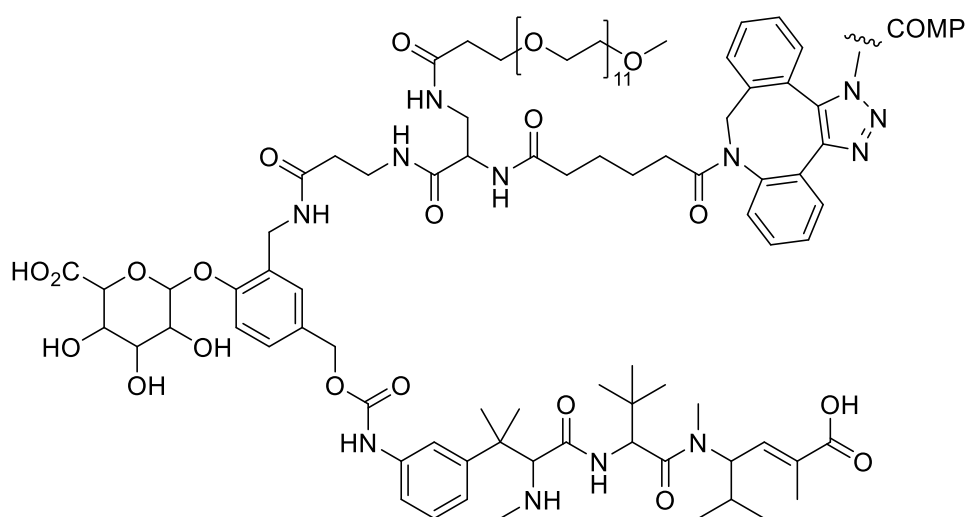
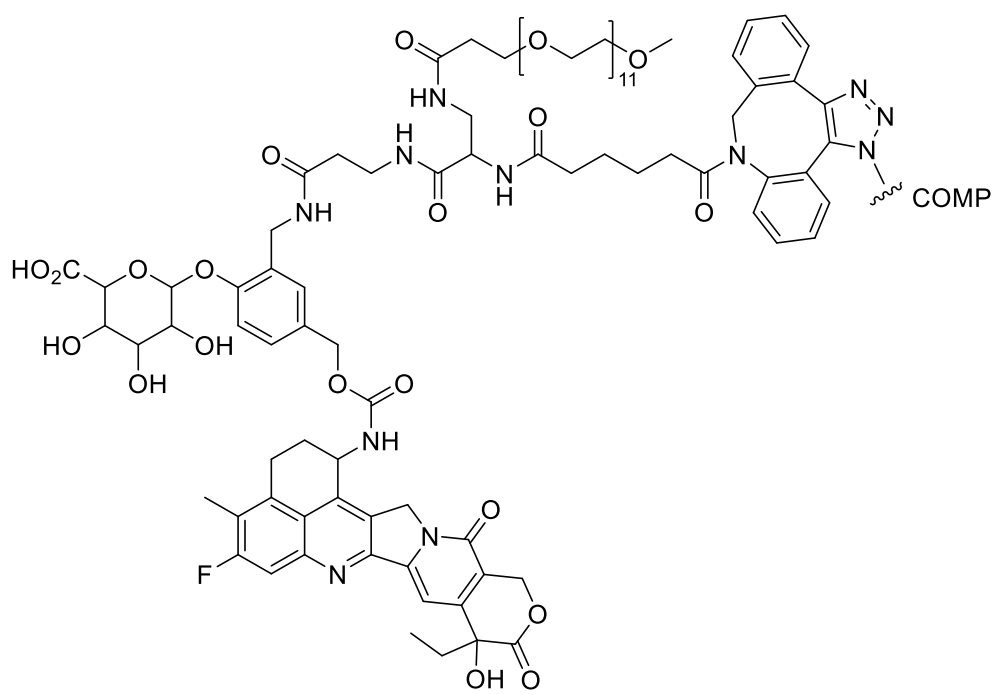
87. The conjugate of claim 86, wherein the cytotoxic payload is a tubulin inhibitor, a DNA topoisomerase I inhibitor, or a DNA topoisomerase II inhibitor.

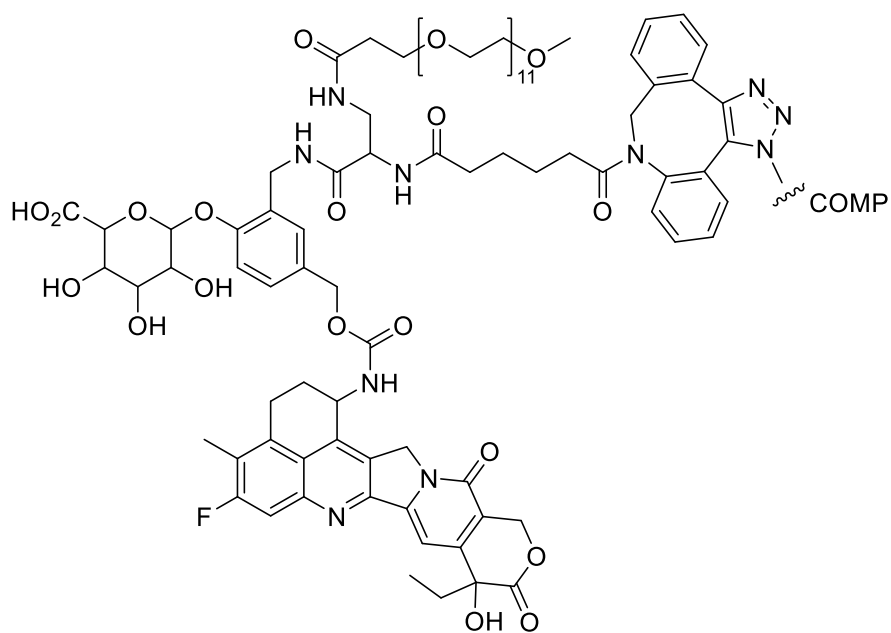
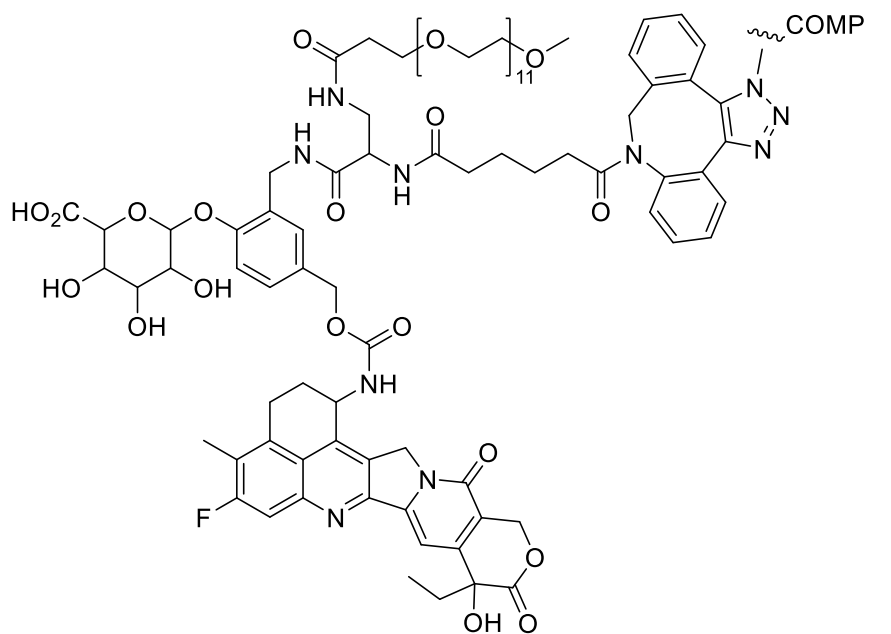
88. The conjugate of any one of claims 49-87, wherein **D** is selected from the group consisting of hemiasterlins, camptothecins, anthracyclines, PNU-159682, and EDA PNU-159682 derivatives.

89. The conjugate of any one of claims 49-88, wherein **D** is hemiasterlin, exatecan, PNU-159682, or EDA PNU-159682 derivatives.

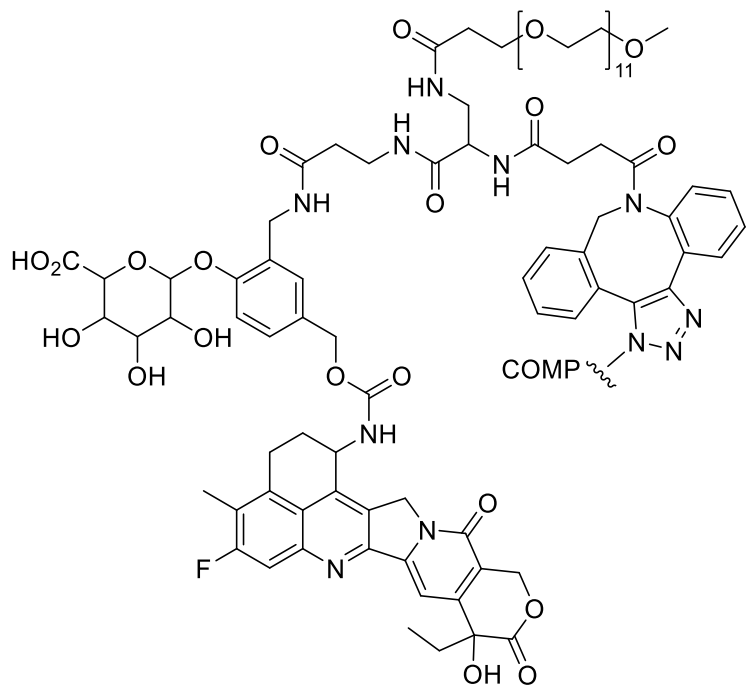
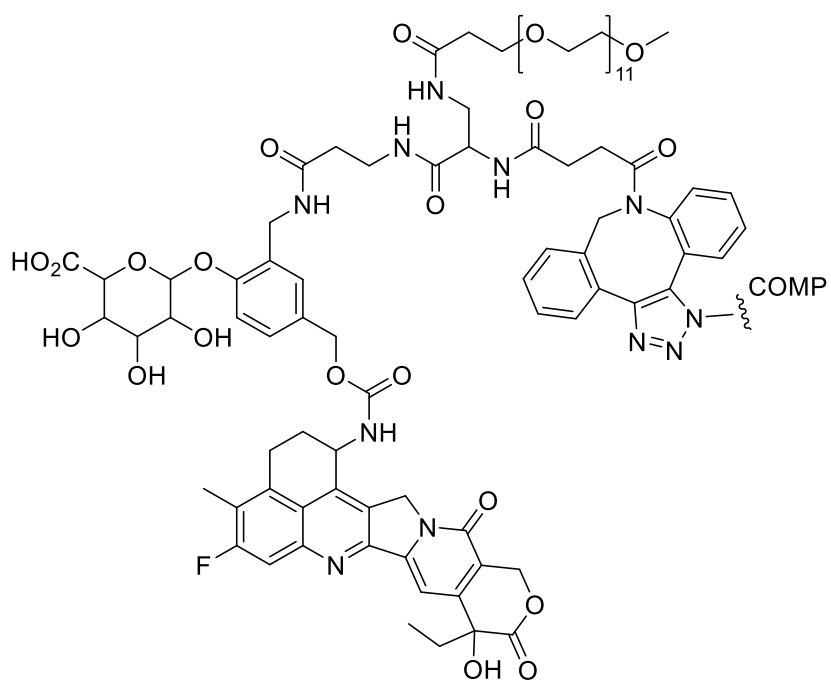
90. The conjugate of any one of claims 49-89, wherein the compound is selected from



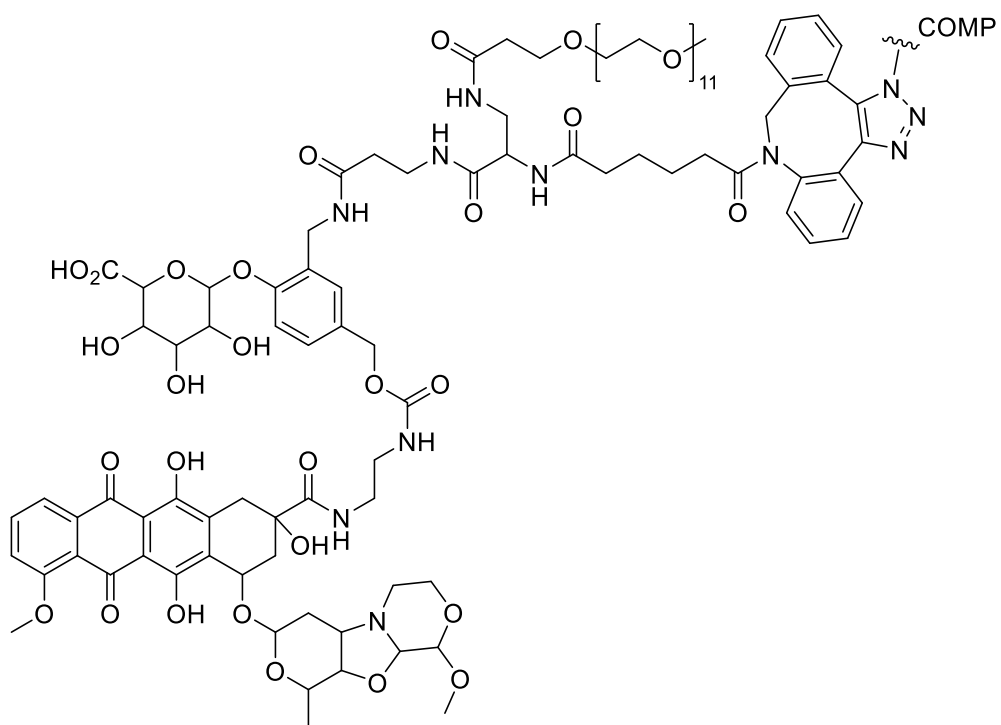




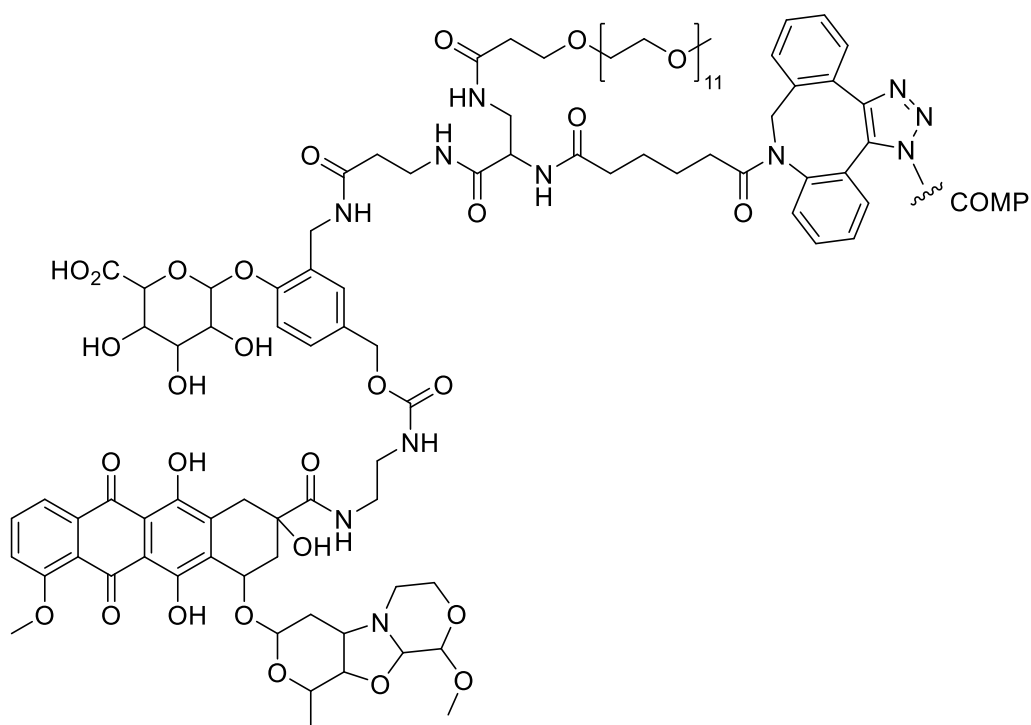
;



;



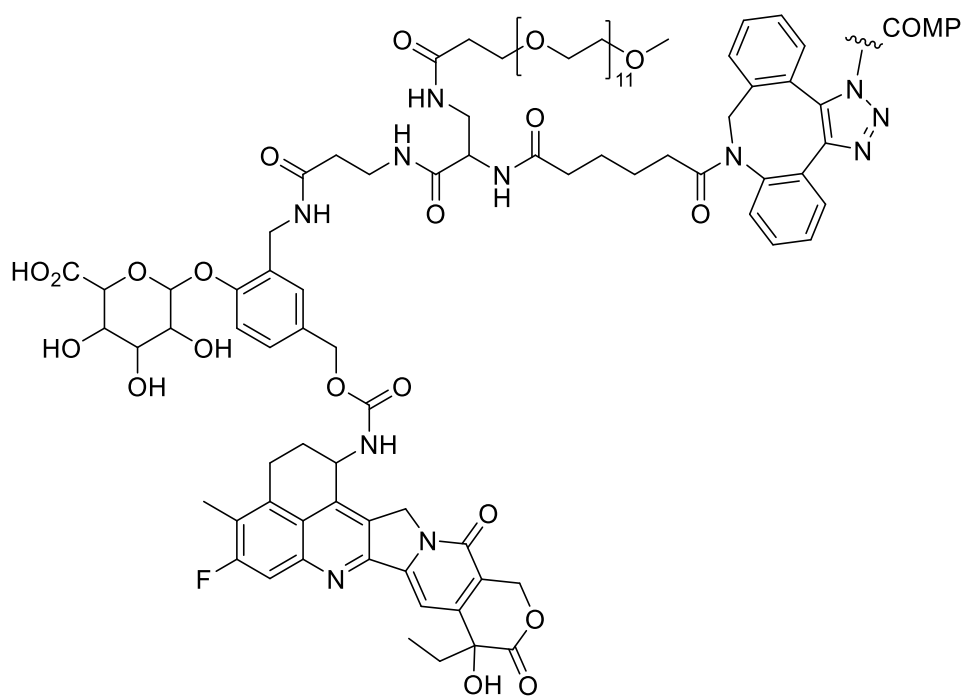
; and



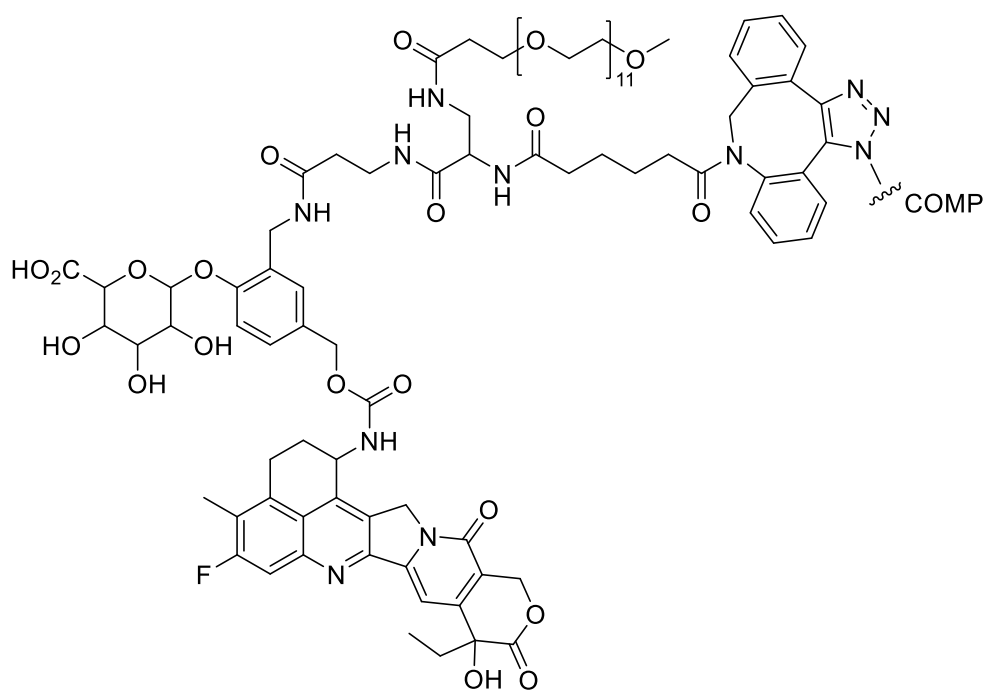
; or

a pharmaceutically acceptable salt of any one thereof, wherein COMP is the residue of the second compound.

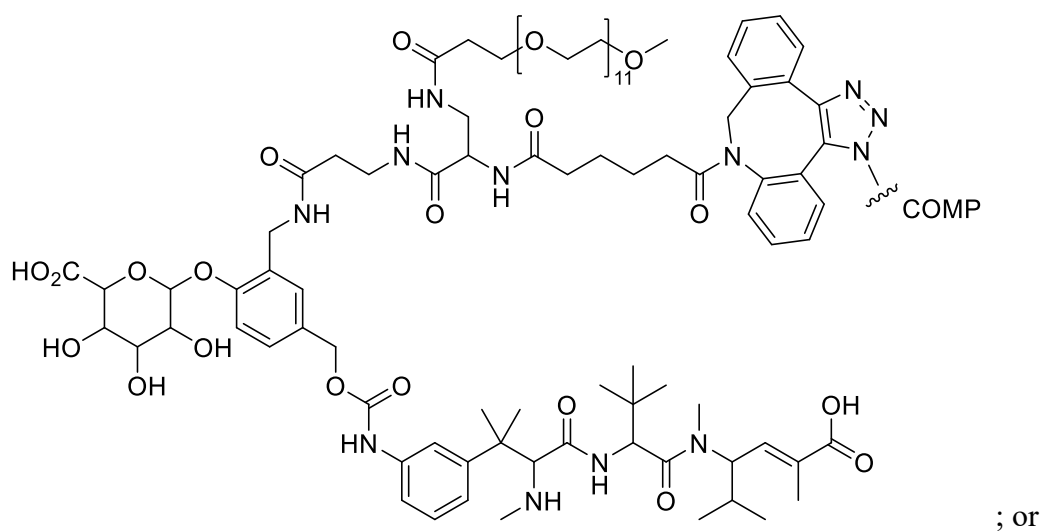
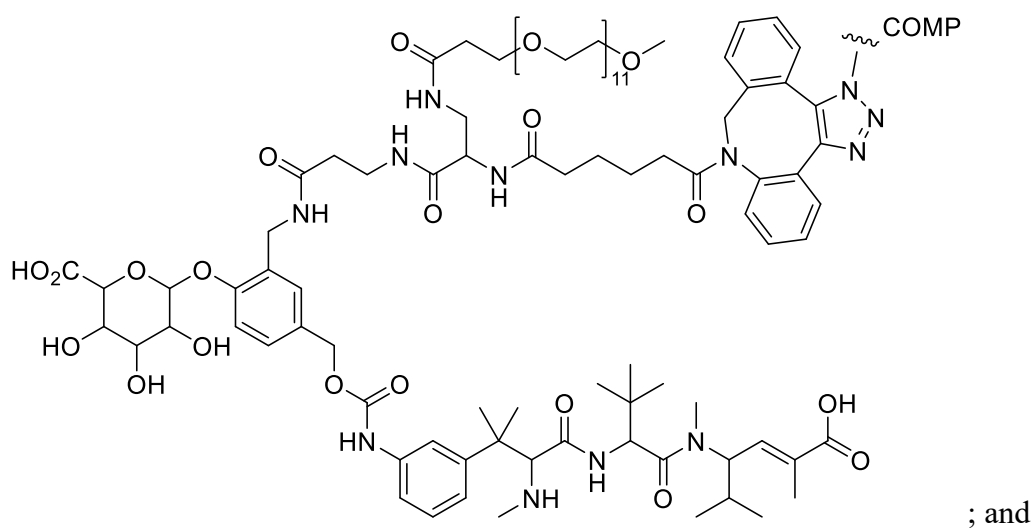
91. The conjugate of any one of claims 50-90, wherein the compound is selected from



;

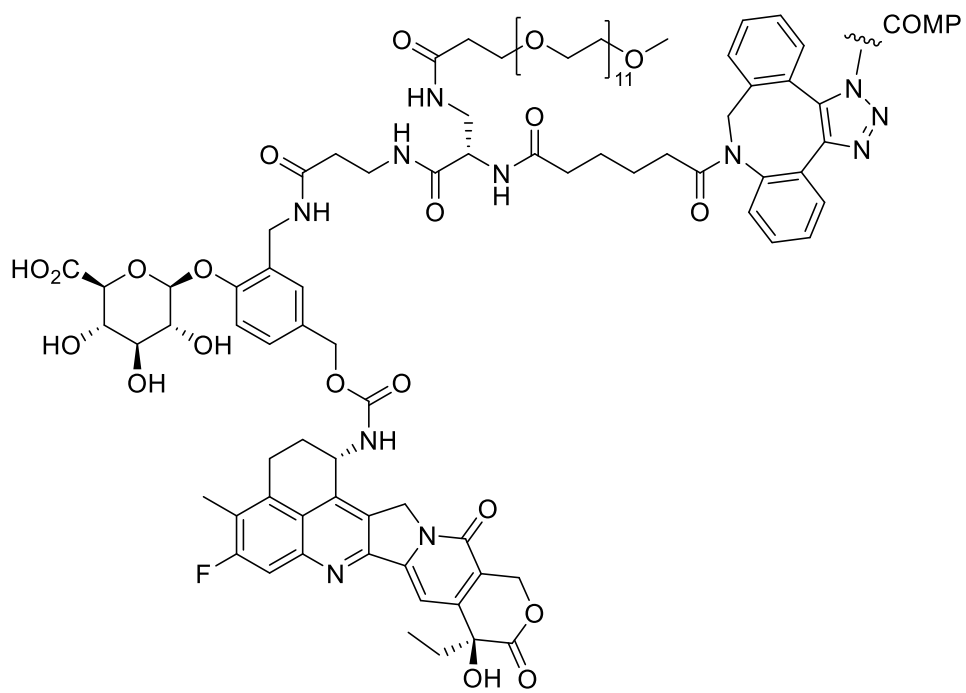


;

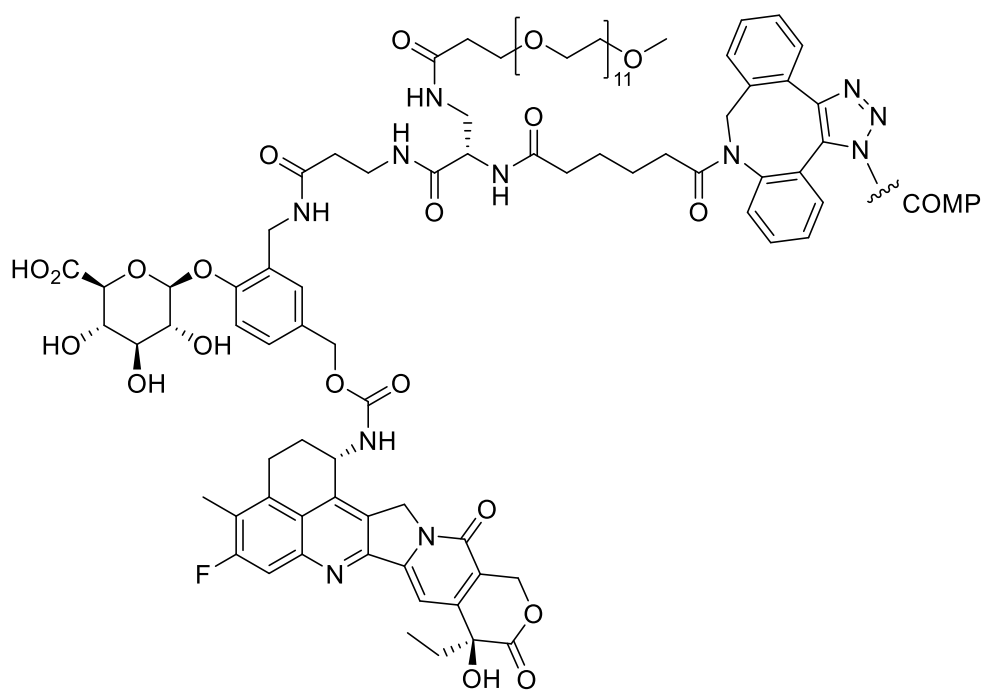


a pharmaceutically acceptable salt of any one thereof, wherein COMP is the residue of the second compound.

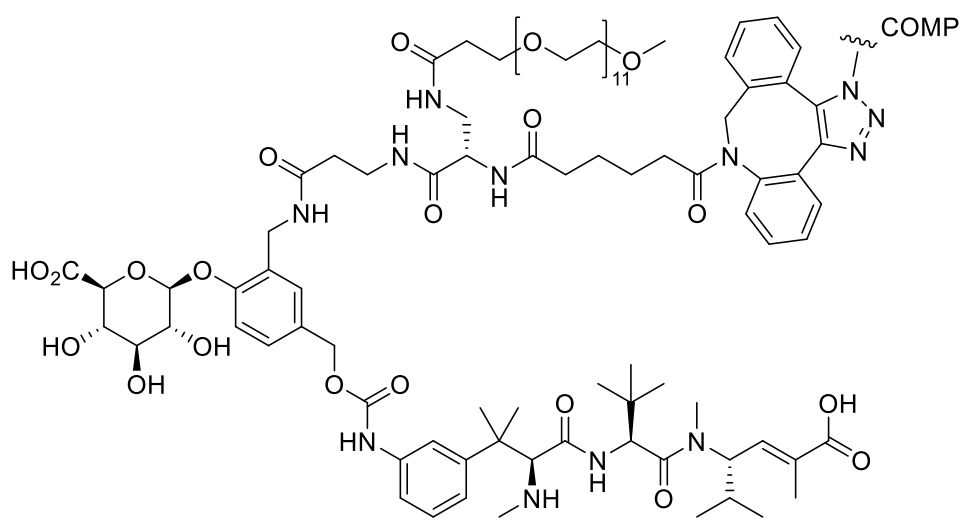
92. The conjugate of any one of claims 50-91, wherein the compound is selected from



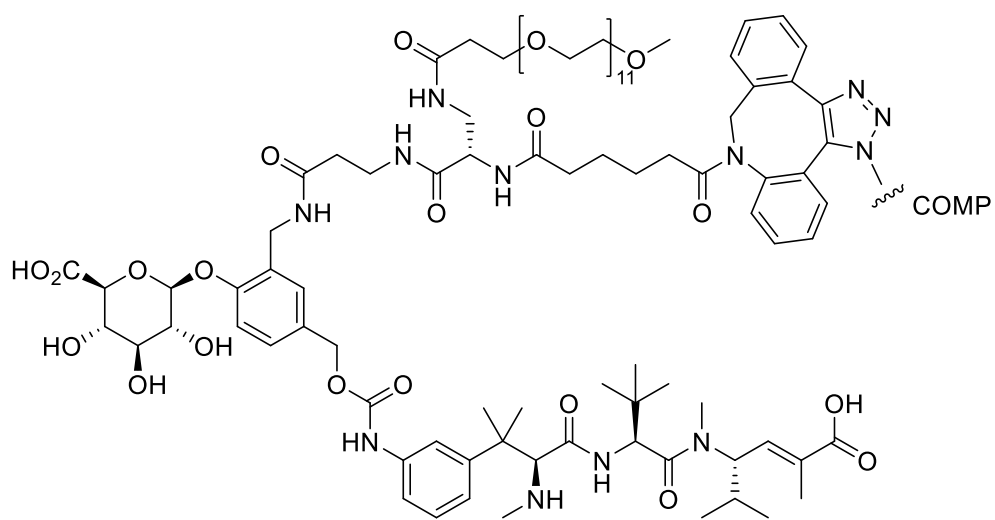
;



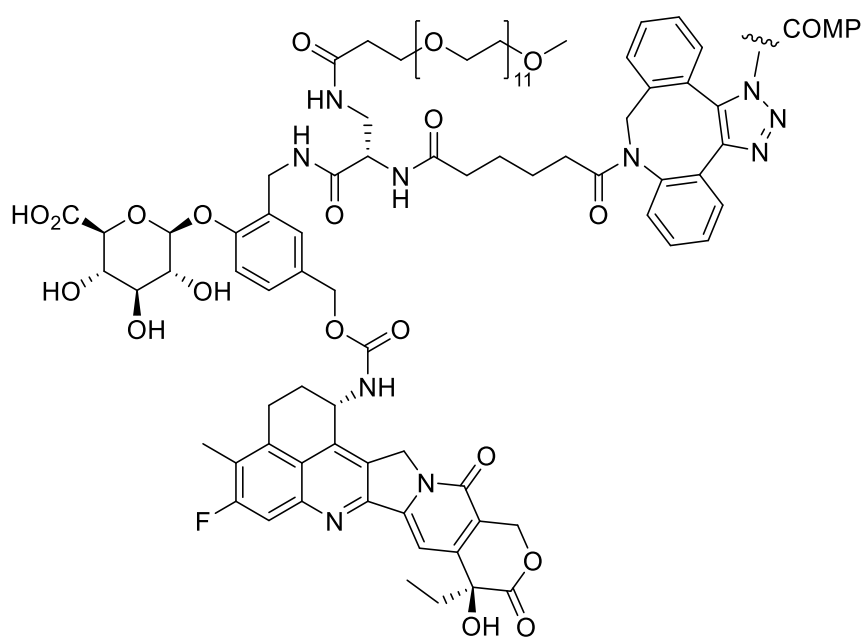
;



;

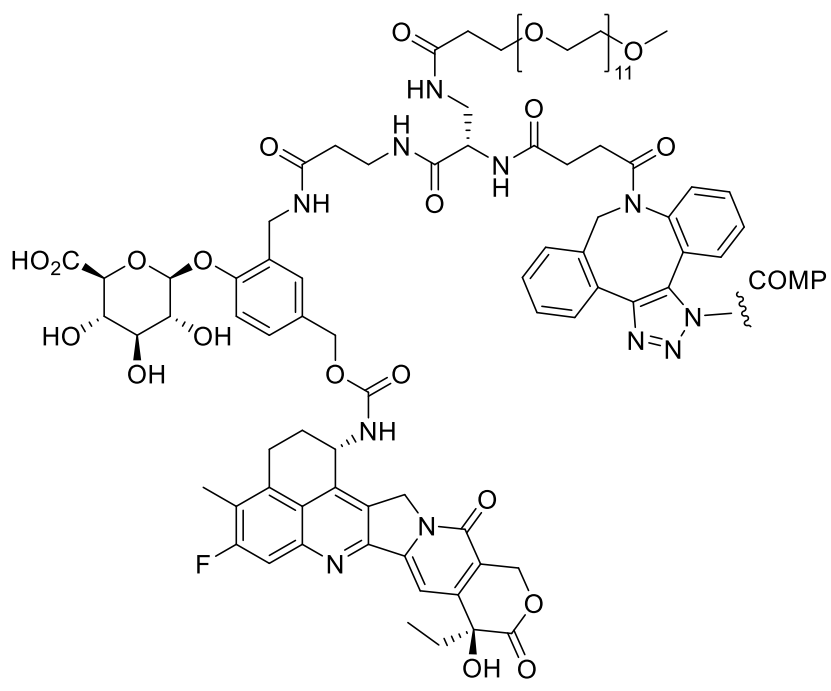
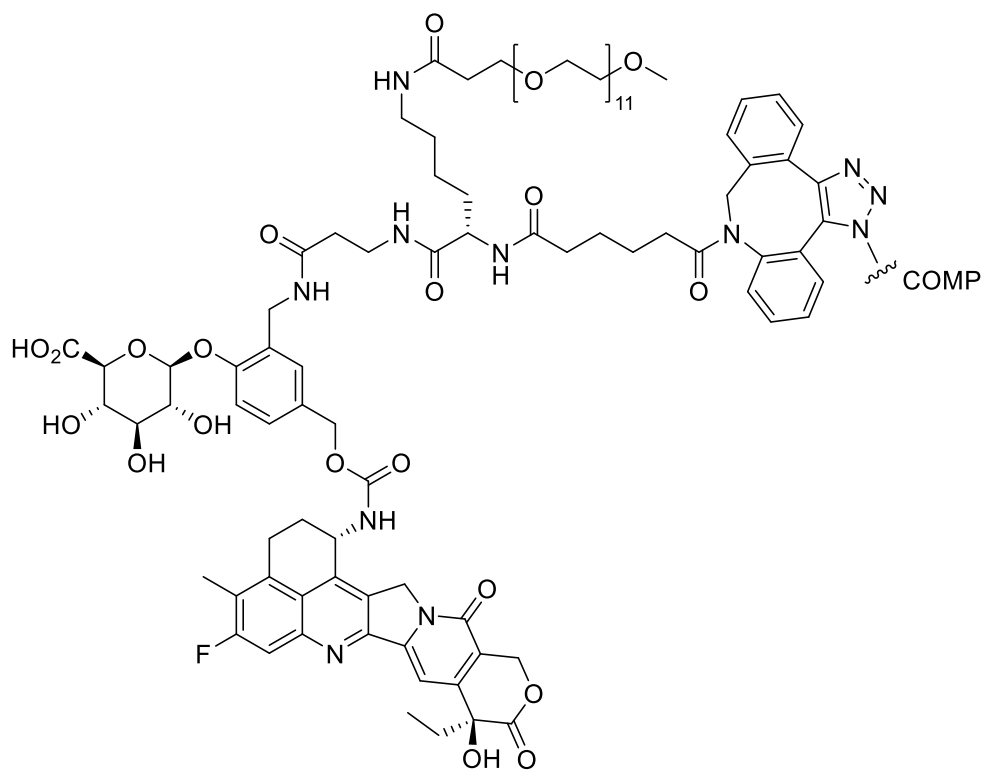


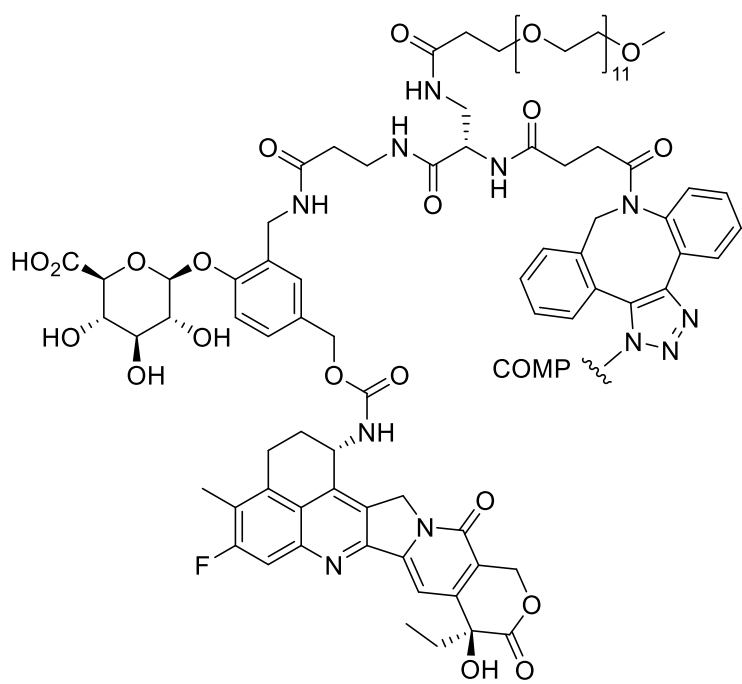
;



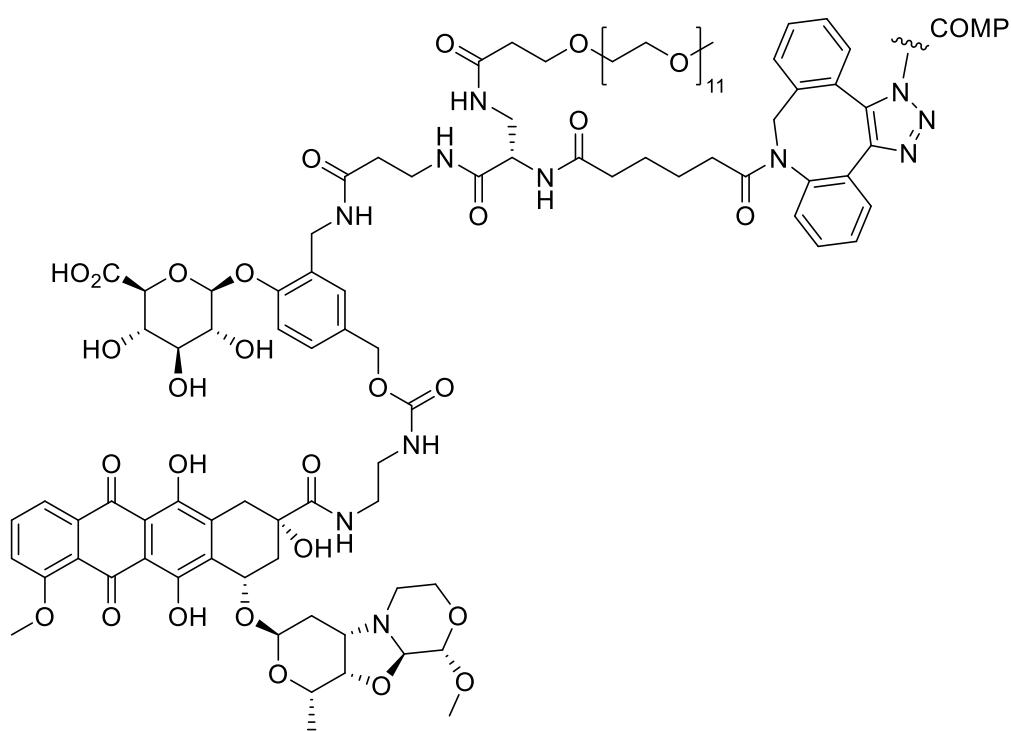
;

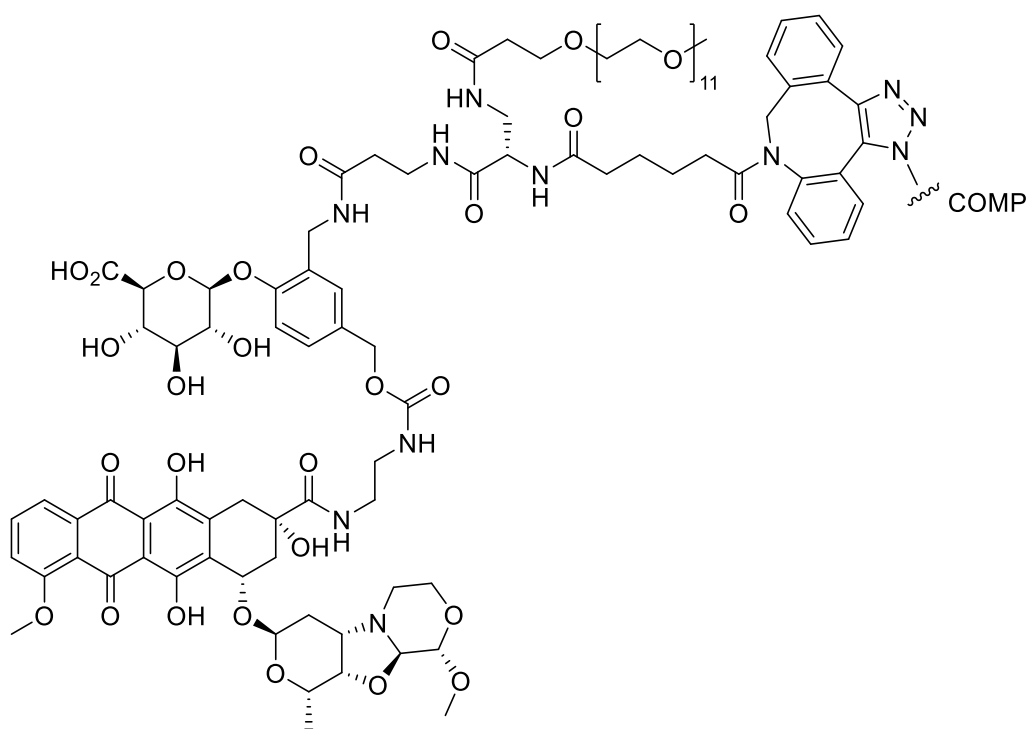






; and



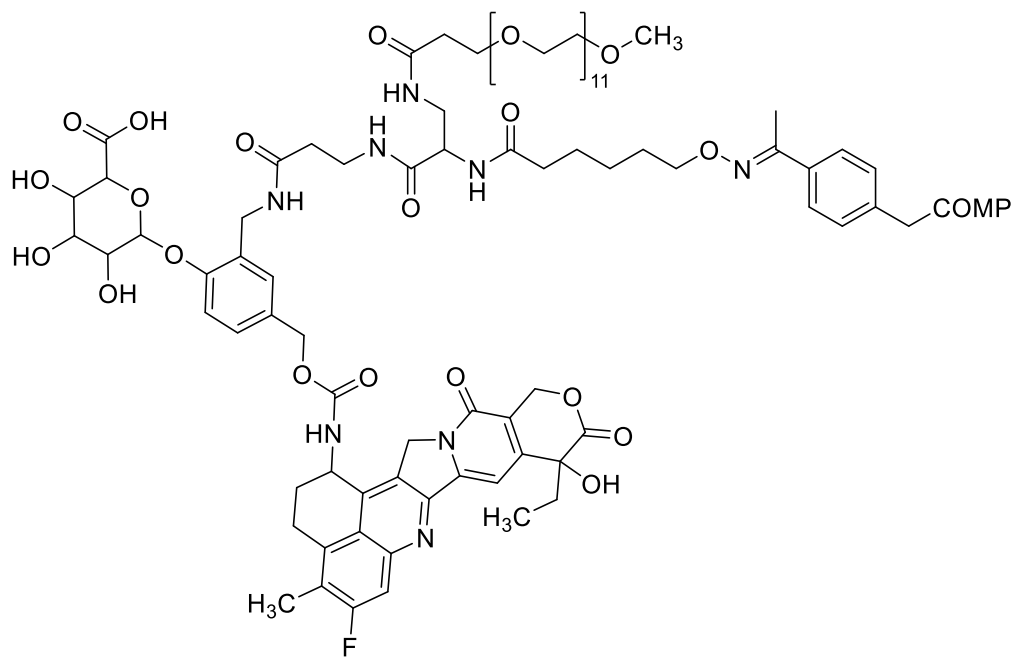
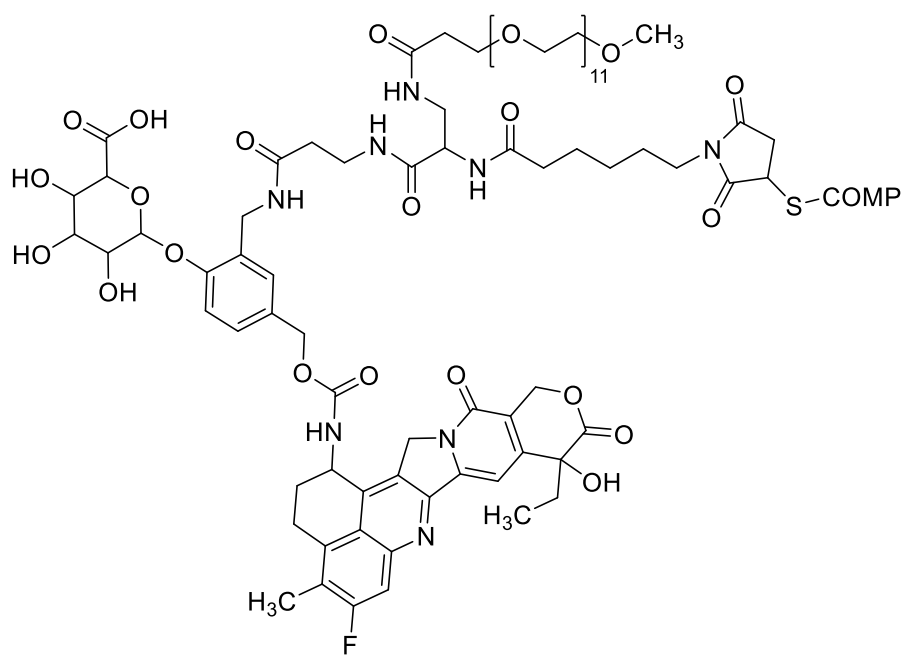


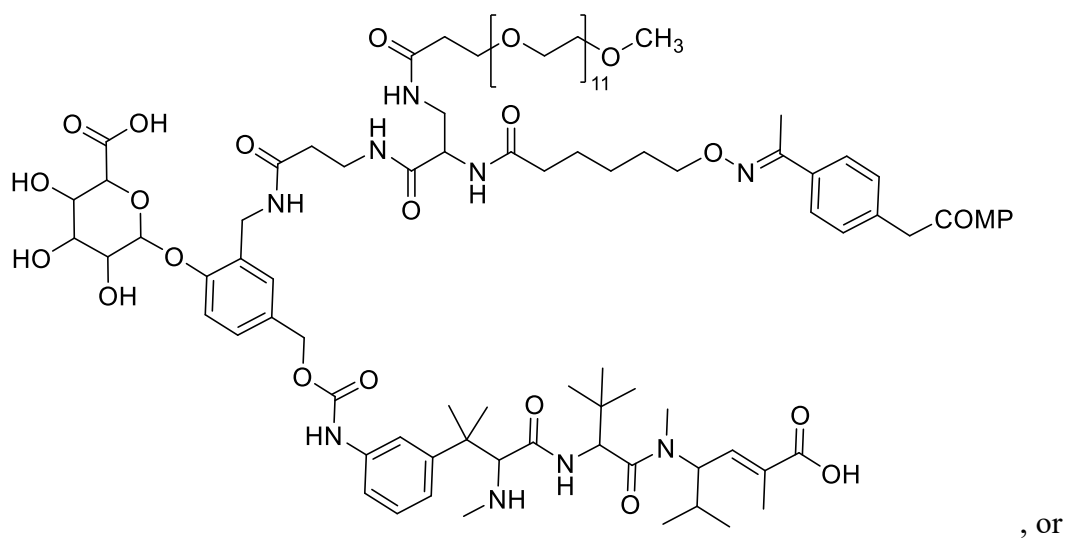
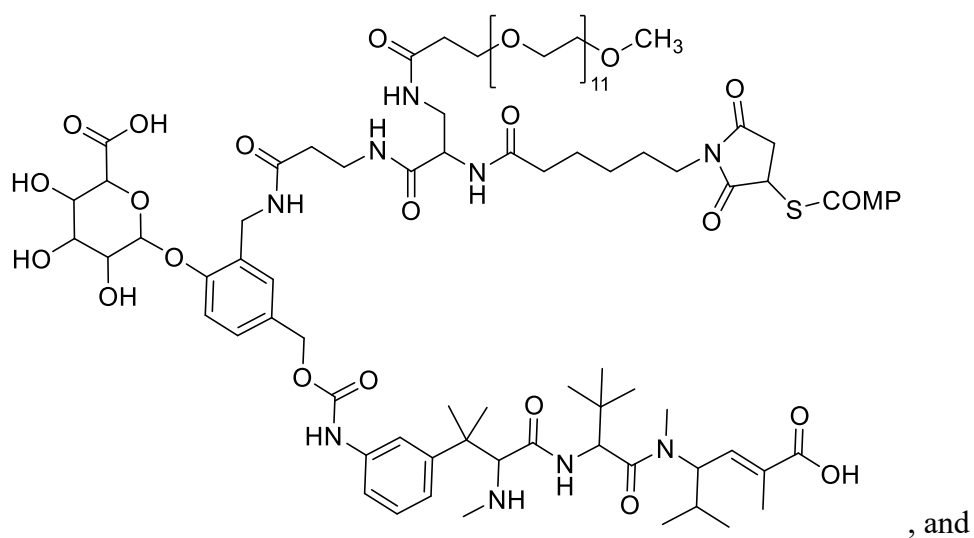
; or

a pharmaceutically acceptable salt of any one thereof,

wherein COMP is the residue of the second compound.

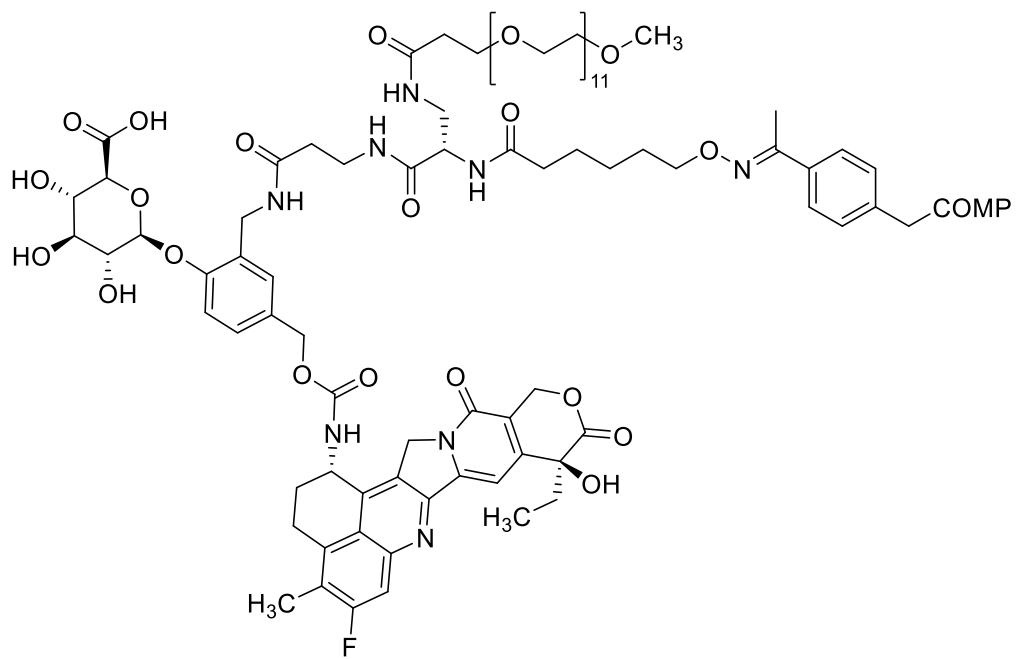
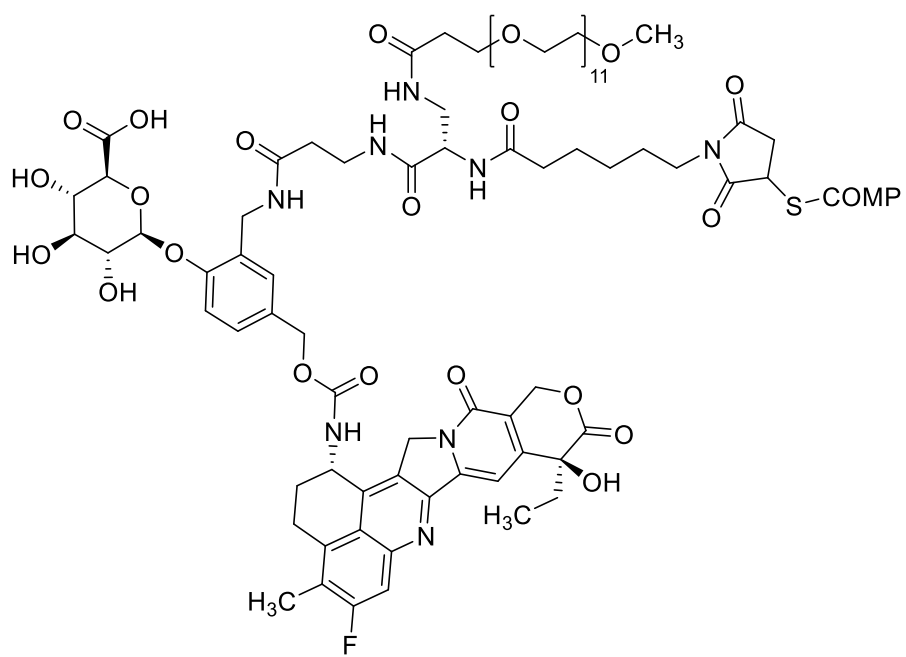
93. The conjugate of any one of claims 49, 51-55, or 61-89, wherein the conjugate is selected from

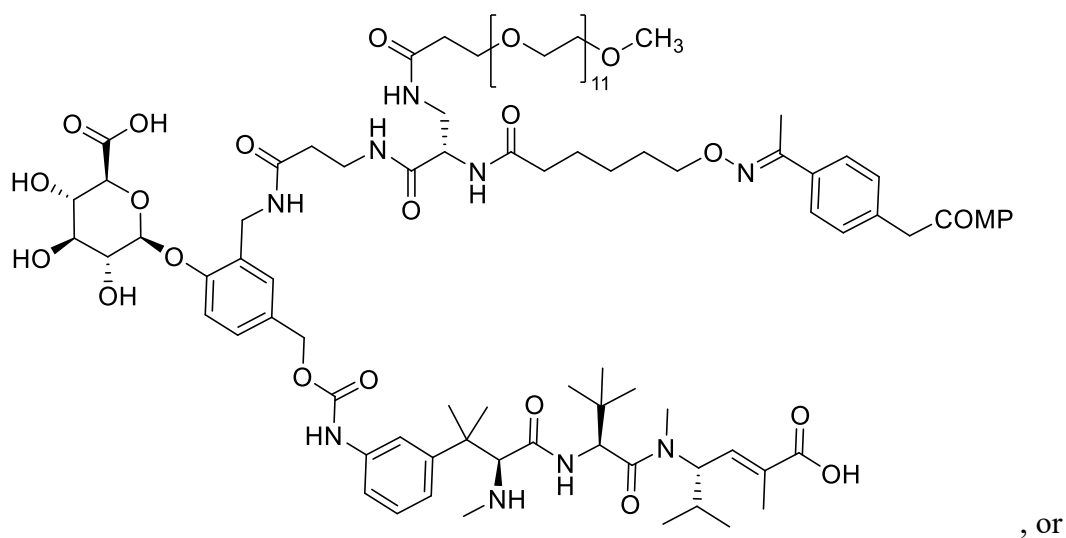
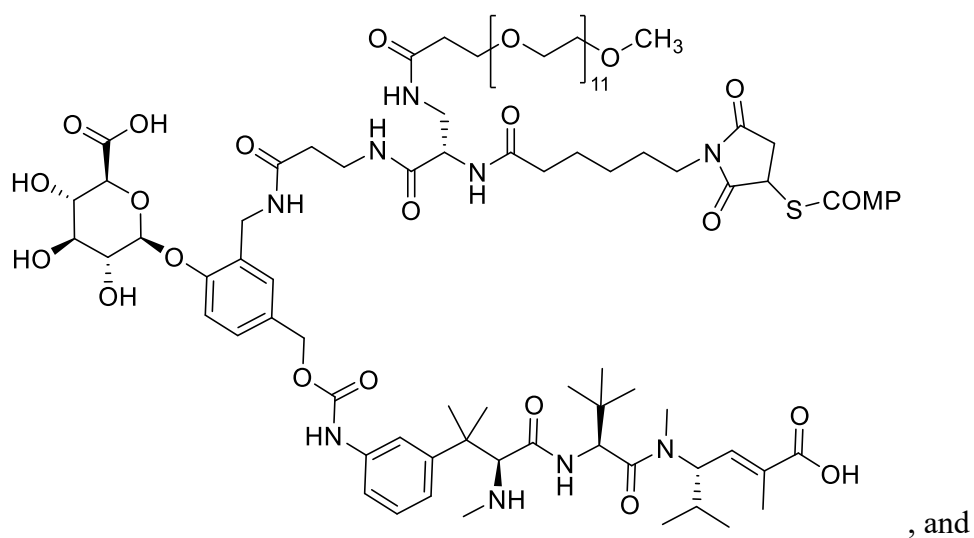




a pharmaceutically acceptable salt of any one thereof,
 wherein **COMP** is the residue of the second compound.

94. The conjugate of any one of claims 49, 51-55, or 61-89, wherein the conjugate is selected from



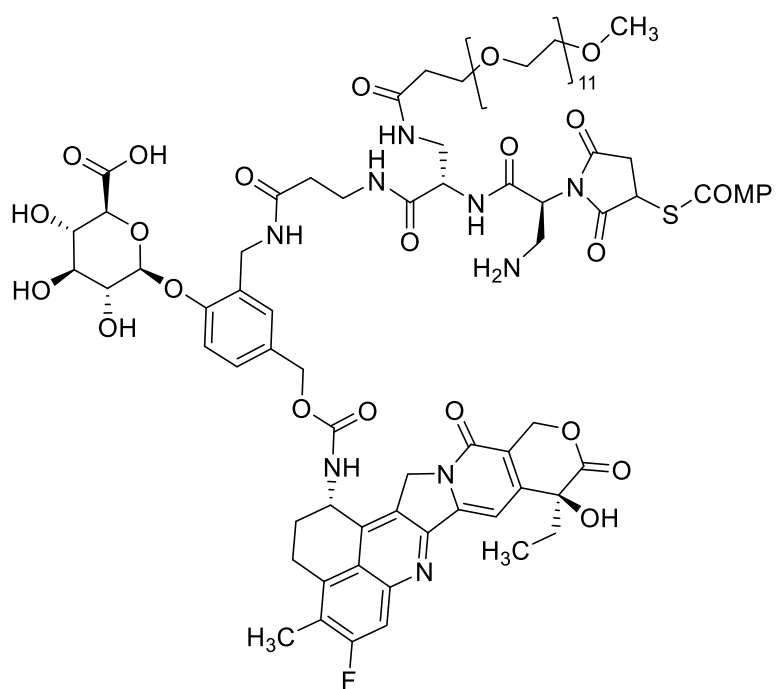


a pharmaceutically acceptable salt of any one thereof,
 wherein **COMP** is the residue of the second compound.

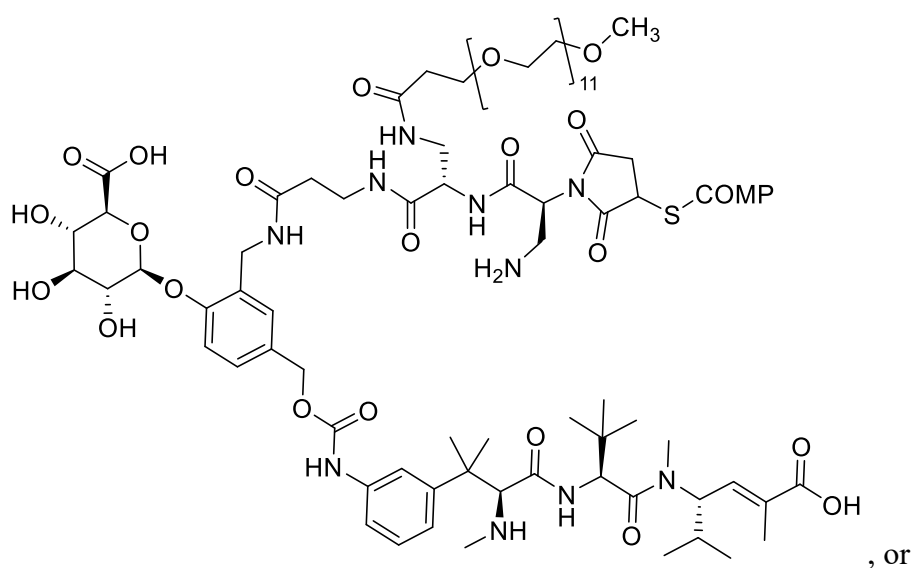
95. The conjugate of any one of claims 49-60 or 66-89, wherein the conjugate is selected from



96. The conjugate of any one of claims 49-60 or 66-89, wherein the conjugate is selected from



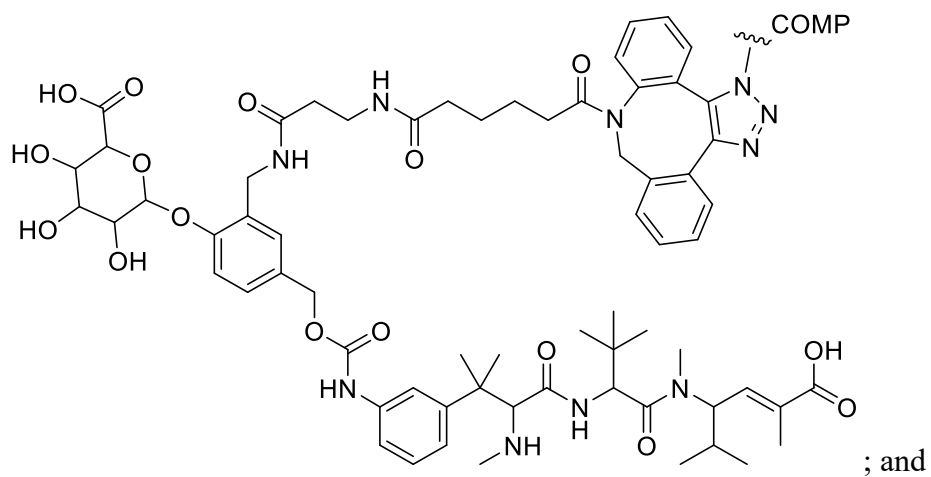
and



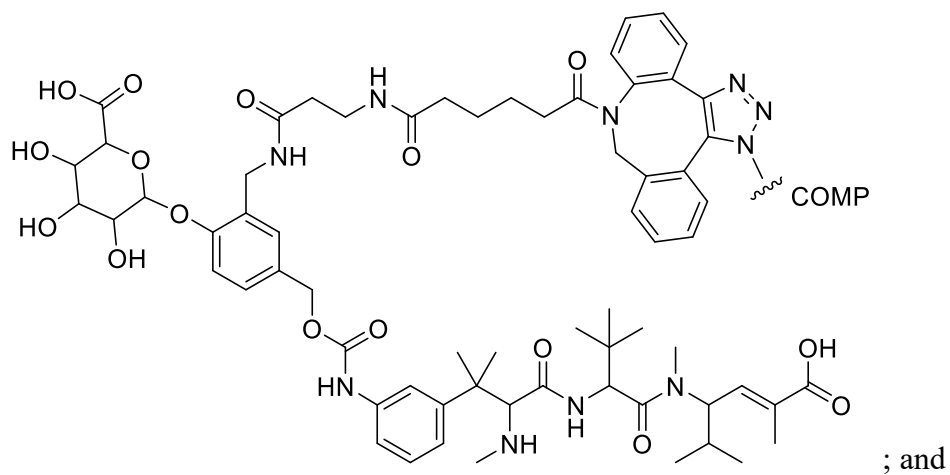
a pharmaceutically acceptable salt of any one thereof,

wherein **COMP** is the residue of the second compound.

97. A conjugate having the following chemical structure



; and

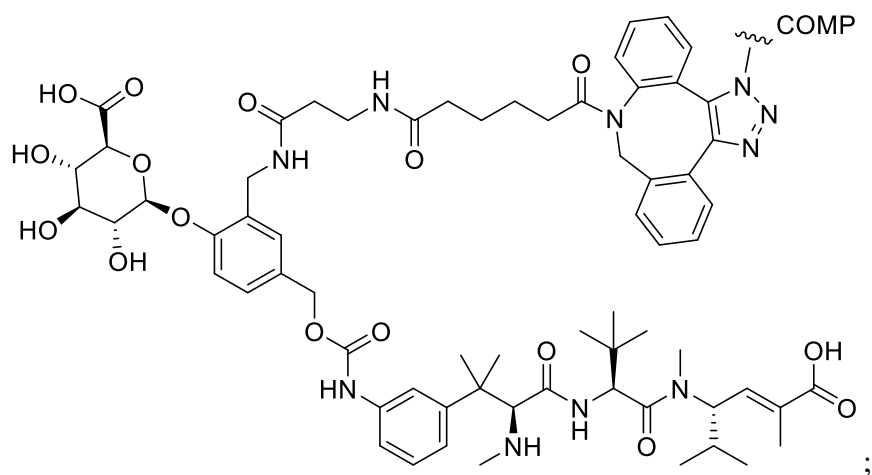


; and

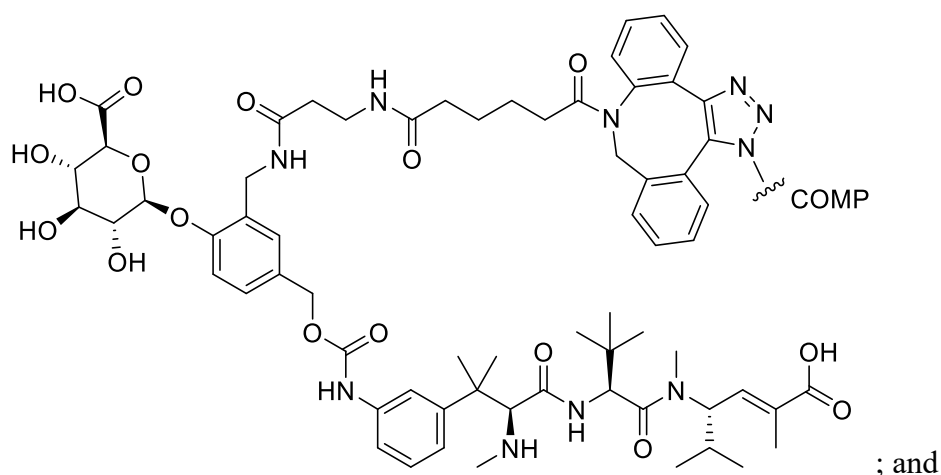
a pharmaceutically acceptable salt of any one thereof,

wherein ^{COMP} is the residue of the second compound.

98. A conjugate having the following chemical structure



;



a pharmaceutically acceptable salt of any one thereof,

wherein COMP is the residue of the second compound.

99. A pharmaceutical composition comprising the compound of any one of claims 1-47 or conjugate of any one of claims 48-98; and a pharmaceutically acceptable excipient, carrier, or diluent.

100. The compound of any one of claims 1-47, the conjugate of any one of claims 48-98, or the pharmaceutical composition of claim 99 for use in therapy.

101. The compound of any one of claims 1-47, the conjugate of any one of claims 48-98, or the pharmaceutical composition of claim 99 for use in the treatment of cancer.

102. The compound of any one of claims 1-47, the conjugate of any one of claims 48-98, or the pharmaceutical composition of claim 99 for use as a medicament.

103. The compound of any one of claims 1-47, the conjugate of any one of claims 48-98, or the pharmaceutical composition of claim 99 for use in inhibiting tubulin polymerization.

104. The compound of any one of claims 1-47, the conjugate of any one of claims 48-98, or the pharmaceutical composition of claim 99 for use in reducing cell proliferation.

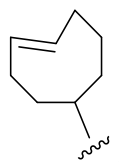
105. Use of the compound of any one of claims 1-47, the conjugate of any one of claims 48-98, or the pharmaceutical composition of claim 99 in the manufacture of a medicament for the treatment of cancer.

106. The compound, conjugate, or pharmaceutical composition for use of claim 101, or the use of claim 105, where the cancer is small cell lung cancer, non-small cell lung cancer, ovarian cancer, platinum-resistant ovarian cancer, ovarian adenocarcinoma, endometrial

cancer, breast cancer, breast cancer which overexpresses Her2, triple-negative breast cancer, a lymphoma, large cell lymphoma; diffuse mixed histiocytic and lymphocytic lymphoma; follicular B cell lymphoma, colon cancer, colon carcinoma, colon adenocarcinoma, colorectal adenocarcinoma, melanoma, prostate cancer, or multiple myeloma.

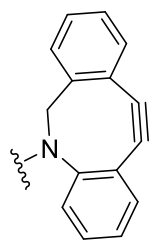
107. A method of producing a conjugate, comprising contacting the compound of any of claims 1-47 with a second compound under conditions suitable for conjugating the compound of any of claims 1-47 with the second compound; wherein the second compound comprises an alkyne, cyclooctyne strained alkene, tetrazine, methylcyclopropene, thiol, maleimide, carbonyl, amine, oxyamine, or azide.

108. The method of claim 107, wherein the second compound comprises a tetrazine; and **RL** comprises a strained alkene.



109. The method of claim 107 or 108, wherein **RL** is

110. The method of claim 107, wherein the second compound comprises an azide; and **RL** comprises an alkyne.

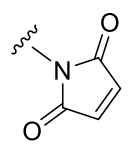


111. The method of claim 107 or 110, wherein **RL** is

112. The method of claim 107, wherein the second compound comprises an alkyne; and **RL** comprises an azide.

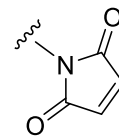
113. The method of claim 107, wherein the second compound comprises a strained alkene; and **RL** comprises a tetrazine.

114. The method of claim 107, wherein the second compound comprises a thiol; and **RL** comprises a maleimide.



115. The method of claim 107 or 114, wherein **RL** is

116. The method of claim 107, wherein the second compound comprises a maleimide; and **RL** comprises a thiol.

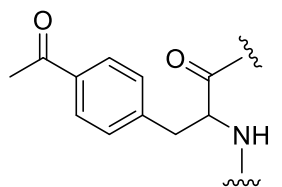


117. The method of claim 107 or 116, wherein the second compound comprises

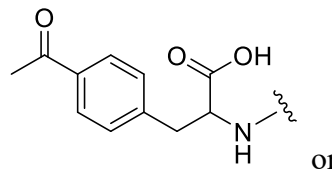
118. The method of claim 107, wherein the second compound comprises a carbonyl; and **RL** comprises an oxyamine.

119. The method of claim 107 or 118, wherein **RL** is $\text{H}_2\text{N}-\text{O}-$.

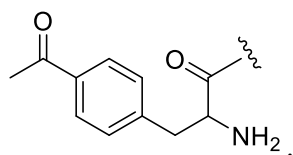
120. The method of claim 107, 118, or 119, wherein second compound comprises



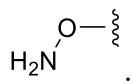
121. The method of claim 107, wherein the second compound comprises an oxyamine; and **RL** comprises a carbonyl.



122. The method of claim 107 or 121, wherein **RL** is



123. The method of claim 107, 121, or 122, wherein the second compound comprises



124. The method of any of claims 107-123, wherein the second compound is a polypeptide.

125. The method of any of claims 107-123, wherein the second compound is an antibody.

126. The method of any of claims 107-123, wherein the second compound is an antibody chain.