CONJUGATES AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of:

U.S. Provisional Patent Application No. 63/503,387 filed on May 19, 2023;

U.S. Provisional Patent Application No. 63/535,991 filed on August 31, 2023;

U.S. Provisional Patent Application No. 63/606,521 filed on December 05, 2023; and

U.S. Provisional Patent Application No. 63/558,052 filed on February 26, 2024;

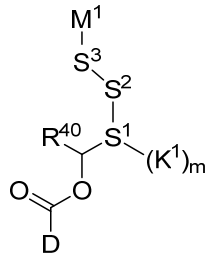
the entire contents of each of which are incorporated herein by reference.

BACKGROUND

[0002] Currently, small cytotoxic molecules for antibody drug conjugates can include camptothecin derivatives, which have antitumor effects by inhibiting topoisomerase I. Camptothecin derivatives can be used in antibody drug conjugates (ADC). However, there is still a need for further development of camptothecin derivatives and ADC drugs with better efficacy and/or safety.

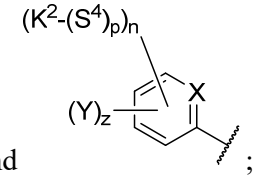
SUMMARY OF THE INVENTION

[0003] In an aspect, the present disclosure provides a Drug-Linker of Formula (X):



Formula (X)

or a pharmaceutically acceptable salt thereof, wherein;

R^{40} is independently selected from hydrogen, Y, and ;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

z is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–;

wherein the optional substituents on M^1, K^1, K^2, S^1, S^2, S^3, and S^4 are independently selected at each occurrence from:

(i) halogen, -OR^{30}, -$N(R^{30})_2$, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -$S(O)_2OR^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, and -CN;

(ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{30}, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -$S(O)_2OR^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle; and

(iii) C_{3-10} carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{30}, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

M^1 is a group which can react with a ligand to form a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, or –$P(O)(R^{20})_2$–;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, or –$P(O)(R^{20})_2$–;

(iii) an oligosaccharide; and

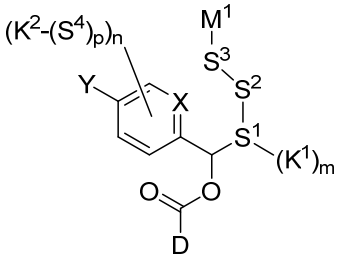
(iv) a polyether;

each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -NO_2, -NH_2, -

$N(C_{1-6}\,alkyl)_2$, C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -NO_2, -NH_2, -$N(C_{1-6}\,alkyl)_2$, C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle.

[0004] In an aspect, the present disclosure provides a Drug-Linker of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, 5- to 6-membered heterocyclene, or –$P(O)(R^{20})_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, or –$P(O)(R^{20})_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino

acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, or $–P(O)(R^{20})_2–$; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$;

wherein the optional substituents on M^1, K^1, K^2, S^1, S^2, S^3, and S^4, are independently selected at each occurrence from:

(i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN;

(ii) $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, $C_{3\text{-}10}$ carbocycle and 3- to 10-membered heterocycle; and

(iii) $C_{3\text{-}10}$ carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, and $C_{2\text{-}6}$ alkynyl;

M^1 is a group which can react with a ligand to form a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, or $–P(O)(R^{20})_2$;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, or $–P(O)(R^{20})_2$;

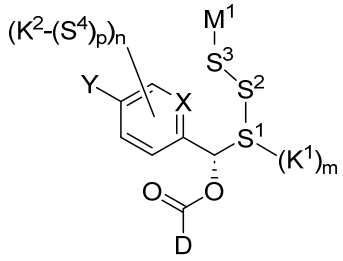
(iii) an oligosaccharide; and

(iv) a polyether;

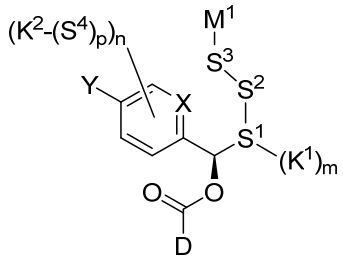
each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle.

[0005] In an aspect, the present disclosure provides a Drug-Linker of Formula (Ia) or Formula (Ib):



Formula (Ia),



Formula (Ib),

or a pharmaceutically acceptable salt of any one thereof, wherein;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino

acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$;

wherein the optional substituents on M^1, K^1, K^2, S^1, S^2, S^3, and S^4, are independently selected at each occurrence from:

(i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN;

(ii) $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, $C_{3\text{-}10}$ carbocycle and 3- to 10-membered heterocycle; and

(iii) $C_{3\text{-}10}$ carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, and $C_{2\text{-}6}$ alkynyl;

M^1 is a group which can react with a ligand to form a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, or $–P(O)(R^{20})_2$;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from: (i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2$;

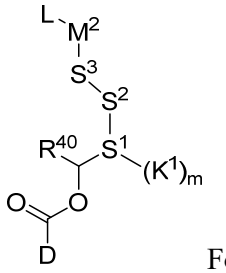
(iii) an oligosaccharide; and

(iv) a polyether;

each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

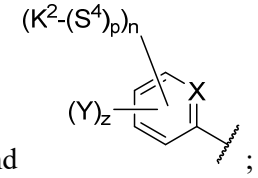
each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle.

[0006] In an aspect, the present disclosure provides a conjugate of the Formula (XX):



Formula (XX)

or a pharmaceutically acceptable salt thereof, wherein;



R^{40} is independently selected from hydrogen, Y, and ;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

z is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–;

wherein the optional substituents on M^2, K^1, K^2, S^1, S^2, S^3, and S^4 are independently selected at each occurrence from:

(i) halogen, -OR^{30}, -N(R^{30})$_2$, -SR^{30}, -N(R^{30})$_2$, -C(O)R^{30}, -C(O)N(R^{30})$_2$, -N(R^{30})C(O)R^{30}, -C(O)OR^{30}, -OC(O)R^{30}, -S(O)R^{30}, -S(O)$_2$$R^{30}$, -O-S(O)$_2OR^{30}$, -P(O)(O$R^{30}$)$_2$, -OP(O)(O$R^{30}$)$_2$, -NO$_2$, =O, =S, =N($R^{30}$), and -CN;

(ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle; and

(iii) C_{3-10} carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

L is a Targeting Unit;

M^2 is a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

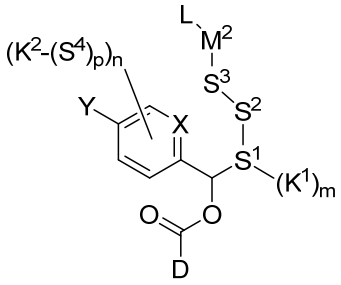
(iii) an oligosaccharide; and

(iv) a polyether;

each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle.

[0007] In an aspect, the present disclosure provides a conjugate of the Formula (A):



Formula (A)

or a pharmaceutically acceptable salt thereof, wherein;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

X is selected from CH and N;

Y is a $-O-T^1$ and $-NH-T^2$;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –

C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C$_3$-C$_{30}$ alkenylene, wherein one or more alkenylene units of the C$_3$-C$_{30}$ alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C$_3$-C$_{10}$ carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C$_1$-C$_{30}$ alkylene wherein one or more alkylene units of the C$_1$-C$_{30}$ alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–;

wherein the optional substituents on M^2, K^1, K^2, S^1, S^2, S^3, and S^4, are independently selected at each occurrence from:

(i) halogen, -OR^{30}, -N(R^{30})$_2$, -SR^{30}, -N(R^{30})$_2$, -C(O)R^{30}, -C(O)N(R^{30})$_2$, -N(R^{30})C(O)R^{30}, -C(O)OR^{30}, -OC(O)R^{30}, -S(O)R^{30}, -S(O)$_2$R^{30}, -O-S(O)$_2$OR^{30}, -P(O)(OR^{30})$_2$, -OP(O)(OR^{30})$_2$, -NO$_2$, =O, =S, =N(R^{30}), and -CN;

(ii) C$_{1\text{-}10}$ alkyl, C$_{2\text{-}10}$ alkenyl, C$_{2\text{-}10}$ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{30}, -SR^{30}, -N(R^{30})$_2$, -C(O)R^{30}, -C(O)N(R^{30})$_2$, -N(R^{30})C(O)R^{30}, -C(O)OR^{30}, -OC(O)R^{30}, -S(O)R^{30}, -S(O)$_2$R^{30}, -O-S(O)$_2$OR^{30}, -P(O)(OR^{30})$_2$, -OP(O)(OR^{30})$_2$, -NO$_2$, =O, =S, =N(R^{30}), -CN, C$_{3\text{-}10}$ carbocycle and 3- to 10-membered heterocycle; and

(iii) C$_{3\text{-}10}$ carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{30}, -SR^{30}, -N(R^{30})$_2$, -C(O)R^{30}, -C(O)N(R^{30})$_2$, -N(R^{30})C(O)R^{30}, -C(O)OR^{30}, -OC(O)R^{30}, -S(O)R^{30}, -S(O)$_2$R^{30}, -P(O)(OR^{30})$_2$, -OP(O)(OR^{30})$_2$, -NO$_2$, =O, =S, =N(R^{30}), -CN, C$_{1\text{-}6}$ alkyl, C$_{2\text{-}6}$ alkenyl, and C$_{2\text{-}6}$ alkynyl;

L is a Targeting Unit;

M^2 is a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C$_1$-C$_{30}$ alkylene wherein one or more alkylene units of the C$_1$-C$_{30}$ alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –

$C(O)N(R^{20})$–, $–N(R^{20})S(O)_2$–, $– S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2$–, or $–P(O)(R^{20})_2$–;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})$–, $–N(R^{20})C(O)$–, $–C(O)N(R^{20})$–, $–N(R^{20})S(O)_2$–, $– S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2$–, or $–P(O)(R^{20})_2$–;

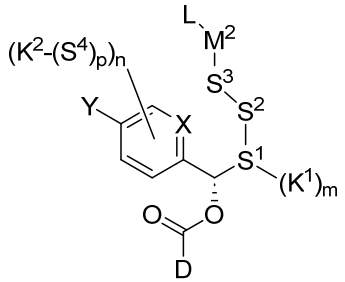
(iii) an oligosaccharide; and

(iv) a polyether;

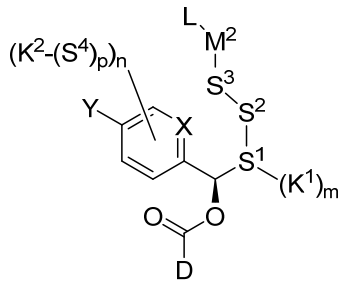
each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle.

[0008] In an aspect, the present disclosure provides a conjugate of the Formula (Aa) or Formula (Ab):



Formula (Aa),



Formula (Ab), or

or a pharmaceutically acceptable salt thereof, wherein;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino

acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$;

wherein the optional substituents on M^2, K^1, K^2, S^1, S^2, S^3, and S^4, are independently selected at each occurrence from:

(i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN;

(ii) $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, $C_{3\text{-}10}$ carbocycle and 3- to 10-membered heterocycle; and

(iii) $C_{3\text{-}10}$ carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, and $C_{2\text{-}6}$ alkynyl;

L is a Targeting Unit;

M^2 is a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

(iii) an oligosaccharide; and

(iv) a polyether;

each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle.

[0009] In an aspect, the present disclosure provides a method of treating a subject with a disease or disorder comprising administering to a subject in need thereof a Drug-Linker or salt of Formula (I), Formula (I-A), Formula (I-B), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), or Formula (II-B) (each of which further comprises a targeting unit), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), or a pharmaceutical composition of any one thereof.

INCORPORATION BY REFERENCE

[0010] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "figure" and "FIG." herein), of which:

[0012] **FIG. 1** illustrates the stability of different ADCs in mouse plasma;

[0013] **FIG. 2** illustrates the stability of different ADCs in human plasma;

[0014] **FIG. 3** illustrates the percentage of cellular binding of different ADCs;

[0015] **FIG. 4** illustrates the median fluorescence intensity (MFI) of different ADCs binding to JeKo cells;

[0016] **FIG. 5** illustrates the percentage of inhibition of Jeko-1 cell growth of different ADCs;

[0017] **FIG. 6** illustrates internalization of different ADCs;

[0018] **FIG. 7** illustrates the release of exatecan from the ADCs;

[0019] **FIG. 8** illustrates in vivo antitumor activity of ADCs in the Jeko-1 xenograft model;

[0020] **FIG. 9** illustrates in vivo antitumor activity of ADCs in the H1975 xenograft model;

[0021] **FIG. 10** illustrates Pharmacokinetic Parameters of various ADCs;

[0022] **FIG. 11** illustrates the stability of different ADCs in mouse plasma;

[0023] **FIG. 12** illustrates the stability of different ADCs in human plasma;

[0024] **FIG. 13** illustrates the percentage of cellular binding of different ADCs;

[0025] **FIG. 14** illustrates the median fluorescence intensity (MFI) of different ADCs;

[0026] **FIG. 15** illustrates the percentage of inhibition of Jeko-1 cell growth of different ADCs;

[0027] **FIG. 16** illustrates internalization of different ADCs;

[0028] **FIG. 17** illustrates the release of exatecan from the ADCs;

[0029] **FIG. 18** illustrates Pharmacokinetic Parameters of various ADCs.

[0030] **FIG. 19** Chiral HPLC Chromatograms of Compound 37, Compound 107-S and Compound 118-R;

[0031] **FIG. 20** illustrates the percentage of cellular binding of different ADC binding to LCLC-103H cells;

[0032] **FIG. 21** illustrates the median fluorescence intensity of different ADC binding to LCLC-103H cells;

[0033] **FIG. 22** illustrates the quench internalization of different ADCs;

[0034] **FIG. 23** illustrates the percentage of inhibition of Jeko-1 cell growth of different ADCs;

[0035] **FIG. 24** illustrates the percentage of inhibition LCLC-103H cell growth of different ADC isomers; and

[0036] **FIG. 25** in vivo antitumor activity of ADCs in the LCLC-103H xenograft model.

[0037] **FIG. 26** in vivo antitumor activity of ADC in the CTG-2215 xenograft model.

[0038] **FIG. 27** in vivo antitumor activity of ADC in the NCI-H526 xenograft model.

[0039] **FIG.28** in vivo antitumor activity and dose titration of ADCs in the LCLC-103H xenograft model.

DETAILED DESCRIPTION OF THE INVENTION

[0040] The following description sets forth numerous exemplary configurations, methods, parameters, and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure, but is instead provided as a description of exemplary embodiments.

[0041] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the disclosure. However, one skilled in the art will understand that the disclosure may be practiced without these details.

Definitions

[0042] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference.

[0043] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, and preferably having from one to fifteen carbon atoms (*i.e.*, C_1-C_{15} alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*i.e.*, C_1-C_{13} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*i.e.*, C_1-C_8 alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*i.e.*, C_1-C_5 alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*i.e.*, C_1-C_4 alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*i.e.*, C_1-C_3 alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*i.e.*, C_1-C_2 alkyl). In other embodiments, an alkyl comprises one carbon atom (*i.e.*, C_1 alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*i.e.*, C_5-C_{15} alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*i.e.*, C_5-C_8 alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*i.e.*, C_2-C_5 alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*i.e.*, C_3-C_5 alkyl). In certain embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond.

[0044] The terms "C_{x-y}" and "C_x-C_y" when used in conjunction with a chemical moiety, such as alkyl, alkenyl, or alkynyl is meant to include groups that contain from x to y carbons in the chain. For example, the terms "C_{1-6}alkyl" or "C_1-C_6 alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from 1 to 6 carbons. The terms –C_{x-y}alkylene- or –C_x-$C_y$alkylene- refers to a substituted or unsubstituted alkylene chain with from x to y carbons in the alkylene chain. For example –C_{1-6}alkylene- or –C_1-C_6alkylene- may be selected from methylene, ethylene, propylene, butylene, pentylene, and hexylene, any one of which is optionally substituted.

[0045] "Alkoxy" refers to a radical bonded through an oxygen atom of the formula –O-alkyl, where alkyl is an alkyl chain as defined above.

[0046] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and preferably having from two to twelve carbon atoms (*i.e.,* C_2-C_{12} alkenyl). In certain embodiments, an alkenyl comprises two to eight carbon atoms (*i.e.*, C_2-C_8 alkenyl). In certain

embodiments, an alkenyl comprises two to six carbon atoms (*i.e.*, C_2-C_6 alkenyl). In other embodiments, an alkenyl comprises two to four carbon atoms (*i.e.*, C_2-C_4 alkenyl). The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

[0047] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, and preferably having from two to twelve carbon atoms (*i.e.*, C_2-C_{12} alkynyl). In certain embodiments, an alkynyl comprises two to eight carbon atoms (*i.e.*, C_2-C_8 alkynyl). In other embodiments, an alkynyl comprises two to six carbon atoms (*i.e.*, C_2-C_6 alkynyl). In other embodiments, an alkynyl comprises two to four carbon atoms (*i.e.*, C_2-C_4 alkynyl). The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like.

[0048] The terms "C_{x-y}alkenyl" and "C_{x-y}alkynyl" refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively. The term –C_{x-y}alkenylene- refers to a substituted or unsubstituted alkenylene chain with from x to y carbons in the alkenylene chain. For example, –C_{2-6}alkenylene- may be selected from ethenylene, propenylene, butenylene, pentenylene, and hexenylene, any one of which is optionally substituted. An alkenylene chain may have one double bond or more than one double bond in the alkenylene chain. The term –C_{x-y}alkynylene- refers to a substituted or unsubstituted alkynylene chain with from x to y carbons in the alkenylene chain. For example, –C_{2-6}alkenylene- may be selected from ethynylene, propynylene, butynylene, pentynylene, and hexynylene, any one of which is optionally substituted. An alkynylene chain may have one triple bond or more than one triple bond in the alkynylene chain.

[0049] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation, and preferably having from one to twelve carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group may be through any two carbons within the chain. In certain embodiments, an alkylene comprises one to ten carbon atoms (*i.e.,* C_1-C_8 alkylene). In certain embodiments, an alkylene comprises one to eight carbon atoms (*i.e.*, C_1-C_8 alkylene). In other embodiments, an alkylene comprises one to five carbon atoms (*i.e.*, C_1-C_5 alkylene). In other embodiments, an alkylene comprises one to four carbon atoms (*i.e.*, C_1-C_4 alkylene). In other embodiments, an

alkylene comprises one to three carbon atoms (*i.e.*, C_1-C_3 alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*i.e.*, C_1-C_2 alkylene). In other embodiments, an alkylene comprises one carbon atom (*i.e.*, C_1 alkylene). In other embodiments, an alkylene comprises five to eight carbon atoms (*i.e.*, C_5-C_8 alkylene). In other embodiments, an alkylene comprises two to five carbon atoms (*i.e.*, C_2-C_5 alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*i.e.*, C_3-C_5 alkylene).

[0050] "Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon double bond, and preferably having from two to twelve carbon atoms. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group may be through any two carbons within the chain. In certain embodiments, an alkenylene comprises two to ten carbon atoms (*i.e.,* C_2-C_{10} alkenylene). In certain embodiments, an alkenylene comprises two to eight carbon atoms (*i.e.,* C_2-C_8 alkenylene). In other embodiments, an alkenylene comprises two to five carbon atoms (*i.e.,* C_2-C_5 alkenylene). In other embodiments, an alkenylene comprises two to four carbon atoms (*i.e.,* C_2-C_4 alkenylene). In other embodiments, an alkenylene comprises two to three carbon atoms (*i.e.,* C_2-C_3 alkenylene). In other embodiments, an alkenylene comprises two carbon atom (*i.e.,* C_2 alkenylene). In other embodiments, an alkenylene comprises five to eight carbon atoms (*i.e.*, C_5-C_8 alkenylene). In other embodiments, an alkenylene comprises three to five carbon atoms (*i.e.*, C_3-C_5 alkenylene).

[0051] "Alkynylene" or "alkynylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon triple bond, and preferably having from two to twelve carbon atoms. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group may be through any two carbons within the chain. In certain embodiments, an alkynylene comprises two to ten carbon atoms (*i.e.*, C_2-C_{10} alkynylene). In certain embodiments, an alkynylene comprises two to eight carbon atoms (*i.e.*, C_2-C_8 alkynylene). In other embodiments, an alkynylene comprises two to five carbon atoms (*i.e.*, C_2-C_5 alkynylene). In other embodiments, an alkynylene comprises two to four carbon atoms (*i.e.*, C_2-C_4 alkynylene). In other embodiments, an alkynylene comprises two to three carbon atoms (*i.e.*, C_2-C_3 alkynylene). In other embodiments, an alkynylene comprises two carbon atom (*i.e.*, C_2 alkynylene). In other embodiments, an alkynylene

comprises five to eight carbon atoms (*i.e.*, C_5-C_8 alkynylene). In other embodiments, an alkynylene comprises three to five carbon atoms (*i.e.*, C_3-C_5 alkynylene).

[0052] "Aryl" refers to a radical derived from an aromatic monocyclic or aromatic multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or aromatic multicyclic hydrocarbon ring system contains only hydrogen and carbon and from five to eighteen carbon atoms, where at least one of the rings in the ring system is aromatic, *i.e*., it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene.

[0053] "Aralkyl" refers to a radical of the formula -R^c-aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like.

[0054] "Aralkenyl" refers to a radical of the formula –R^d-aryl where R^d is an alkenylene chain as defined above. "Aralkynyl" refers to a radical of the formula -R^e-aryl, where R^e is an alkynylene chain as defined above.

[0055] "Activated $C{\equiv}C$ group" refers to a cyclic alkyne which is highly reactive due to ring strain towards azide group to form a triazole.

[0056] "Activated disulfide group" refers to a disulfide which is capable to react with a thiol to form a new disulfide bond.

[0057] "Carbocycle" refers to a saturated, unsaturated or aromatic rings in which each atom of the ring is carbon. Carbocycle may include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. An aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, are included in the definition of carbocyclic. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, phenyl, indanyl, and naphthyl. Bicyclic carbocycles may be fused, bridged or spiro-ring systems. In some cases, spiro-ring carbocycles have at least two molecular rings with only one common atom.

[0058] "Carbocyclene" refers to a divalent carbocycle linking the rest of the molecule to a radical group.

[0059] The term "unsaturated carbocycle" refers to carbocycles with at least one degree of unsaturation and excluding aromatic carbocycles. Examples of unsaturated carbocycles include cyclohexadiene, cyclohexene, and cyclopentene.

[0060] "Cycloalkyl" refers to a fully saturated monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, and preferably having from three to twelve carbon atoms. In certain embodiments, a cycloalkyl comprises three to ten carbon atoms. In other embodiments, a cycloalkyl comprises five to seven carbon atoms. The cycloalkyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like.

[0061] "Cycloalkenyl" refers to an unsaturated non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, preferably having from three to twelve carbon atoms and comprising at least one double bond. In certain embodiments, a cycloalkenyl comprises three to ten carbon atoms. In other embodiments, a cycloalkenyl comprises five to seven carbon atoms. The cycloalkenyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkenyls includes, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl.

[0062] "Cycloalkylalkyl" refers to a radical of the formula $–R^c$-cycloalkyl where R^c is an alkylene chain as described above.

[0063] "Cycloalkylalkoxy" refers to a radical bonded through an oxygen atom of the formula $–O-R^c$-cycloalkyl where R^c is an alkylene chain as described above.

[0064] "Halo" or "halogen" refers to halogen substituents such as bromo, chloro, fluoro and iodo substituents.

[0065] As used herein, the term "haloalkyl" or “haloalkane” refers to an alkyl radical, as defined above, that is substituted by one or more halogen radicals, for example, trifluoromethyl, dichloromethyl, bromomethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally further substituted. Examples of halogen substituted alkanes (“haloalkanes”) include halomethane (e.g., chloromethane, bromomethane, fluoromethane, iodomethane), di-and trihalomethane (e.g., trichloromethane, tribromomethane, trifluoromethane, triiodomethane), 1-haloethane, 2-haloethane, 1,2-dihaloethane, 1-halopropane, 2-halopropane, 3-halopropane, 1,2-dihalopropane, 1,3-dihalopropane, 2,3-dihalopropane, 1,2,3-trihalopropane, and any other suitable combinations of alkanes (or substituted alkanes) and halogens (e.g., Cl, Br, F, I, etc.). When an alkyl group is substituted with more than one halogen radicals, each halogen may be independently selected e.g., 1-chloro,2-fluoroethane.

[0066] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like.

[0067] "Aminoalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more amine radicals, for example, propan-2-amine, butane-1,2-diamine, pentane-1,2,4-triamine and the like.

[0068] "Hydroxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more hydroxy radicals, for example, propan-1-ol, butane-1,4-diol, pentane-1,2,4-triol, and the like.

[0069] "Alkoxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more alkoxy radicals, for example, methoxymethane, 1,3-dimethoxybutane, 1-methoxypropane, 2-ethoxypentane, and the like.

[0070] "Cyanoalkyl" as used herein refers to an alkyl radical, as defined above, that is substituted by one or more cyano radicals, for example, acetonitrile, 2-ethyl-3-methylsuccinonitrile, butyronitrile, and the like.

[0071] “Heterocycle” refers to a saturated or unsaturated or aromatic ring comprising one or more heteroatoms. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycles include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic heterocycle may be selected from saturated, unsaturated, and aromatic rings. Bicyclic heterocycles may be fused, bridged or spiro-ring systems. In some cases, spiro-ring heterocycles have at least two molecular rings with only one common atom. The spiro-ring heterocycle includes at least one heteroatom.

[0072] “Heterocyclene” refers to a divalent heterocycle linking the rest of the molecule to a radical group.

[0073] "Heteroaryl" or “aromatic heterocycle” refers to a radical derived from a heteroaromatic ring radical that comprises one to eleven carbon atoms and at least one heteroatom wherein each heteroatom may be selected from N, O, and S. As used herein, the heteroaryl ring may be selected from monocyclic or bicyclic and fused or bridged ring systems rings wherein at least one of the rings in the ring system is aromatic, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The heteroatom(s) in the heteroaryl radical may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule through any atom of the heteroaryl, valence permitting, such as a carbon or nitrogen atom of the heteroaryl. Examples of heteroaryls include, but are not limited to, pyridine, pyrimidine, oxazole, furan, pyran, thiophene, isoxazole, benzimidazole, benzthiazole, and imidazopyridine.

[0074] An “X-membered heteroaryl” refers to the number of endocylic atoms, i.e., X, in the ring. For example, a 5-membered heteroaryl ring or 5-membered aromatic heterocycle has 5 endocyclic atoms, e.g., triazole, oxazole, thiophene, etc.

[0075] The term “unsaturated heterocycle” refers to heterocycles with at least one degree of unsaturation and excluding aromatic heterocycles. Examples of unsaturated heterocycles include dihydropyrrole, dihydrofuran, oxazoline, pyrazoline, and dihydropyridine. Heterocycles may be optionally substituted by one or more substituents such as those substituents described herein.

[0076] The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons or substitutable heteroatoms, e.g., NH, of the structure. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *i.e.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. In certain embodiments, substituted refers to moieties having substituents replacing two hydrogen atoms on the same carbon atom, such as substituting the two hydrogen atoms on a single carbon with an oxo, imino or thioxo group.

[0077] As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. In some embodiments, substituents may include any substituents described herein, for example: halogen, hydroxy, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazino (=N-NH_2), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); and alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, cycloalkylalkyl, and heterocycle, any of which may be optionally substituted by alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine (=N-NH_2), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-$

$N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); wherein each R^a is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, wherein each R^a, valence permitting, may be optionally substituted with alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine (=N-NH_2), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); and wherein each R^b is independently selected from a direct bond or a straight or branched alkylene, alkenylene, or alkynylene chain, and each R^c is a straight or branched alkylene, alkenylene or alkynylene chain.

[0078] As used in the specification and claims, the singular form “a”, “an” and “the” includes plural references unless the context clearly dictates otherwise.

[0079] The term “salt” or “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0080] The phrases “parenteral administration” and “administered parenterally” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal,

intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0081] 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 animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0082] The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[0083] In certain embodiments, the term “prevent” or “preventing” as related to a disease or disorder may refer to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

[0084] The terms “treat,” “treating” or “treatment,” as used herein, may include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the

disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

[0085] The term "ligand" generally refers to a macromolecular compound capable of recognizing and binding to an antigen or receptor associated with a target cell. The ligand can be used to bring the drug to the target cell population that binds to the ligand, including but not limited to protein hormones, lectins, growth factors, antibodies, or others that can bind to cells, receptors and/or antigens molecule. The ligand can be an antibody. The ligand can be an antigen binding fragment.

[0086] The term “targeting moiety” or “Targeting Unit” refers to a structure that has a selective affinity for a target molecule relative to other non-target molecules. The targeting moiety binds to a target molecule. A Targeting Unit may include, for example, an antibody, a peptide, a ligand, a receptor, or a binding portion thereof. The target biological molecule may be a biological receptor or other structure of a cell such as a tumor antigen.

[0087] The term “antibody” means whole antibodies and any antigen binding fragment (i.e., “antigen-binding portion”) or single chain variants thereof. A whole antibody is a protein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain comprises a heavy chain variable region (VH) and a heavy chain constant region comprising three domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (VL or Vk) and a light chain constant region comprising one single domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with more conserved framework regions (FRs). Each VH and VL comprises three CDRs and four FRs, arranged from amino- to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The variable regions contain a binding domain that interacts with an antigen. The constant regions may mediate the binding of the antibody to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system. An antibody is said to “specifically bind” to an antigen X if the antibody binds to antigen X with a KD of 1 x 10^{-7} M or less, 5×10^{-8} M or less, more preferably 1×10^{-8} M or less, more preferably 6×10^{-9} M or less, more preferably 3×10^{-9}M or less, even more preferably 2×10^{-9}M or less. The antibody can be chimeric, humanized, or, preferably, human. The heavy chain constant region can be engineered to affect glycosylation type or extent, to extend antibody half-life, to enhance or reduce inter-actions with effector cells or the complement system, or to modulate some other property. The engineering can be accomplished by replacement, addition, or deletion of one or more amino acids or by replacement of a domain with a domain from another immunoglobulin type, or a combination of the foregoing.

[0088] The term “antigen binding fragment” and “antigen binding portion” of an antibody (or simply “antibody portion” or “antibody fragment”) mean one or more fragments of an antibody that retain the ability to specifically bind to an antigen. It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody, such as (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab’)2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fab’ fragment, which is essentially an Fab with part of the hinge region (see, for example, Abbas et al., Cellular and Molecular Immunology, 6th Ed., Saunders Elsevier 2007); (iv) a Fd fragment consisting of the VH and CH1 domains; (v) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (vi) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a VH domain; (vii) an isolated complementarity determining region (CDR); and (viii) a nanobody, a heavy chain variable region containing a single variable domain and two constant domains. Preferred antigen binding fragments are Fab, F(ab’)2, Fab’, Fv, and Fd fragments. Furthermore, although the two domains of the Fv fragment, VL and VH, are encoded by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv, or scFv); see, e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibodies are also encompassed within the term “antigen-binding portion” of an antibody.

[0089] The term “isolated antibody” means an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds antigen X is substantially free of antibodies that specifically bind antigens other than antigen X). An isolated antibody that specifically binds antigen X may, however, have cross-reactivity to other antigens, such as antigen X molecules from other species. In certain embodiments, an isolated antibody specifically binds to human antigen X and does not cross-react with other (non-human) antigen X antigens. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0090] The term “monoclonal antibody” or “monoclonal antibody composition” means a preparation of antibody molecules of single molecular composition, which displays a single binding specificity and affinity for a particular epitope.

[0091] The term “human antibody” means an antibody having variable regions in which both the framework and CDR regions (and the constant region, if present) are derived from human germline immunoglobulin sequences. Human antibodies may include later modifications, including natural or synthetic modifications. Human antibodies may include amino acid residues

not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo). However, “human antibody” does not include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0092] The term “human monoclonal antibody” means an antibody displaying a binding specificity, which has variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. In one embodiment, human monoclonal antibodies are produced by a hybridoma that includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

The term "epitope" refers to the amino acids conventionally bound by an immunoglobulin VH/VL pair, such as the antibodies, antigen binding portions thereof and other binding agents described herein. Other binding agents comprise non-antibody scaffolds. An epitope can be formed on a polypeptide from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5, about 9, or about 8-10 amino acids in a unique spatial conformation. An epitope defines the minimum binding site for an antibody, antigen binding portions thereof and other binding agent, and thus represents the target of specificity of an antibody, antigen binding portion thereof or other immunoglobulin-based binding agent. In the case of a single domain antibody, an epitope represents the unit of structure bound by a variable domain in isolation. An epitope may include non-amino acid components, such as glycan structures.

[0093] The term “specifically binds” refers to the ability of a molecule (e.g., an antibody or antigen binding portion thereof or non-antibody scaffold) described herein to bind to a target with a KD of 10^{-5} M (10000 nM) or less, e.g., 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, or less. Specific binding can be influenced by, for example, the affinity and avidity of the antibody, antigen binding portion or other binding agent and the concentration of target polypeptide.

[0094] The term "about" when used in connection with percentages can mean +/-1%.

[0095] The term “cleavable unit” refers to a chemical group that may be cleaved by action of an internal or external, preferably external, stimulus. The stimulus triggering the cleavage of the cleavable unit may be for instance pH or temperature conditions, or the presence of an enzyme.

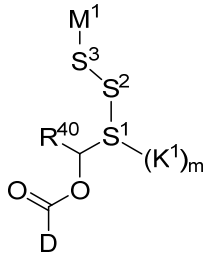
Cleavage of the cleavable unit preferably triggers self-immolation of the phenyl-comprising linker of the compounds of the invention, and release of the active agent D.

[0096] The term "cleavable sugar unit" or "sugar cleavable unit" can refer to a sugar moiety, preferably a glucuronide or a galactoside.

[0097] The term "peptide cleavable unit" can refer to a polypeptide, preferably a dipeptide or a tripeptide.

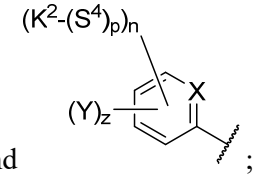
Linkers, Drug-Linkers and Conjugates of the Disclosure

[0098] In an aspect, the present disclosure provides a Drug-Linker of Formula (X):



Formula (X)

or a pharmaceutically acceptable salt thereof, wherein;

R^{40} is independently selected from hydrogen, Y, and 

;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

z is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –

$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, or –$P(O)(R^{20})_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, 5- to 6-membered heterocyclene, or –$P(O)(R^{20})_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, or –$P(O)(R^{20})_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, 5- to 6-membered heterocyclene, or –$P(O)(R^{20})_2$–;

wherein the optional substituents on M^1, K^1, K^2, S^1, S^2, S^3, and S^4 are independently selected at each occurrence from:

(i) halogen, -OR^{30}, -$N(R^{30})_2$, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -O-$S(O)_2OR^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, and -CN;

(ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{30}, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -O-$S(O)_2OR^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle; and

(iii) C_{3-10} carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{30}, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

M^1 is a group which can react with a ligand to form a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

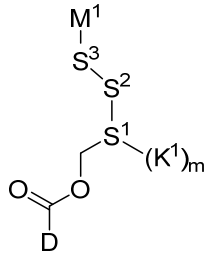
(iii) an oligosaccharide; and

(iv) a polyether;

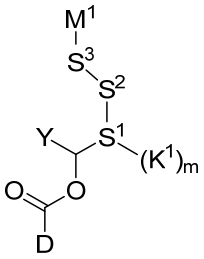
each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-memberedheterocycle.

[0099] In some embodiments, Formula (X) is represented by



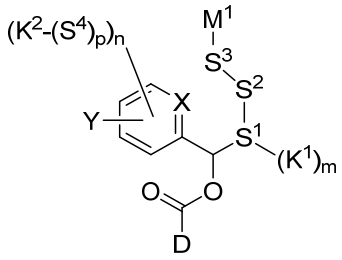
Formula (XI) or



Formula (XII)

or a pharmaceutically acceptable salt thereof.

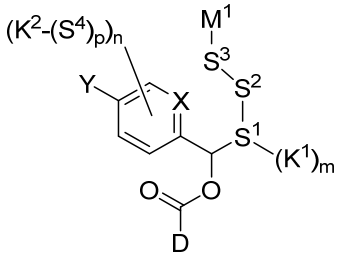
[00100] In some embodiments, Formula (X) is represented by



Formula (XIII)

or a pharmaceutically acceptable salt thereof.

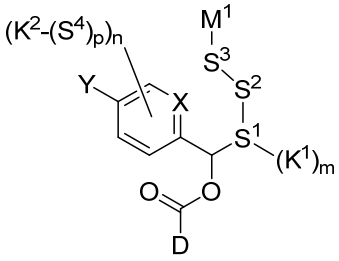
[00101] In some embodiments, Formula (X) or Formula (XIII) is represented by



Formula (I)

or a pharmaceutically acceptable salt thereof.

[00102] In an aspect, the present disclosure provides a Drug-Linker of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, –$S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, 5- to 6-membered heterocyclene, or –$P(O)(R^{20})_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, –$S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, or –$P(O)(R^{20})_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, –$S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, 5- to 6-membered heterocyclene, or –$P(O)(R^{20})_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, –$S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, or –$P(O)(R^{20})_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, –$S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, 5- to 6-membered heterocyclene, or –$P(O)(R^{20})_2$–;

wherein the optional substituents on M^1, K^1, K^2, S^1, S^2, S^3, and S^4, are independently selected at each occurrence from:

(i) halogen, -OR^{30}, -$N(R^{30})_2$, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -O-$S(O)_2OR^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, and -CN;

(ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle; and

(iii) C_{3-10} carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

M^1 is a group which can react with a ligand to form a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

(iii) an oligosaccharide; and

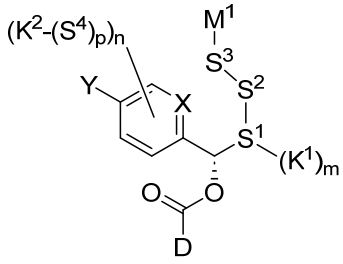
(iv) a polyether;

each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

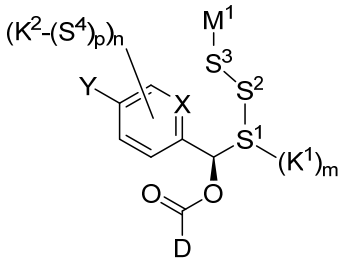
each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted

with one or more substituents independently selected from halogen, -OH, -CN, -NO_2, -NH_2, -$N(C_{1\text{-}6}\ alkyl)_2$, $C_{1\text{-}10}$ alkyl, -$C_{1\text{-}10}$ haloalkyl, -O-$C_{1\text{-}10}$ alkyl, oxo, $C_{3\text{-}12}$ carbocycle, and 3- to 12-membered heterocycle.

[00103] In an aspect, the present disclosure provides a Drug-Linker of Formula (Ia) or Formula (Ib):



Formula (Ia)



Formula (Ib)

or a pharmaceutically acceptable salt thereof, wherein;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, 5- to 6-membered heterocyclene, or –$P(O)(R^{20})_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, or –$P(O)(R^{20})_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino

acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$;

wherein the optional substituents on M^1, K^1, K^2, S^1, S^2, S^3, and S^4, are independently selected at each occurrence from:

(i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN;

(ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle; and

(iii) C_{3-10} carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

M^1 is a group which can react with a ligand to form a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

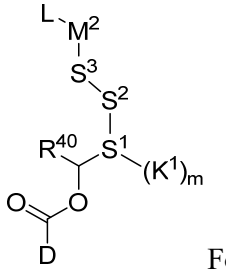
(iii) an oligosaccharide; and

(iv) a polyether;

each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

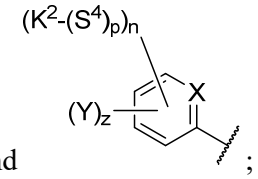
each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle.

[00104] In an aspect, the present disclosure provides a conjugate of the Formula (XX):



Formula (XX)

or a pharmaceutically acceptable salt thereof, wherein;

R^{40} is independently selected from hydrogen, Y, and ;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

z is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$;

wherein the optional substituents on M^2, K^1, K^2, S^1, S^2, S^3, and S^4 are independently selected at each occurrence from:

(i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN;

(ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle; and

(iii) C_{3-10} carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

L is a Targeting Unit;

M^2 is a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–;

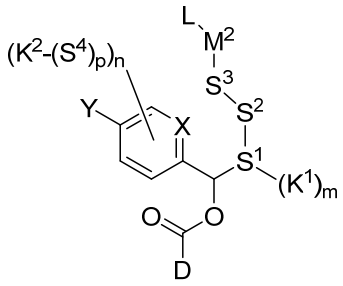
(iii) an oligosaccharide; and

(iv) a polyether;

each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -NO_2, -NH_2, -N(C_{1-6} alkyl)$_2$, C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -NO_2, -NH_2, -N(C_{1-6} alkyl)$_2$, C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle.

[00105] In an aspect, the present disclosure provides a conjugate of the Formula (A):



Formula (A)

or a pharmaceutically acceptable salt thereof, wherein;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –

$N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$;

wherein the optional substituents on M^2, K^1, K^2, S^1, S^2, S^3, and S^4, are independently selected at each occurrence from:

(i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN;

(ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle; and

(iii) C_{3-10} carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

L is a Targeting Unit;

M^2 is a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

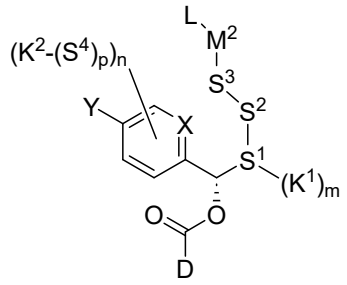
(iii) an oligosaccharide; and

(iv) a polyether;

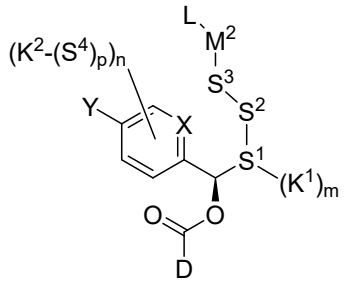
each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle.

[00106] In an aspect, the present disclosure provides a conjugate of the Formula (Aa) or Formula (Ab):



Formula (Aa),



Formula (Ab), or

or a pharmaceutically acceptable salt thereof, wherein;

D is selected from a Drug unit;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$;

wherein the optional substituents on M^2, K^1, K^2, S^1, S^2, S^3, and S^4, are independently selected at each occurrence from:

(i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN;

(ii) $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, $C_{3\text{-}10}$ carbocycle and 3- to 10-membered heterocycle; and

(iii) $C_{3\text{-}10}$ carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, and $C_{2\text{-}6}$ alkynyl;

L is a Targeting Unit;

M^2 is a connector unit;

K^1 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(i) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$;

(iii) an oligosaccharide; and

(iv) a polyether;

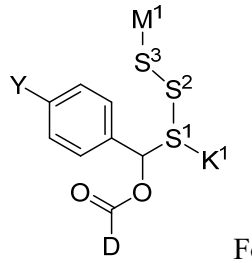
each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle.

[00107] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (Ia), Formula (Ib), Formula (X), Formula (XIII) or conjugate of Formula (A), Formula (Aa), Formula (Ab), Formula (XX), or Formula (XXIII), n is 0. In some cases, n is 1.

[00108] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (Ia), Formula (Ib), Formula (X), Formula (XIII) or conjugate of Formula (A), Formula (Aa), Formula (Ab), Formula (XX), or Formula (XXIII), p is 0. In some cases, p is 1.

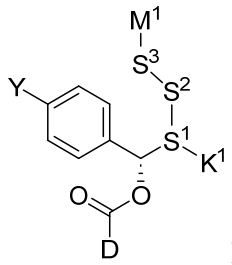
[00109] In some embodiments, Formula (I) is represented by



Formula (I-AA)

or a pharmaceutically acceptable salt thereof.

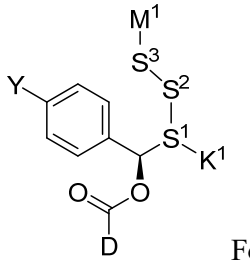
[00110] In some embodiments, Formula (I) or Formula (Ia) is represented by



Formula (I-AAa)

or a pharmaceutically acceptable salt thereof.

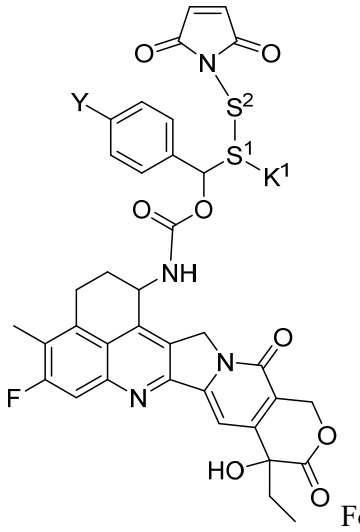
[00111] In some embodiments, Formula (I) or Formula (Ib) is represented by



Formula (I-AAb)

or a pharmaceutically acceptable salt thereof.

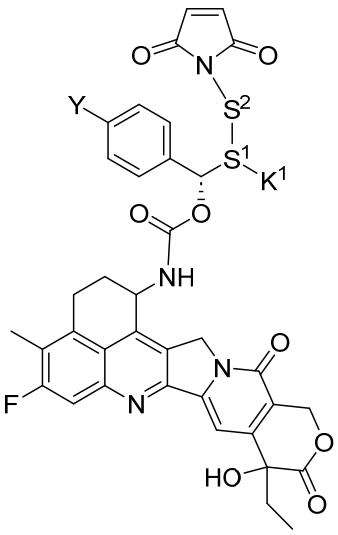
[00112] In some embodiments, Formula (I) is represented by



Formula (I-AB)

or a pharmaceutically acceptable salt thereof.

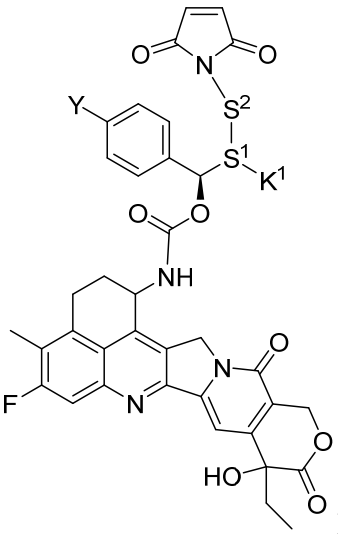
[00113] In some embodiments, Formula (I) or Formula (Ia) is represented by



Formula (I-ABa)

or a pharmaceutically acceptable salt thereof.

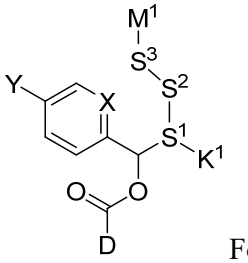
[00114] In some embodiments, Formula (I) or Formula (Ib) is represented by



Formula (I-ABb)

or a pharmaceutically acceptable salt thereof.

[00115] In some embodiments, Formula (I) is represented by



Formula (I-A)

or a pharmaceutically acceptable salt thereof.

[00116] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A),

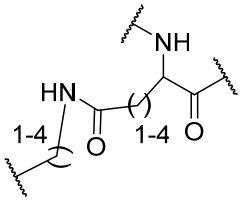
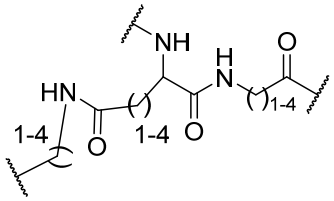
Formula (II-B), Formula (II-C), Formula (II-D), Formula (II-G), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), or Formula (A-4), S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$. In some cases, S^1 is selected from: (i) an optionally substituted C_6-C_{10} alkylene wherein one or more alkylene units of the C_6-C_{10} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, or –C(O)–. In some cases, S^1 is an optionally substituted C_1 alkylene. In some cases, S^1 is an optionally substituted C_2 alkylene. In some cases, S^1 is an optionally substituted C_3 alkylene. In some cases, S^1 is an optionally substituted C_4 alkylene. In some cases, S^1 is an optionally substituted C_5 alkylene. In some cases, S^1 is an optionally substituted C_6 alkylene. In some cases, S^1 is an optionally substituted C_7 alkylene. In some cases, S^1 is an optionally substituted C_8 alkylene. In some cases, S^1 is an optionally substituted C_9 alkylene. In some cases, S^1 is an optionally substituted C_{10} alkylene. In some cases, S^1 is an optionally substituted C_{11} alkylene. In some cases, S^1 is an optionally substituted C_{12} alkylene. In some cases, S^1 is an optionally substituted C_{13} alkylene. In some cases, S^1 is an optionally substituted C_{14} alkylene. In some cases, S^1 is an optionally substituted C_{15} alkylene. In some cases, S^1 is an optionally substituted C_{16} alkylene. In some cases, S^1 is an optionally substituted C_{17} alkylene. In some cases, S^1 is an optionally substituted C_{18} alkylene. In some cases, S^1 is an optionally substituted C_{19} alkylene. In some cases, S^1 is an optionally substituted C_{20} alkylene. In some cases, the one or more alkylene units of the alkylene of S^1 are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $– S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$. In some cases, the one or more alkylene units of the alkylene of S^1 are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, or –C(O)–. In some cases, the one or more alkylene units of the alkylene of S^1 are optionally and independently replaced by $–N(R^{20})–$. In some cases, the one or more alkylene units of the alkylene of S^1 are optionally and independently replaced by $–N(R^{20})C(O)–$. In some cases, the one or more alkylene units of the alkylene of S^1 are optionally and independently replaced by $–C(O)N(R^{20})–$. In some cases, the one or more alkylene units of the alkylene of S^1 are optionally and independently replaced by –C(O)–. In some cases, the one or more alkylene units of the alkylene of S^1 are optionally and independently replaced by –O–. In some cases, if an alkylene unit of the alkylene is replaced, the alkylene may be referred to as a resulting alkylene. In some cases, if two or more of the alkylene units of S^1 are replaced, the replaced alkylene units are not adjacent

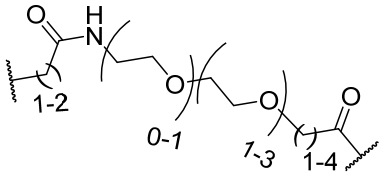
alkylene units. In some cases, if two or more of the alkylene units of S^1 are replaced, the adjacent alkylene units of the resulting alkylene are not replaced. In some cases, if two or more of the alkylene units of S^1 are replaced, the resulting alkylene has no repeating heteroatoms of adjacent alkylene units. In some cases, if two or more of the alkylene units of S^1 are replaced, the resulting alkylene has no repeating of the same heteroatoms of adjacent alkylene units. In some cases, if two or more of the alkylene units of S^1 are replaced, the resulting alkylene unit has no -N-N- or -O-O-. In some cases, if two or more of the alkylene units of S^1 are replaced, the resulting alkylene unit is a stable alkylene. In some cases, if two or more of the alkylene units of S^1 are replaced, the resulting alkylene unit is an unreactive alkylene. In some cases, the resulting alkylene has only 1 heteroatom. In some cases, the resulting alkylene has only 2 heteroatoms, wherein the 2 heteroatoms are different from each other. In some cases, the resulting alkylene has only 2 heteroatoms, wherein the 2 heteroatoms are not adjacent to each other. In some cases, the resulting alkylene has only 3 heteroatoms, wherein the 3 heteroatoms are not adjacent to each other. In some cases, the alkylene has 0 replaced units. In some cases, the alkylene has 1 replaced unit. In some cases, the alkylene has 2 replaced units. In some cases, the alkylene has 3 replaced units. In some cases, the alkylene has 4 replaced units. In some cases, the alkylene has 5 replaced units. In some cases, the alkylene has 6 replaced units. In some cases, no adjacent alkylene units of the alkylene are replaced. In some cases, no adjacent alkylene units resulting in two or more adjacent heteroatoms are present in the resulting alkylene (e.g., adjacent –$N(R^{20})S(O)_2$– and –$N(R^{20})$)– are not allowed, but the singular –$N(R^{20})S(O)_2$– is allowed). In some cases, two heteroatoms can be present in a resulting alkylene if they come from a singular replaced alkylene unit. In some cases, two heteroatoms can be present in a resulting alkylene if they come from a singular replaced alkylene unit. In some cases, a resulting alkylene has two heteroatoms, the two heteroatoms are from a singular replaced alkylene unit. In some cases, there are two heteroatoms in a resulting alkylene if they result from a singular replacement of an alkylene unit. In some cases, the optional substituents on S^1 are independently selected at each occurrence from: (i) halogen, -OR^{30}, -$N(R^{30})_2$, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -O-$S(O)_2OR^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, and -CN; (ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{30}, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -O-$S(O)_2OR^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle. In some cases, the optional substituents on S^1 are independently selected at each occurrence from: (i) halogen, -OR^{30}, -$N(R^{30})_2$, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -

$C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN. In some cases, the optional substituents on S^1 are independently selected at each occurrence from: halogen, $-OR^{30}$, $-N(R^{30})_2$, =O, and -CN. In some cases, the optional substituents on S^1 are independently selected at each occurrence from: =O.

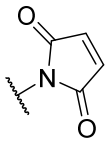
[00117] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (X), Formula (XIII),

X is CH;

S^1 is selected from  and ;

S^2 is selected from ;

S^3 is absent;

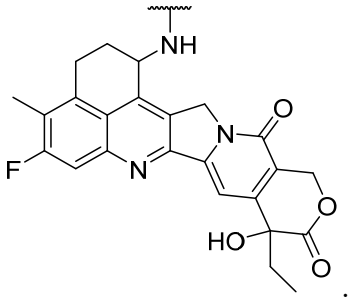
M^1 is ;

n is 0;

m is 1;

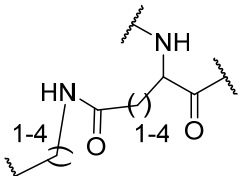
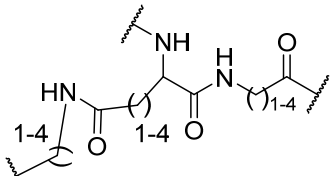
Y is selected from a cleavable sugar and cleavable peptide (e.g., dipeptide);

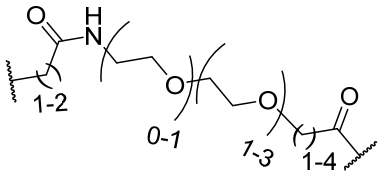
K^1 is selected from a peptide unit and oligosaccharide; and

D is .

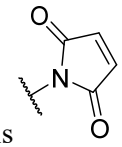
[00118] In some embodiments, for a Drug-Linker or salt of Formula (Ia), Formula (Ib), Formula (I-AAa), or Formula (I-AAb),

X is CH:

S^1 is selected from  and ;

S^2 is selected from ;

S^3 is absent;

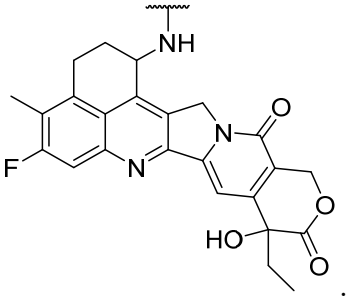
M^1 is ;

n is 0;

m is 1;

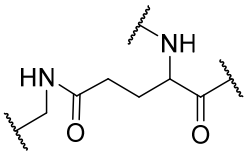
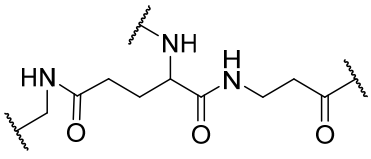
Y is selected from a cleavable sugar and cleavable peptide (e.g., dipeptide);

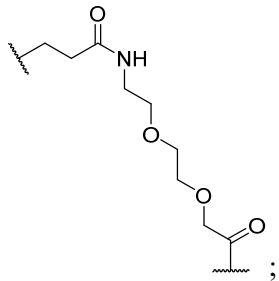
K^1 is selected from a peptide unit and oligosaccharide; and

D is .

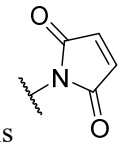
[00119] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (X), Formula (XIII),

X is CH;

S^1 is selected from  and ;

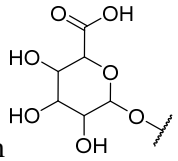
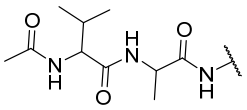
S^2 is  ;

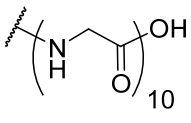
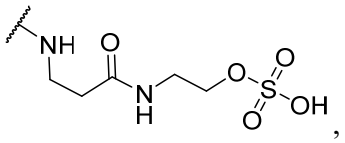
S^3 is absent;

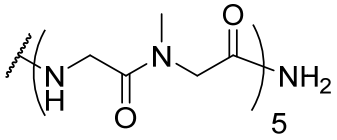
M^1 is  ;

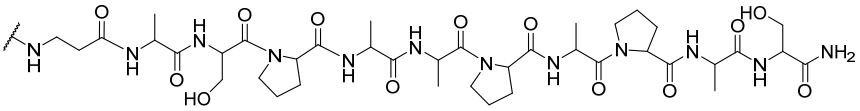
n is 0;

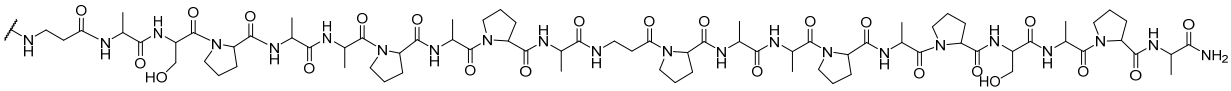
m is 1;

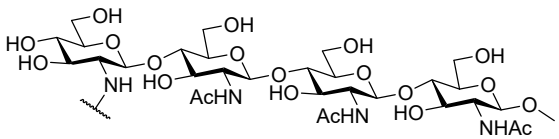
Y is selected from  and  ;

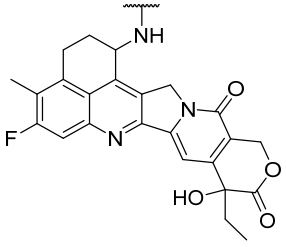
K^1 is selected from  (SEQ ID NO: 7),  ,

 (SEQ ID NO: 8);

 (SEQ ID NO: 9),

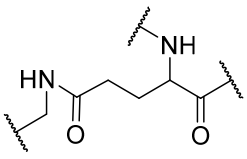
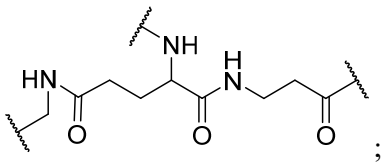


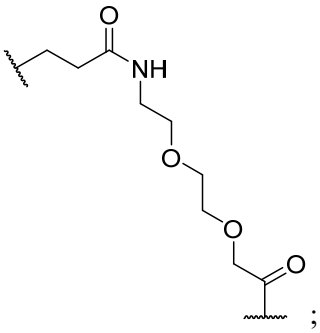
 (SEQ ID NO: 10), and ; and

D is  .

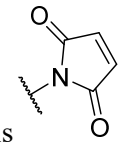
[00120] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (X), Formula (XIII),

X is CH;

S^1 is selected from  and ;

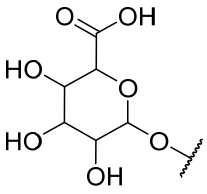
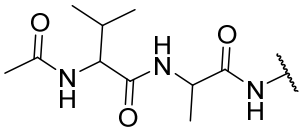
S^2 is ;

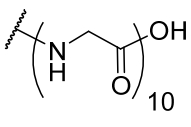
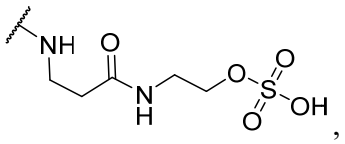
S^3 is absent;

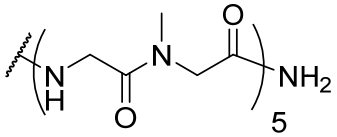
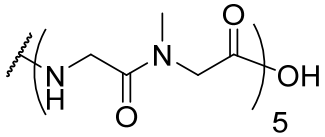
M^1 is ;

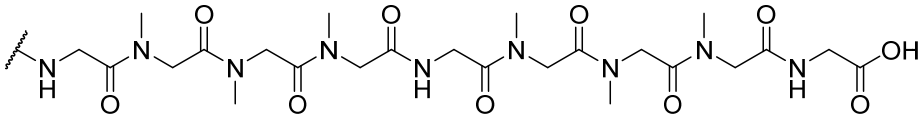
n is 0;

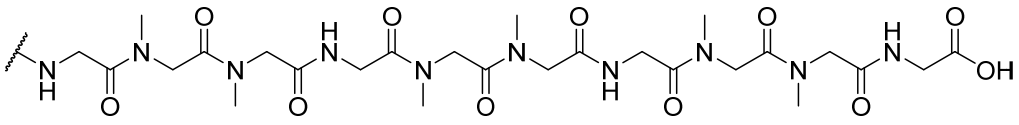
m is 1;

Y is selected from  and ;

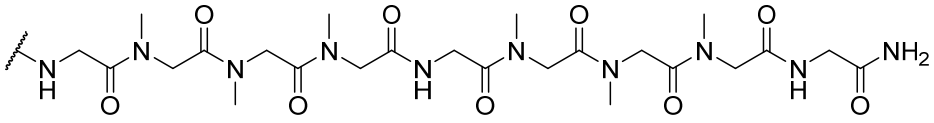
K^1 is selected from  (SEQ ID NO: 7), ,

 (SEQ ID NO: 8),  (SEQ ID NO: 8),

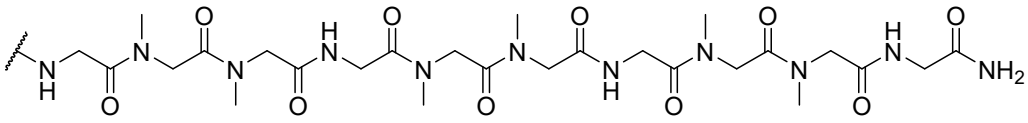
 (SEQ ID NO: 11),



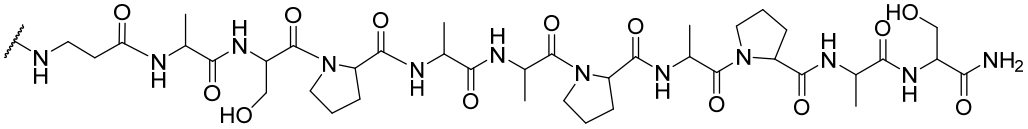
(SEQ ID NO: 12),



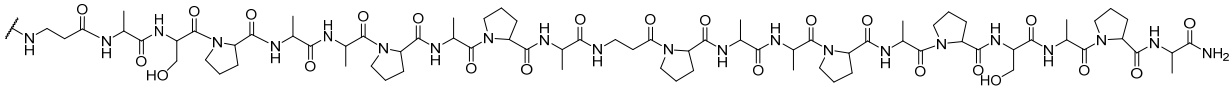
(SEQ ID NO: 11),

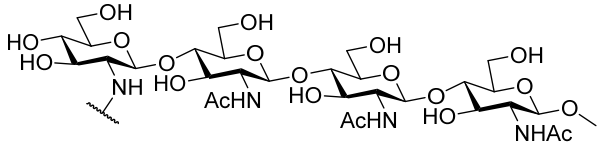


(SEQ ID NO: 12),

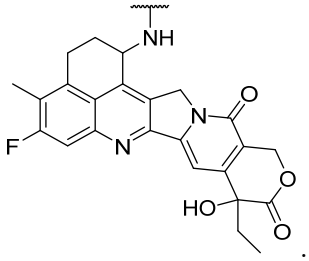


(SEQ ID NO: 9),





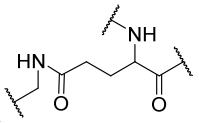
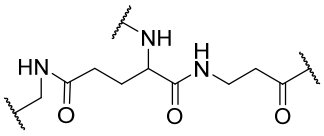
(SEQ ID NO: 10), and ; and

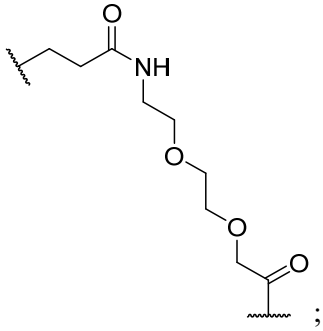


D is .

[00121] In some embodiments, for a Drug-Linker or salt of Formula (Ia), Formula (Ib),

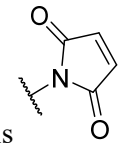
X is CH;

S^1 is selected from  and ;



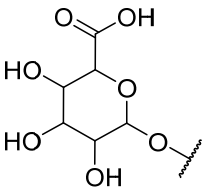
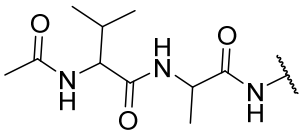
S^2 is ;

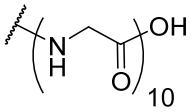
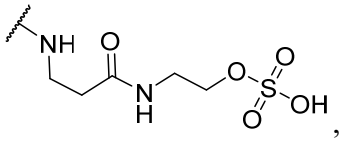
S^3 is absent;

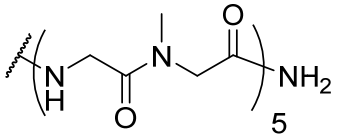
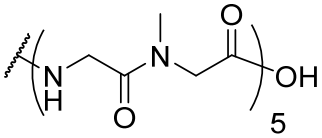
M^1 is  ;

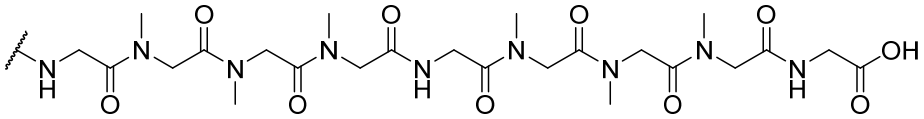
n is 0;

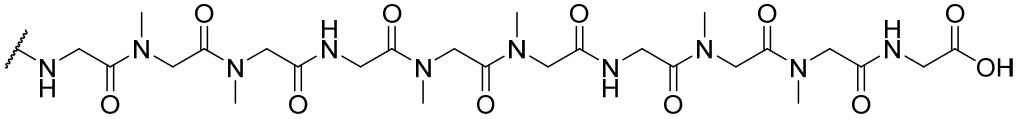
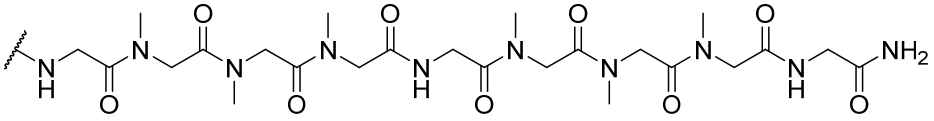
m is 1;

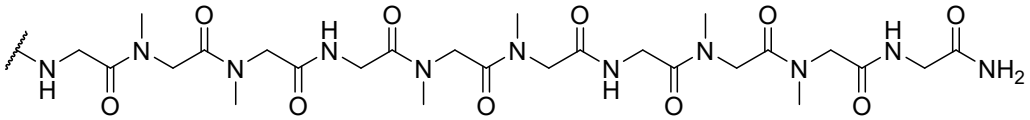
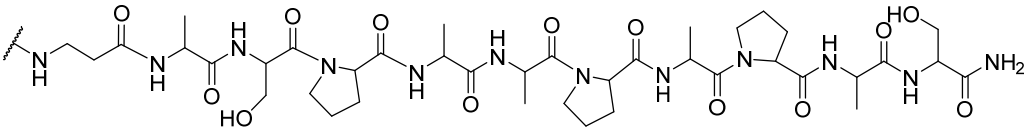
Y is selected from  and  ;

K^1 is selected from  (SEQ ID NO: 7), ,

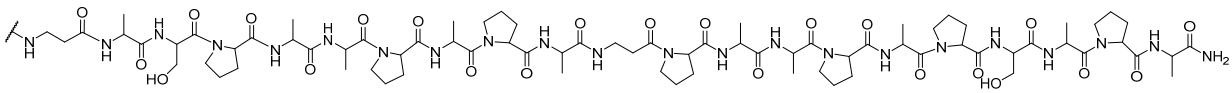
 (SEQ ID NO: 8),  (SEQ ID NO: 8),

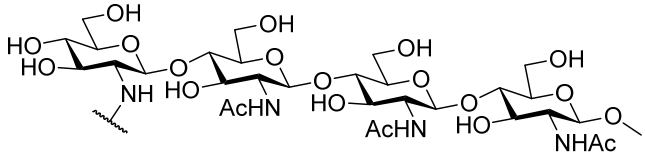
 (SEQ ID NO: 11),

 (SEQ ID NO: 12),  (SEQ ID NO: 11),

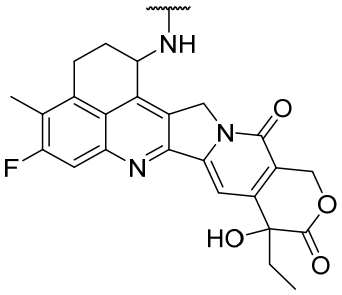
 (SEQ ID NO: 12), 

(SEQ ID NO: 9),



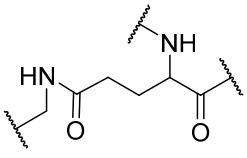


(SEQ ID NO: 10), and ; and

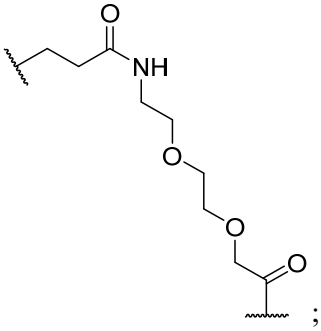


D is .

[00122] In some embodiments, for a Drug-Linker or salt of Formula (I-AAa), or Formula (I-Aab),

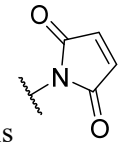


S^1 is selected from and ;



S^2 is ;

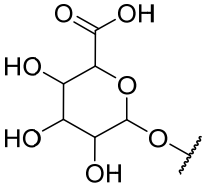
S^3 is absent;

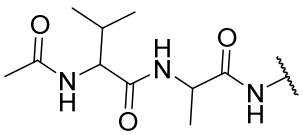


M^1 is ;

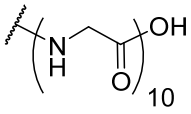
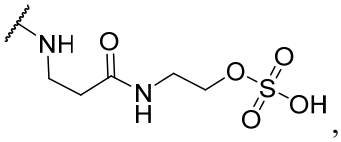
n is 0;

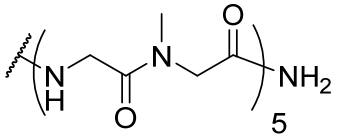
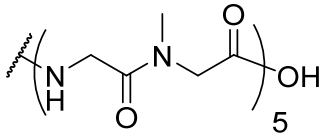
m is 1;

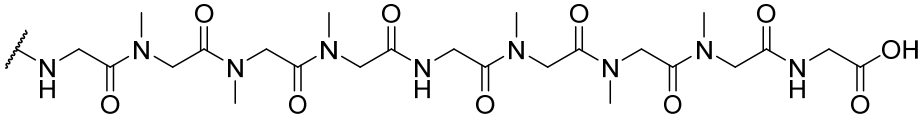


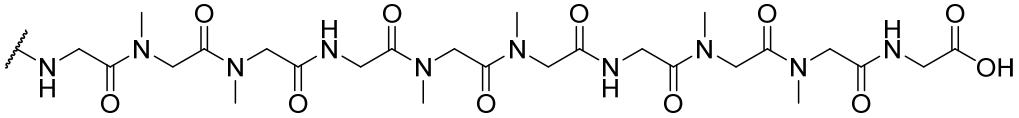


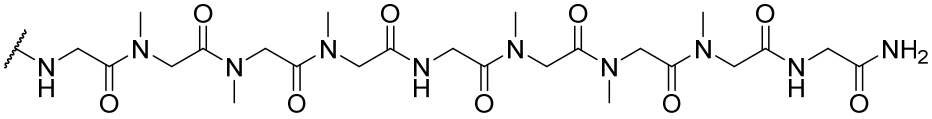
Y is selected from and ;

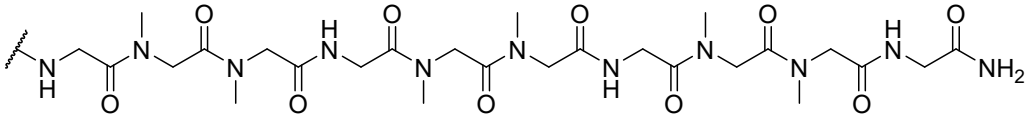
K^1 is selected from  (SEQ ID NO: 7), ,

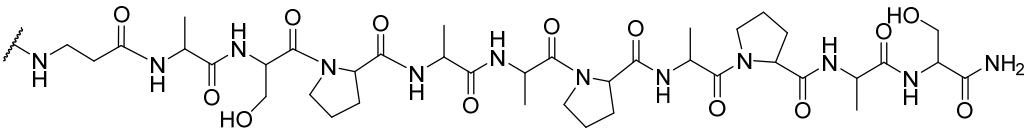
 (SEQ ID NO: 8),  (SEQ ID NO: 8),

 (SEQ ID NO: 11),

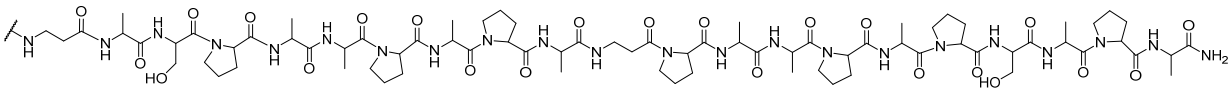
 (SEQ ID NO: 12),

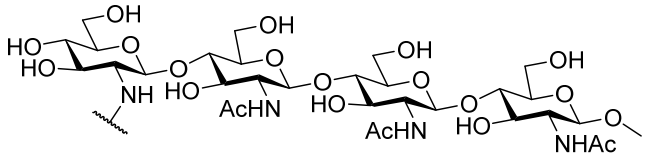
 (SEQ ID NO: 11),

 (SEQ ID NO: 12),

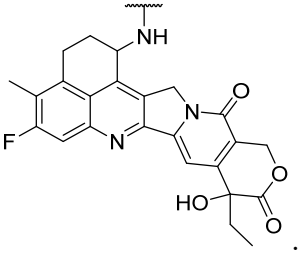


(SEQ ID NO: 9),





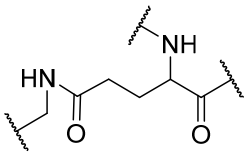
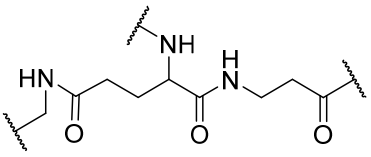
(SEQ ID NO: 10), and ; and

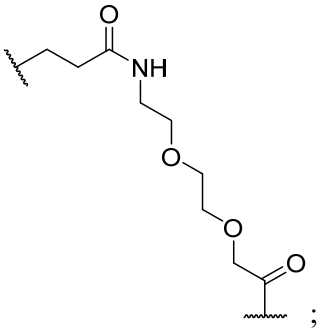


D is .

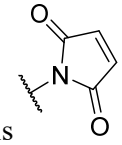
[00123] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (X), Formula (XIII),

X is N;

S^1 is selected from  and ;

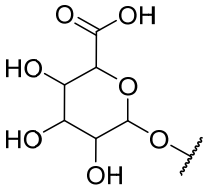
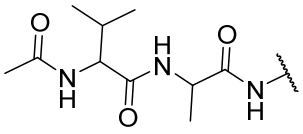
S^2 is ;

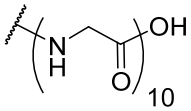
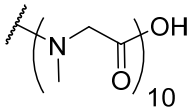
S^3 is absent;

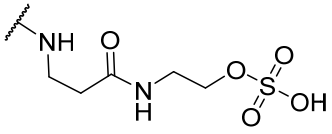
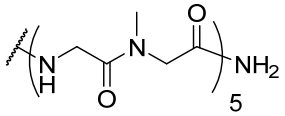
M^1 is ;

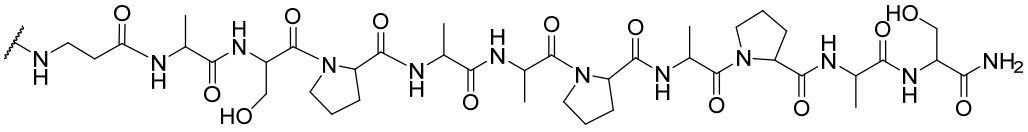
n is 0;

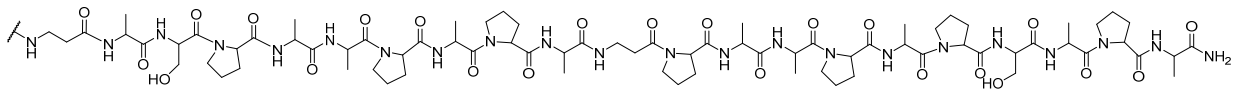
m is 1;

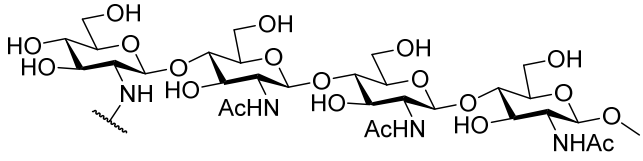
Y is selected from  and ;

K^1 is selected from  (SEQ ID NO: 7),  (SEQ ID NO: 13),

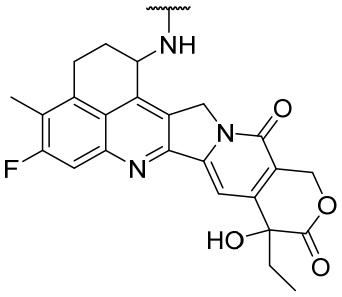
,  (SEQ ID NO: 8),

 (SEQ ID NO: 9),





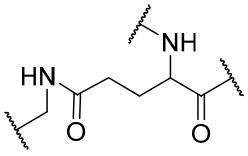
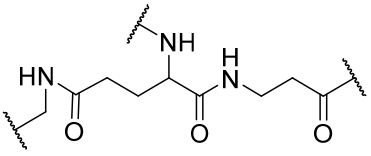
(SEQ ID NO: 10), and ; and

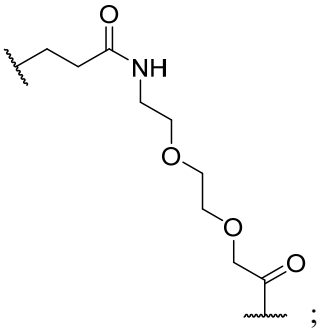


D is .

[00124] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (X), Formula (XIII),

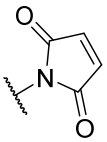
X is N;

S^1 is selected from  and ;



S^2 is ;

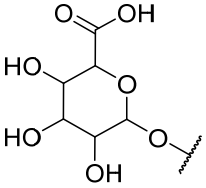
S^3 is absent;

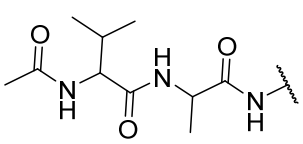


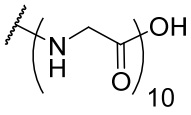
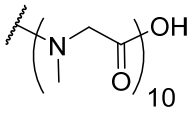
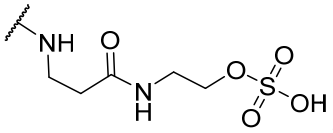
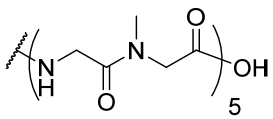
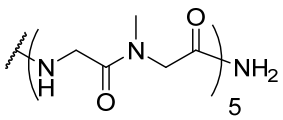
M^1 is ;

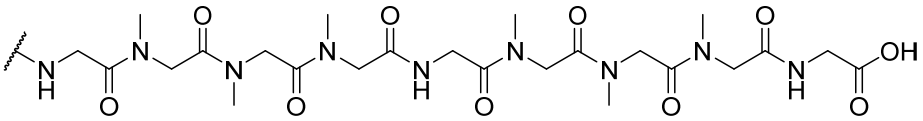
n is 0;

m is 1;

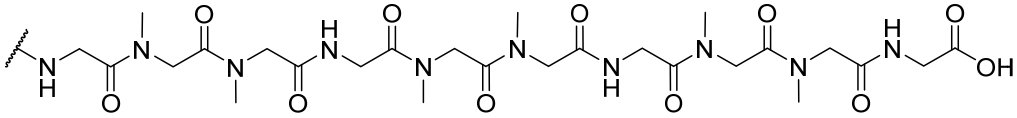
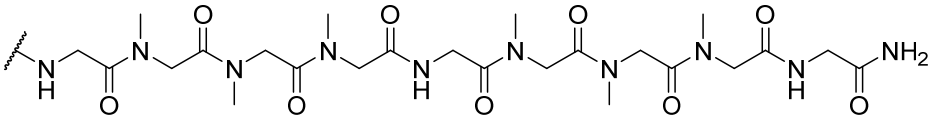


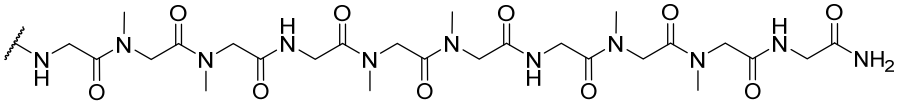
Y is selected from and ;

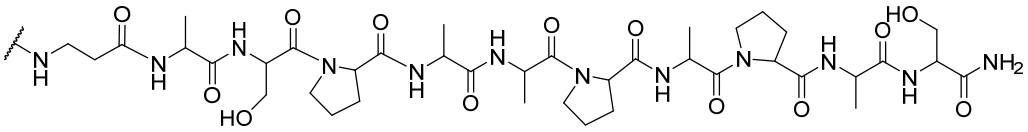
K^1 is selected from  (SEQ ID NO: 7),  (SEQ ID NO: 13), ,  (SEQ ID NO: 8), 

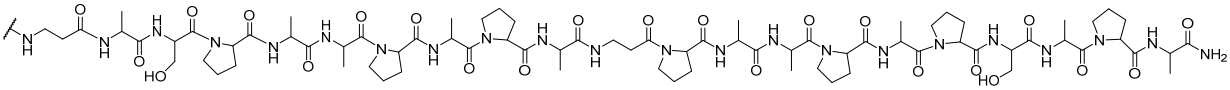
(SEQ ID NO: 8), 

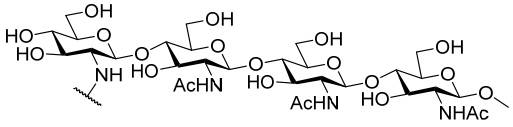
(SEQ ID NO: 11),

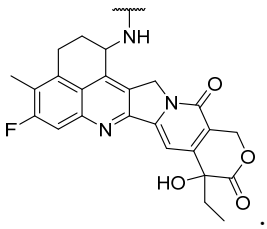
 (SEQ ID NO: 12),  (SEQ ID NO: 11),

 (SEQ ID NO: 12),

 (SEQ ID NO: 9),

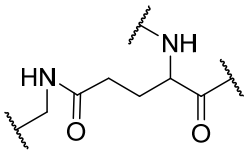
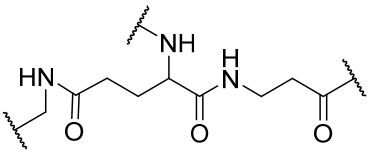


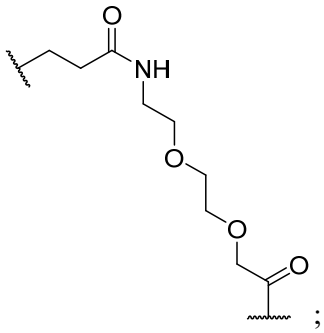
(SEQ ID NO: 10), and ; and

D is .

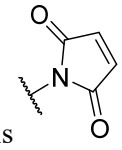
[00125] In some embodiments, for a Drug-Linker or salt of Formula (Ia), Formula (Ib), Formula (I-AAa), or Formula (I-AAb),

X is N;

S^1 is selected from  and ;

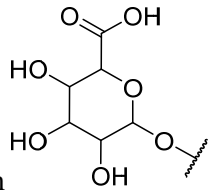
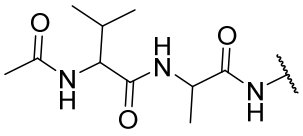
S^2 is ;

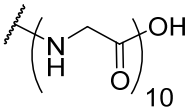
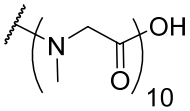
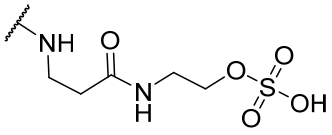
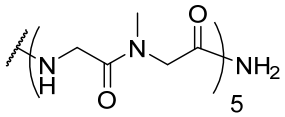
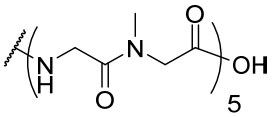
S^3 is absent;

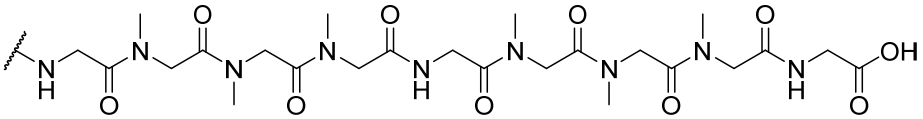
M^1 is ;

n is 0;

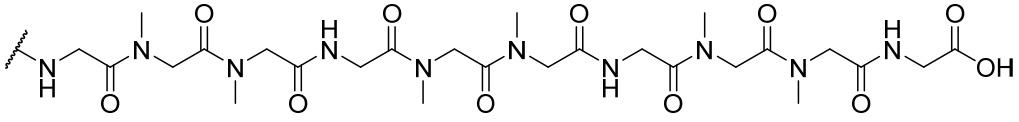
m is 1;

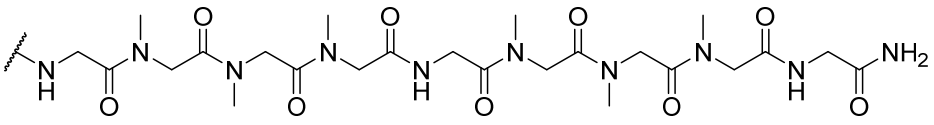
Y is selected from  and ;

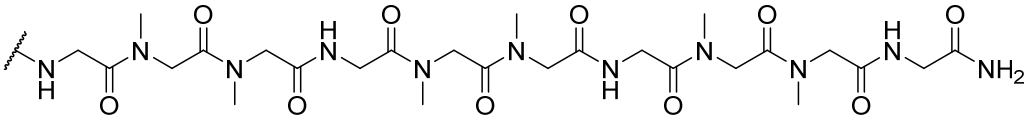
K^1 is selected  (SEQ ID NO: 7),  (SEQ ID NO: 13), ,  (SEQ ID NO: 8), 

(SEQ ID NO: 8), 

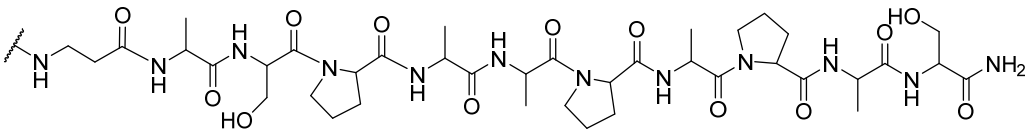
(SEQ ID NO: 11),

(SEQ ID

NO: 12),  (SEQ ID

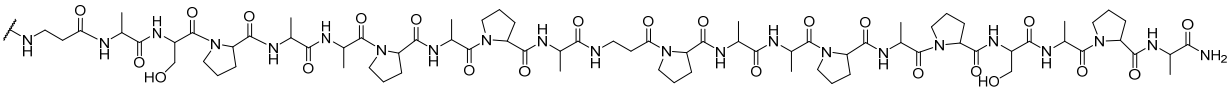
NO: 11), 

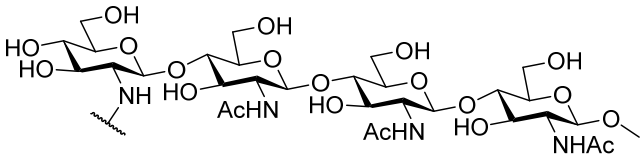
(SEQ ID NO: 12),



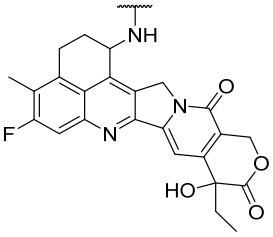
(SEQ ID

NO: 9),





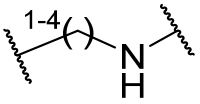
(SEQ ID NO: 10), and ; and

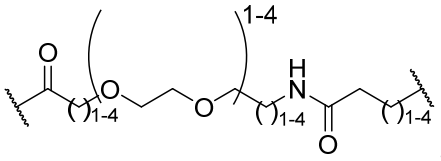


D is .

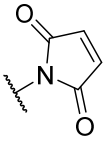
[00126] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (X), Formula (XIII),

X is CH;

S^1 is ;

S^2 is ;

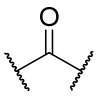
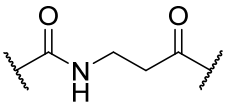
S^3 is absent;

M^1 is ;

n is 1;

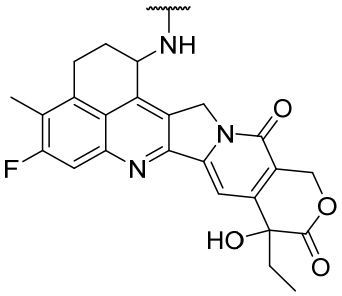
m is 0;

p is 1;

S^4 is selected from  and ;

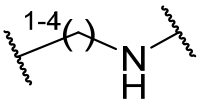
Y is selected from a cleavable sugar and cleavable peptide (e.g., dipeptide);

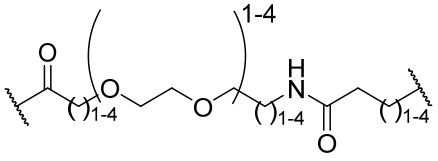
K^2 is selected from a peptide unit and oligosaccharide; and

D is .

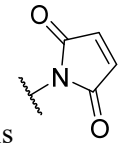
[00127] In some embodiments, for a Drug-Linker or salt of Formula (Ia), Formula (Ib), Formula (I-AAa), or Formula (I-AAb),

X is CH;

S^1 is ;

S^2 is ;

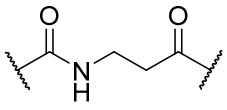
S^3 is absent;

M^1 is ;

n is 1;

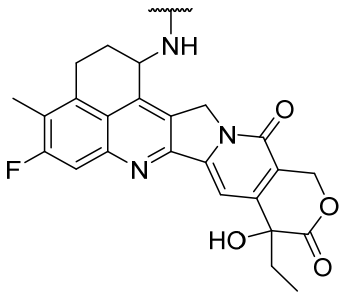
m is 0;

p is 1;

S^4 is selected from  and ;

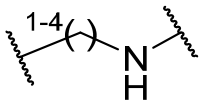
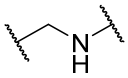
Y is selected from a cleavable sugar and cleavable peptide (e.g., dipeptide);

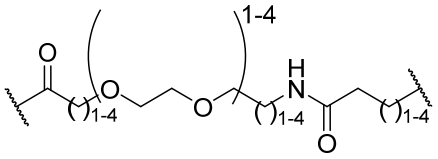
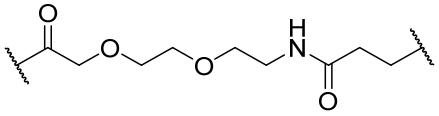
K^2 is selected from a peptide unit and oligosaccharide; and

D is .

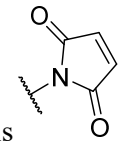
[00128] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (X), Formula (XIII),

X is CH;

S^1 is  (preferably );

S^2 is  (e.g., preferably );

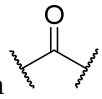
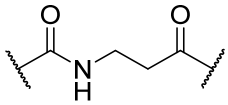
S^3 is absent;

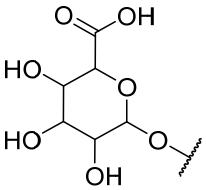
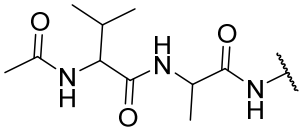
M^1 is ;

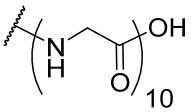
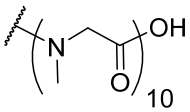
n is 1;

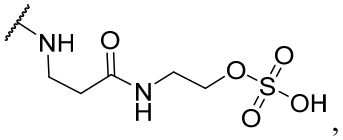
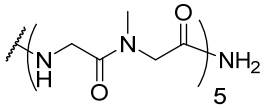
m is 0;

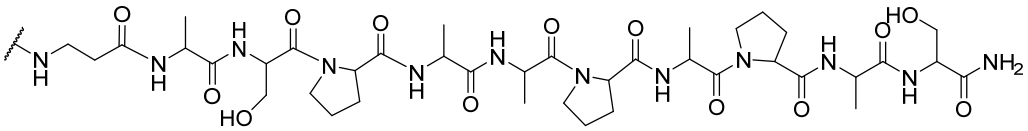
p is 1;

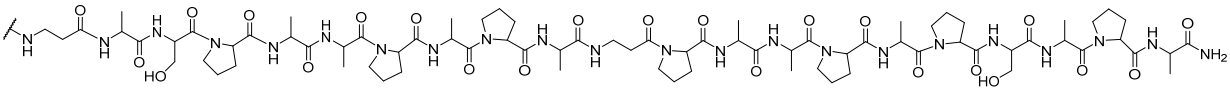
S^4 is selected from  and ;

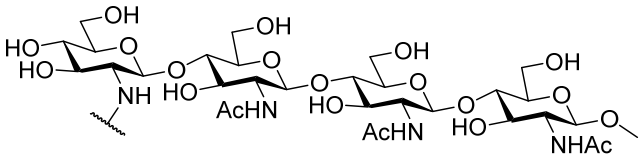
Y is selected from  and ;

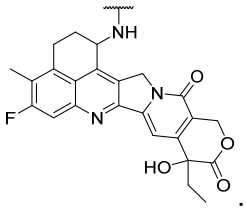
K^2 is selected  (SEQ ID NO: 7),  (SEQ ID NO: 13),

,  (SEQ ID NO: 8);

 (SEQ ID NO: 9),



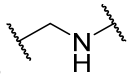
 (SEQ ID NO: 10), and ; and

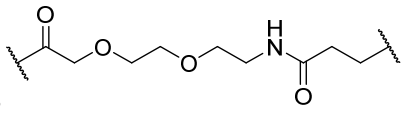


D is .

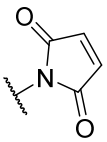
[00129] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (X), Formula (XIII),

X is CH;

S^1 is ;

S^2 is ;

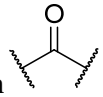
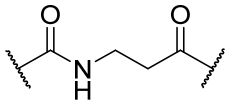
S^3 is absent;

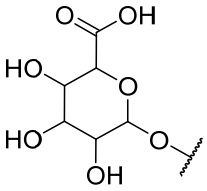
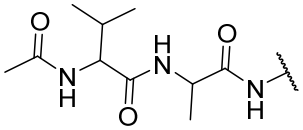
M^1 is ;

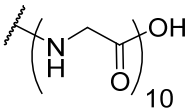
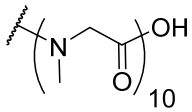
n is 1;

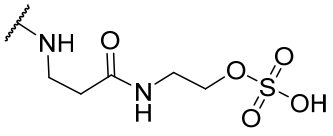
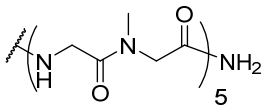
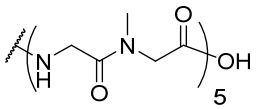
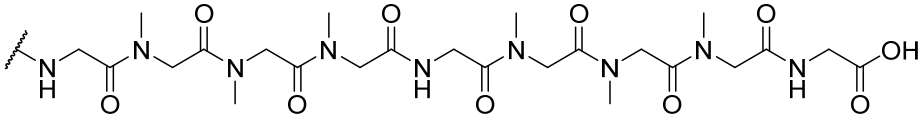
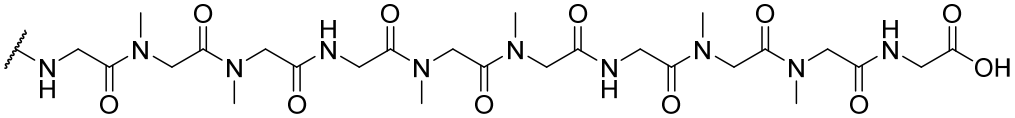
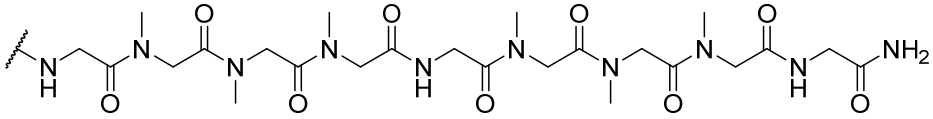
m is 0;

p is 1;

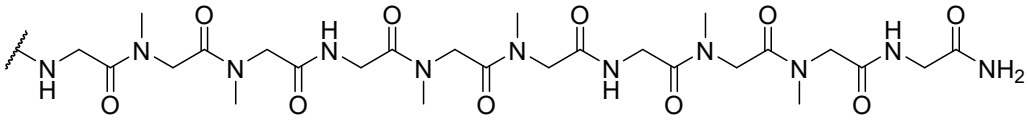
S^4 is selected from  and ;

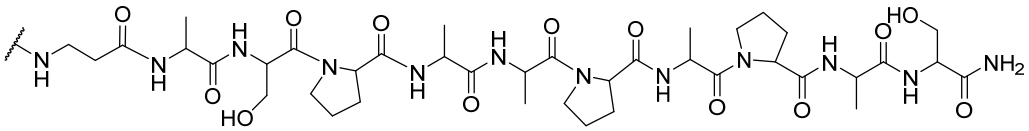
Y is selected from  and ;

K^2 is selected  (SEQ ID NO: 7),  (SEQ ID NO: 13),

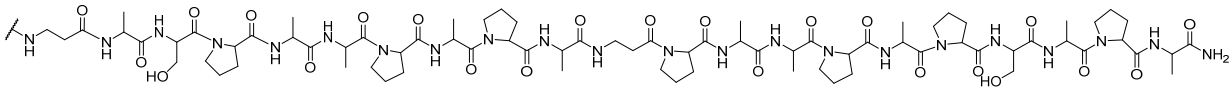
,  (SEQ ID NO: 8),  (SEQ ID NO: 8),  (SEQ ID NO: 11),  (SEQ ID NO: 12), 

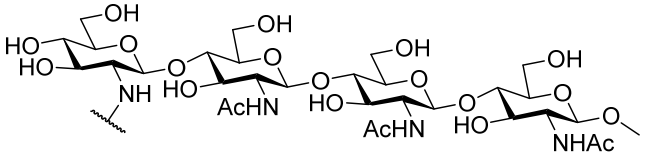
(SEQ ID NO: 11),

 (SEQ ID NO: 12),

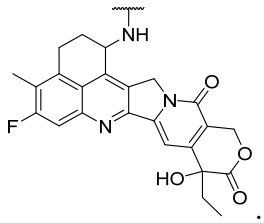


(SEQ ID NO: 9),



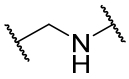


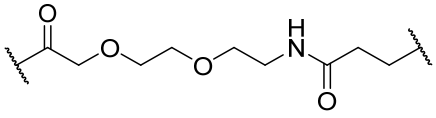
(SEQ ID NO: 10), and ; and

D is .

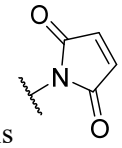
[00130] In some embodiments, for a Drug-Linker or salt of Formula (Ia), Formula (Ib), Formula (I-AAa), or Formula (I-AAb),

X is CH;

S^1 is ;

S^2 is ;

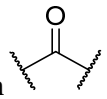
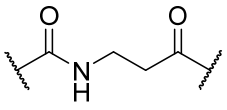
S^3 is absent;

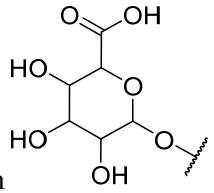
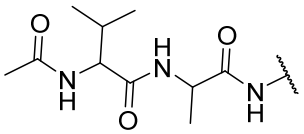
M^1 is ;

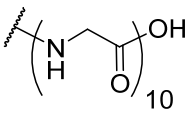
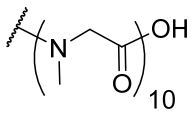
n is 1;

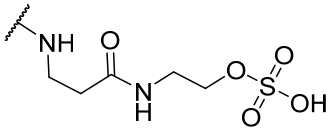
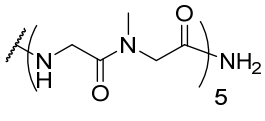
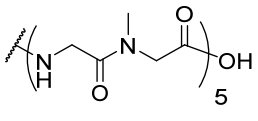
m is 0;

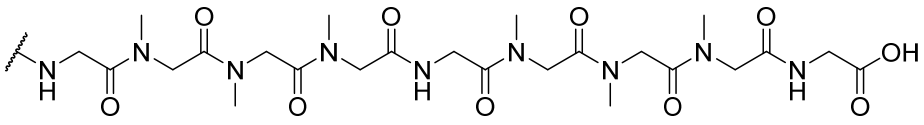
p is 1;

S^4 is selected from  and ;

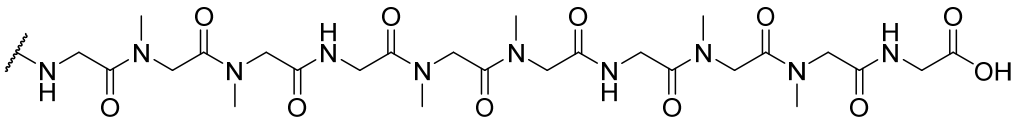
Y is selected from  and ;

K^2 is selected  (SEQ ID NO: 7),  (SEQ ID NO: 13),

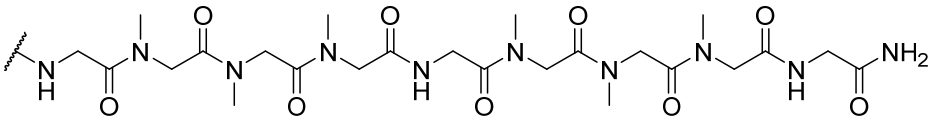
,  (SEQ ID NO: 8),  (SEQ ID NO: 8),



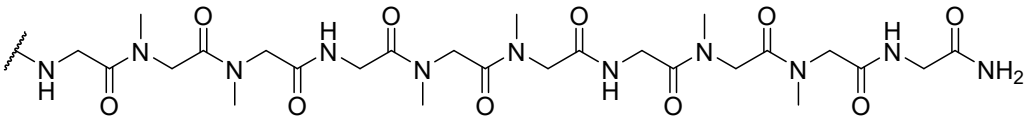
(SEQ ID NO: 11),



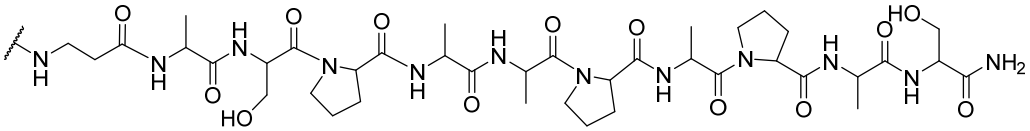
(SEQ ID NO: 12),



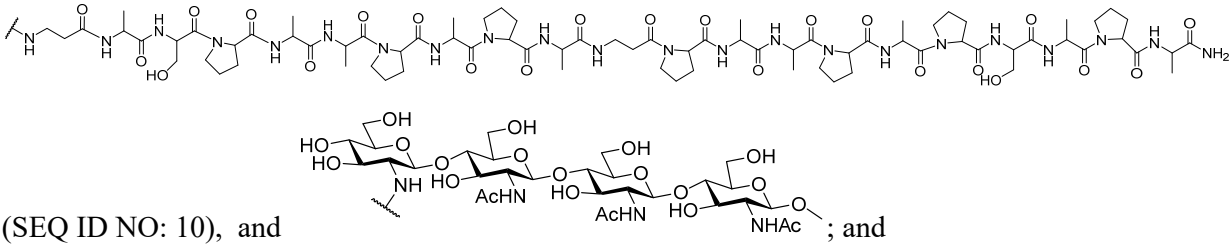
(SEQ ID NO: 11),



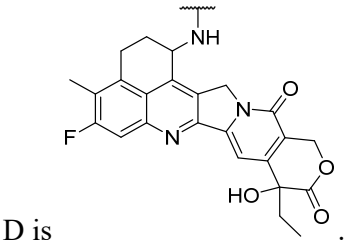
(SEQ ID NO: 12),



(SEQ ID NO: 9),



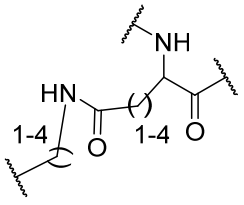
(SEQ ID NO: 10), and



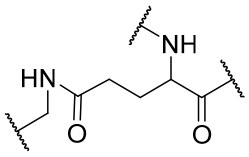
D is .

[00131] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-C), Formula (I-CA), or Formula (II-D), Formula (X), Formula (XI), Formula (XII), Formula (XIII) or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), Formula (A-4), Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), S^1 is a branched alkylene.

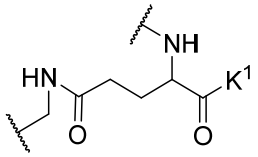
[00132] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), Formula (II-C), Formula

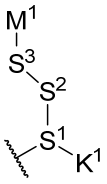
(II-CA), Formula (II-D), Formula (X), Formula (XI), Formula (XII), Formula (XIII) or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), S^1 is selected from 

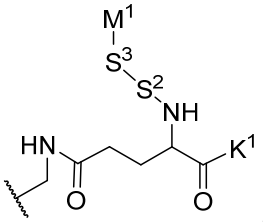
.

[00133] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-D), Formula (X), Formula (XI), Formula (XII), Formula (XIII) or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), In some cases, S^1 is represented by 

.

[00134] In some embodiments, for a Drug-Linker or salt of Formula (I), S^1-K^1 is represented by 

. In some cases, 

is represented by 

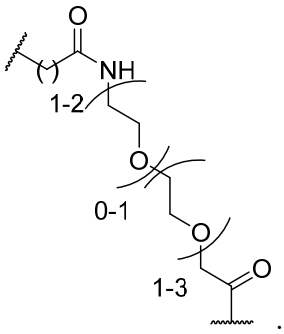
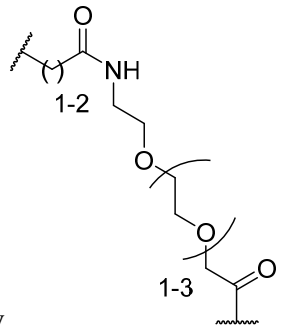
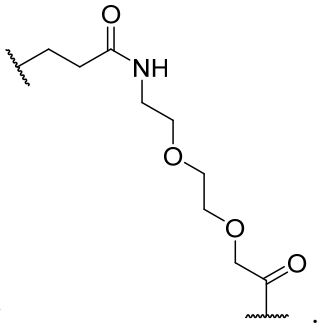
.

[00135] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-CA), Formula (II-D), Formula (II-G), Formula (X), Formula (XI), Formula (XII), Formula (XIII) or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), Formula (A-4), Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), S^2 is selected from: (i) an optionally substituted C_8-C_{12} alkylene wherein one or more alkylene units of the C_8-C_{12} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, –O–, and –C(O)–. In some cases, S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$. In some cases, S^2 is selected from: (i) an optionally substituted C_6-C_{10} alkylene wherein one or more alkylene units of the C_6-C_{10} alkylene are optionally and independently

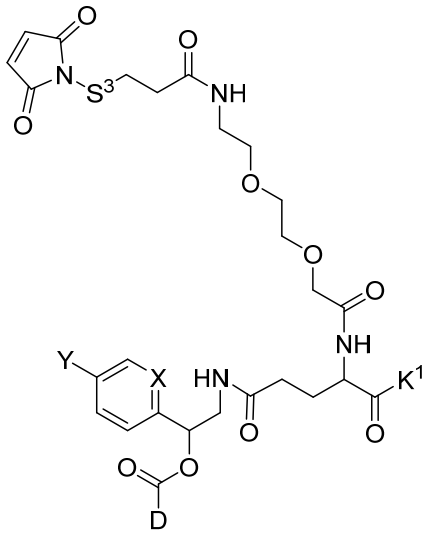
replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, or –C(O)–. In some cases, S^2 is an optionally substituted C_1 alkylene. In some cases, S^2 is an optionally substituted C_2 alkylene. In some cases, S^2 is an optionally substituted C_3 alkylene. In some cases, S^2 is an optionally substituted C_4 alkylene. In some cases, S^2 is an optionally substituted C_5 alkylene. In some cases, S^2 is an optionally substituted C_6 alkylene. In some cases, S^2 is an optionally substituted C_7 alkylene. In some cases, S^2 is an optionally substituted C_8 alkylene. In some cases, S^2 is an optionally substituted C_9 alkylene. In some cases, S^2 is an optionally substituted C_{10} alkylene. In some cases, S^2 is an optionally substituted C_{11} alkylene. In some cases, S^2 is an optionally substituted C_{12} alkylene. In some cases, S^2 is an optionally substituted C_{13} alkylene. In some cases, S^2 is an optionally substituted C_{14} alkylene. In some cases, S^2 is an optionally substituted C_{15} alkylene. In some cases, S^2 is an optionally substituted C_{16} alkylene. In some cases, S^2 is an optionally substituted C_{17} alkylene. In some cases, S^2 is an optionally substituted C_{18} alkylene. In some cases, S^2 is an optionally substituted C_{19} alkylene. In some cases, S^2 is an optionally substituted C_{20} alkylene. In some cases, the one or more alkylene units of the alkylene of S^2 are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S$(O)_2$–, – S$(O)_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S$(O)_2$–, or –P(O)(R^{20})$_2$–. In some cases, the one or more alkylene units of the alkylene of S^2 are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, or –C(O)–. In some cases, the one or more alkylene units of the alkylene of S^2 are optionally and independently replaced by –N(R^{20})–. In some cases, the one or more alkylene units of the alkylene of S^2 are optionally and independently replaced by –N(R^{20})C(O)–. In some cases, the one or more alkylene units of the alkylene of S^2 are optionally and independently replaced by –C(O)N(R^{20})–. In some cases, the one or more alkylene units of the alkylene of S^2 are optionally and independently replaced by –C(O)–. In some cases, the one or more alkylene units of the alkylene of S^2 are optionally and independently replaced by –O–. In some cases, if an alkylene unit of the alkylene is replaced, the alkylene may be referred to as a resulting alkylene. In some cases, if two or more of the alkylene units of S^2 are replaced, the replaced alkylene units are not adjacent alkylene units. In some cases, if two or more of the alkylene units of S^2 are replaced, the adjacent alkylene units of the resulting alkylene are not replaced. In some cases, if two or more of the alkylene units of S^2 are replaced, the resulting alkylene has no repeating heteroatoms of adjacent alkylene units. In some cases, if two or more of the alkylene units of S^2 are replaced, the resulting alkylene has no repeating of the same heteroatoms of adjacent alkylene units. In some cases, if two or more of the alkylene units of S^2 are replaced, the resulting alkylene unit has no -N-N- or -O-O-. In some cases, if two or more of the alkylene units of S^2 are replaced, the resulting alkylene unit is a stable alkylene. In some cases, if two or more of the alkylene units of

S^2 are replaced, the resulting alkylene unit is an unreactive alkylene. In some cases, the resulting alkylene has only 1 heteroatom. In some cases, the resulting alkylene has only 2 heteroatoms, wherein the 2 heteroatoms are different from each other. In some cases, the resulting alkylene has only 2 heteroatoms, wherein the 2 heteroatoms are not adjacent to each other. In some cases, the resulting alkylene has only 3 heteroatoms, wherein the 3 heteroatoms are not adjacent to each other. In some cases, the resulting alkylene has only 4 heteroatoms, wherein the 4 heteroatoms are not adjacent to each other. In some cases, the alkylene has 0 replaced units. In some cases, the alkylene has 1 replaced unit. In some cases, the alkylene has 2 replaced units. In some cases, the alkylene has 3 replaced units. In some cases, the alkylene has 4 replaced units. In some cases, the alkylene has 5 replaced units. In some cases, the optional substituents on S^2, are independently selected at each occurrence from: (i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN; (ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle. In some cases, the optional substituents on S^2, are independently selected at each occurrence from: (i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN. In some cases, the optional substituents on S^2, are independently selected at each occurrence from: halogen, $-OR^{30}$, $-N(R^{30})_2$, =O, and -CN. In some cases, the optional substituents on S^2, are independently selected at each occurrence from: =O. In some cases, two heteroatoms can be present in a resulting alkylene if they come from a singular replaced alkylene unit. In some cases, two heteroatoms can be present in a resulting alkylene if they come from a singular replaced alkylene unit. In some cases, a resulting alkylene has two heteroatoms, the two heteroatoms are from a singular replaced alkylene unit. In some cases, there are two heteroatoms in a resulting alkylene if they result from a singular replacement of an alkylene unit.

[00136] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), or Formula (II-B), Formula (II-C), Formula (II-D), Formula (II-G), Formula (X), Formula (XI), Formula (XII), Formula (XIII) or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), Formula (A-4), Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), S^2 is a linear alkylene.

[00137] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), Formula (X), Formula (XI), Formula (XII), Formula (XIII) or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), Formula (A-4), Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), S^2 is represented by  . In some cases, S^2 is represented by . In some cases, S^2 is represented by .

[00138] In some embodiments, Formula (I) or Formula (I-A) is represented by



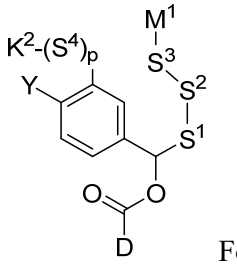
Formula (I-B)

or a pharmaceutically acceptable salt thereof.

[00139] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (Ia), Formula (Ib), Formula (I-A), or Formula (I-B), Formula (X), Formula (XIII) or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (XX), or Formula (XXIII), X is CH.

[00140] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (Ia), Formula (Ib), Formula (I-A), or Formula (I-B), Formula (X), Formula (XIII) or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (XX), or Formula (XXIII), X is N.

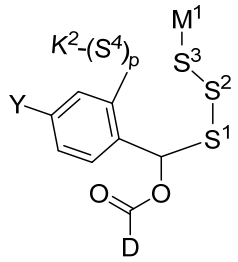
[00141] In some embodiments, Formula (I) is represented by



Formula (II-A)

or a pharmaceutically acceptable salt thereof.

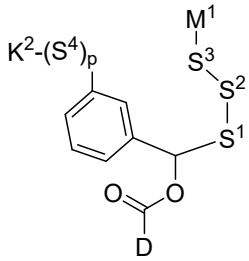
[00142] In some embodiments, Formula (I) is represented by



Formula (II-B)

or a pharmaceutically acceptable salt thereof.

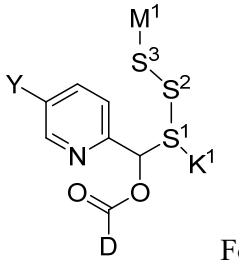
[00143] In some embodiments, Formula (X) is represented by



Formula (II-G)

or a pharmaceutically acceptable salt thereof.

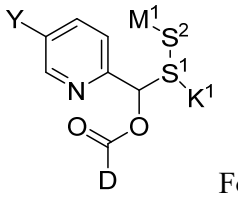
[00144] In some embodiments, Formula (I) is represented by



Formula (II-C)

or a pharmaceutically acceptable salt thereof.

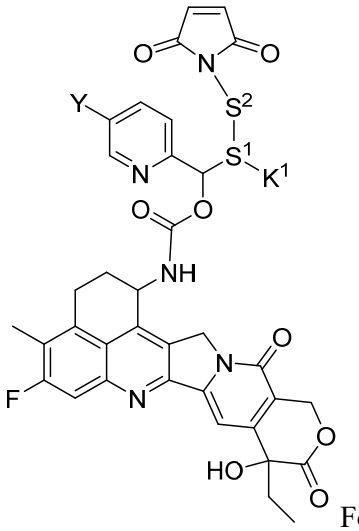
[00145] In some embodiments, Formula (I) is represented by



Formula (II-D)

or a pharmaceutically acceptable salt thereof.

[00146] In some embodiments, Formula (I) is represented by

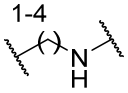
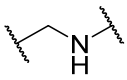


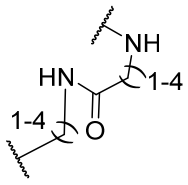
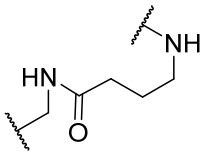
Formula (II-CA)

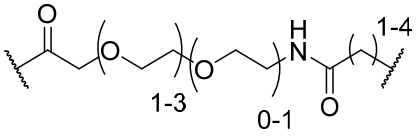
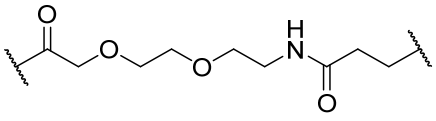
or a pharmaceutically acceptable salt thereof.

[00147] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-CA), Formula (II-D), Formula (II-G), Formula (X), Formula (XI), Formula (XII), Formula (XIII) or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), Formula (A-4), Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), S^1 is selected from: (i) an optionally substituted C_4-C_{10} alkylene wherein one or more alkylene units of the C_4-C_{10} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, or $–C(O)–$.

[00148] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), or Formula (A-4), S^1 is selected from: (i) an optionally substituted C_1-C_3 alkylene wherein one or more alkylene units of the C_1-C_3 alkylene are optionally and independently replaced by $–N(R^{20})–$. In some cases, S^1 is selected from: (i) an optionally substituted C_1-C_2 alkylene wherein one or more alkylene units of the C_1-C_2 alkylene are optionally and independently replaced by $–N(R^{20})–$. In some cases, S^1 is selected from: (i) an

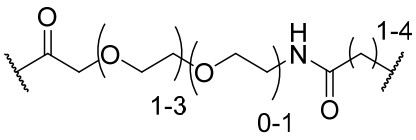
optionally substituted C_2-C_3 alkylene wherein one or more alkylene units of the C_2-C_3 alkylene are optionally and independently replaced by –N(R^{20})–. In some cases, S^1 is selected from . In some cases, S^1 is represented by .

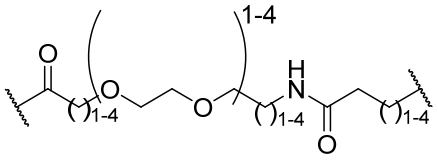
[00149] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-3), or Formula (A-4), S^1 is selected from . In some cases, S^1 is represented by .

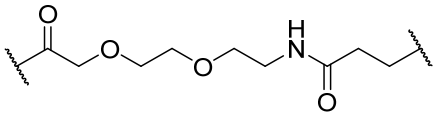
[00150] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-CA), Formula (II-D), Formula (II-G), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), or Formula (A-4), S^2 is selected from: (i) an optionally substituted C_8-C_{12} alkylene wherein one or more alkylene units of the C_8-C_{12} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –O–, and –C(O)–. In some cases, S^2 is selected from . In some cases, S^2 is represented by .

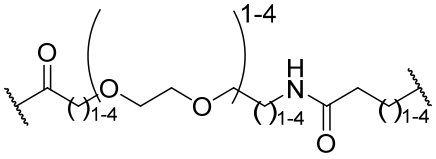
[00151] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-CA), Formula (II-D), Formula (II-G), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula

(XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), or Formula (A-4), S^2 is selected from: (i) an optionally substituted C_8-C_{12} alkylene wherein one or more alkylene units of the C_8-C_{12} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, –O–, and –C(O)–. In some cases, S^2 is selected from



and


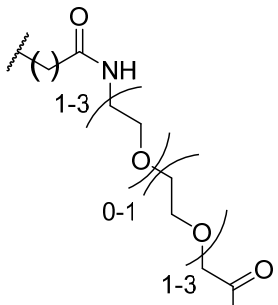
. In some cases, S^2 is represented by


. In some cases, S^2 is represented by


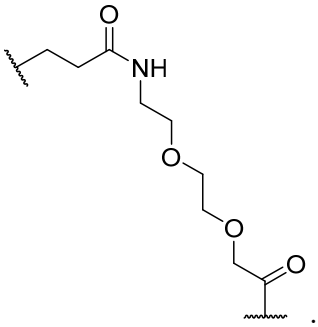
.

[00152] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), or Formula (A-4), S^2 is a linear alkylene.

[00153] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-CA), Formula (II-D), Formula (II-G), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), or Formula

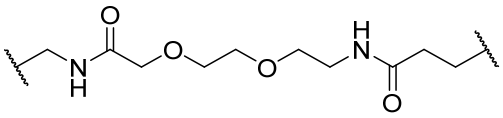


(A-4), S^2 is represented by . In some cases, S^2 is represented by



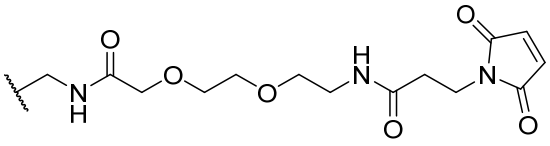
.

[00154] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-3), or Formula (A-4), S^1-S^2 is represented by



.

[00155] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (II-A), Formula (II-B), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-3), or Formula (A-4), S^1-S^2-M^1 is represented by



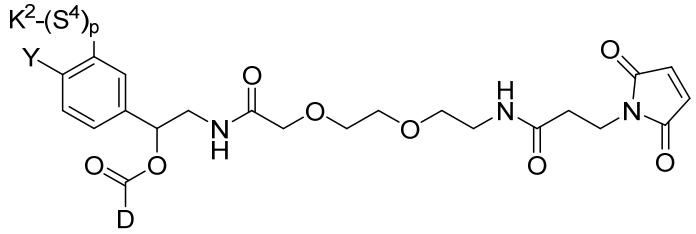
, wherein S^3 is absent.

[00156] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (I-AA), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-D), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), S^3 is present and is a phenylene.

[00157] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (I), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-

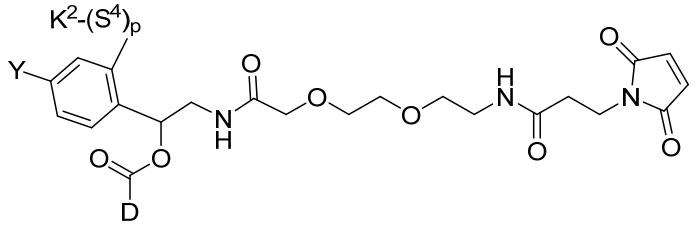
AA), Formula (I-A), Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), S^3 is absent.

[00158] In some embodiments, a Drug-Linker or salt of Formula (I), is represented by

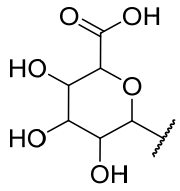


Formula (II-E). In some cases, p is 1.

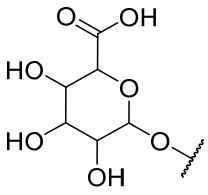
[00159] In some embodiments, a Drug-Linker or salt of Formula (I), is represented by



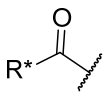
Formula (II-F). In some cases, p is 1.

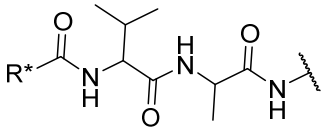
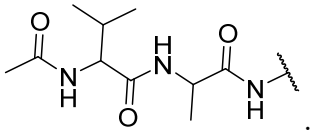
[00160] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-CA), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-CA), Formula (II-D), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (XX), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), the sugar cleavable unit of T^1 includes a sugar. In some cases, the sugar is glucuronide. In some cases, the sugar is selected from fructose, galactose, glucose, xylose and ribose. In some cases, the sugar is a monosaccharide. In some cases, the sugar is a disaccharide. In some cases, the T^1 is .

[00161] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-CA), Formula (II-D), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (XX), Formula (XXIII), Formula (A), Formula (Aa),

Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), Y is .

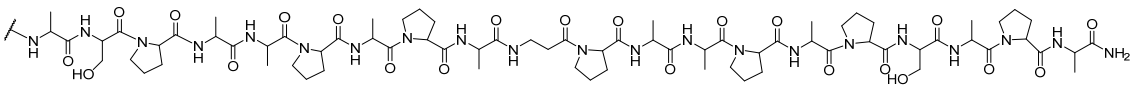
[00162] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-CA),Formula (II-D), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (XX), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), the peptide unit of T^2 includes one or more amino acids selected from a group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, sarcosine, serine, threonine, tryptophan, tyrosine, valine, citrulline, and β-Alanine. In some cases, the peptide unit of T^2 includes one or more amino acids selected from a group consisting of alanine, arginine, asparagine, aspartic acid, glutamine, glycine, lysine, methionine, phenylalanine, proline, serine, valine, citrulline, and β-Alanine. In some cases, the peptide unit of T^2 includes a dipeptide or tripeptide. In some cases, the peptide unit of T^2 includes a dipeptide. In some cases, the dipeptide is selected from Val-Cit, Val-Ala and Phe-Lys.

[00163] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-A), Formula (II-D), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (XX), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), the peptide unit of T^2 includes a capping moiety. In some cases, the capping moiety is a moiety capable of reacting with an amine of the peptide to form an amide, carbamate or sulfonamide. In some cases, the capping moiety is a moiety which results from reacting with an amine to form an amide, carbamate or sulfonamide. In some cases, the capping moiety is a moiety which results from reacting with an amine to form an amide. In some cases, the capping moiety is a moiety which caps the end of an peptide/amino acid. In some cases, the capping moiety is an acyl moiety. In some cases, the capping moiety is , wherein R* is selected

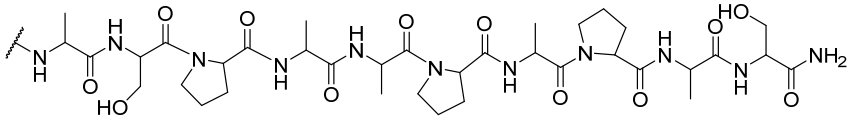
from C_{1-6} alkyl. In some cases, the capping moiety is . In some cases, Y is , wherein R* is selected from C_{1-6} alkyl. In some cases, Y is .

[00164] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), K^1 is not a polysarcosine. In some cases, K^1 does not include adjacent sarcosines. In some cases, when K^1 includes a sarcosine, there is at least one other amino acid present. In some cases, when a peptide unit includes a sarcosine, there is at least one other amino acid present.

[00165] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), K^1 includes PASylation. In some cases, PASylation is a peptide comprising proline, alanine, and serine. In some cases, PASylation is a peptide consisting of only proline, alanine, and serine. In some cases, K^1 includes PASylation of less than PAS100. For example, PAS100 refers to a peptide having 100 amino acids, wherein the amino acids are selected from proline, alanine, and serine. In some cases, K^1 includes PASylation of less than PAS50. In some cases, K^1 includes PASylation of less than PAS25. In some cases, K^1 includes PASylation of more than PAS5. In some cases, K^1 includes PASylation of more than PAS9. In some cases, K^1 includes PASylation of more than PAS15. In some cases, K^1 includes PASylation of PAS5 to PAS25. In some cases, K^1 includes PASylation of PAS10 to PAS20. In some cases, K^1 includes PASylation of PAS10. In some cases, K^1 includes PASylation of PAS20. In some cases, K^1 includes a beta-alanine that links the PASylation to the drug-linker. In some cases, PASylation is used to extend the plasma half-life. In some cases, PASylation is used to increase solubility. In some cases, PASylation is used to increase solubility without generating secondary structures. In some cases, PASylation is



(SEQ ID NO: 14) In some cases, PASylation is



(SEQ ID NO: 15) .

[00166] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), K^1 is not a polysarcosine. In some cases, K^1 includes adjacent sarcosines. In some cases, when K^1 includes a sarcosine, there is at least one other amino acid present. In some cases, when K^1 includes adjacent sarcosines, there is at least one other amino acid present. In some cases, when a peptide unit includes a sarcosine, there is at least one other amino acid present. In some cases, when a peptide unit includes adjacent sarcosines, there is at least one other amino acid present. In some cases, K^1 includes a glycine and two adjacent sarcosines. In some cases, K^1 includes a glycine and three adjacent sarcosines. In some cases, K^1 includes a glycine and four adjacent sarcosines. In some cases, K^1 is a peptide unit selected from a glycine and two adjacent sarcosines. In some cases K^1 is a peptide unit selected from a glycine and three adjacent sarcosines. In some cases, K^1 is a peptide unit selected from a glyicine and four adjacent sarcosines. In some cases, K^1 includes 2 glycines and 8 sarcosines. In some cases, K^1 includes 3 glycines and 8 sarcosines. In some cases, K^1 includes 4 glycines and 7 sarcosines. In some cases, K^1 includes 3 glycines and 7 sarcosines. In some cases, K^1 includes 3 glycines and 6 sarcosines. In some cases, K^1 includes 3 glycines and 5 sarcosines. In some cases, K^1 includes 3 glycines and 4 sarcosines. In some cases, K^1 includes 3 glycines and 3 sarcosines. In some cases, K^1 includes 3 glycines and 9 sarcosines. In some cases, K^1 includes 3 glycines and 10 sarcosines. In some cases, K^1 includes 5 glycines and 5 sarcosines. In some cases, K^1 includes 4 glycines and 4 sarcosines. In some cases, K^1 includes 4 glycines and 5 sarcosines. In some cases, K^1 includes 5 glycines and 4 sarcosines. In some cases, K^1 has at most 9 sarcosines. In some cases, K^1 has at most 8 sarcosines. In some cases, K^1 has at most 7 sarcosines. In some cases, K^1 has at most 6 sarcosines. In some cases, K^1 has at most 5 sarcosines. In some cases, K^1 has at most 4 sarcosines. In some cases, K^1 has at most 3 sarcosines. In some cases, K^1 has at most 2 sarcosines. In some cases, K^1 has at most 1 sarcosine. In some cases, K^1 has at most 9 glycines. In some cases, K^1 has at most 8 glycines. In some cases, K^1 has at most 7 glycines. In some cases, K^1 has at most 6 glycines. In some cases,

K^1 has at most 5 glycines. In some cases, K^1 has at most 4 glycines. In some cases, K^1 has at most 3 glycines. In some cases, K^1 has at most 2 glycines. In some cases, K^1 has at most 1 glycine.

[00167] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), each K^1 is selected from a peptide unit. In some cases, the peptide unit of K^1 has 1 to 50 amino acids. In some cases, the peptide unit of K^1 has 1 to 20 amino acids. In some cases, the peptide unit of K^1 has 1 to 10 amino acids. In some cases, the peptide unit of K^1 has 2 to 50 amino acids. In some cases, the peptide unit of K^1 has 2 to 40 amino acids. In some cases, the peptide unit of K^1 has 2 to 30 amino acids. In some cases, the peptide unit of K^1 has 2 to 20 amino acids. In some cases, the peptide unit of K^1 has 2 to 10 amino acids. In some cases, the peptide unit of K^1 has 5 to 10 amino acids. In some cases, the peptide unit of K^1 has at least 1 amino acids. In some cases, the peptide unit of K^1 has 1 amino acid. In some cases, the peptide unit of K^1 has at least 2 amino acids. In some cases, the peptide unit of K^1 has at least 5 amino acids. In some cases, the peptide unit of K^1 has at least 8 amino acids. In some cases, the peptide unit of K^1 has at least 10 amino acids. In some cases, the peptide unit of K^1 has at most 10 amino acids. In some cases, the peptide unit of K^1 has 10 amino acids. In some cases, the peptide unit of K^1 has at least 12 amino acids. In some cases, the peptide unit of K^1 has at most 12 amino acids. In some cases, the peptide unit of K^1 has at least 20 amino acids. In some cases, the peptide unit of K^1 has at most 20 amino acids. In some cases, the peptide unit of K^1 has 20 amino acids. In some cases, the peptide unit of K^1 has at most 30 amino acids. In some cases, the peptide unit of K^1 has at least 30 amino acids. In some cases, the amino acids of K^1 is selected from a group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, sarcosine, serine, threonine, tryptophan, tyrosine, valine, citrulline, and β-Alanine. In some cases, the amino acids of K^1 is selected from a group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, citrulline, and β-Alanine. In some cases, the amino acids of K^1 is selected from a group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, citrulline, and β-Alanine. In some cases,

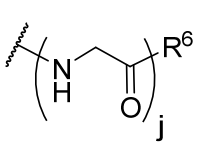
the amino acids of K^1 is selected from a group consisting of glycine, sarcosine, proline, serine, alanine, and β-Alanine. In some cases, the amino acids of K^1 is selected from a group consisting of glycine, proline, serine, alanine, and β-Alanine. In some cases, the amino acids of K^1 is selected from a group consisting of proline, serine, alanine, and β-Alanine. In some cases, the amino acids of K^1 includes at least one glycine and at least one other amino acid. In some cases, the amino acids of K^1 includes at least one glycine and at least one sarcosine. In some cases, the amino acids of K^1 includes at least one glycine and at least one other amino acid selected from proline, serine, alanine, and β-Alanine. In some cases, the amino acids of K^1 is selected from a group consisting of glycine, proline, serine, alanine, and β-Alanine. In some cases, K^1 includes at least one glycine. In some cases, K^1 includes at least one proline. In some cases, K^1 includes at least one serine. In some cases, K^1 includes at least one alanine. In some cases, K^1 includes at least one β-Alanine.

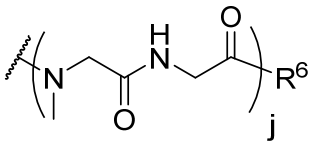
[00168] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), each K^1 is selected from a peptide unit. In some cases, the peptide unit of K^1 has 1 to 50 amino acids. In some cases, the peptide unit of K^1 has 1 to 20 amino acids. In some cases, the peptide unit of K^1 has 1 to 10 amino acids. In some cases, the peptide unit of K^1 has 2 to 50 amino acids. In some cases, the peptide unit of K^1 has 2 to 40 amino acids. In some cases, the peptide unit of K^1 has 2 to 30 amino acids. In some cases, the peptide unit of K^1 has 2 to 20 amino acids. In some cases, the peptide unit of K^1 has 2 to 10 amino acids. In some cases, the peptide unit of K^1 has 5 to 10 amino acids. In some cases, the peptide unit of K^1 has at least 1 amino acids. In some cases, the peptide unit of K^1 has 1 amino acid. In some cases, the peptide unit of K^1 has at least 2 amino acids. In some cases, the peptide unit of K^1 has at least 5 amino acids. In some cases, the peptide unit of K^1 has at least 8 amino acids. In some cases, the peptide unit of K^1 has at least 10 amino acids. In some cases, the peptide unit of K^1 has at most 10 amino acids. In some cases, the peptide unit of K^1 has 10 amino acids. In some cases, the peptide unit of K^1 has at least 12 amino acids. In some cases, the peptide unit of K^1 has at most 12 amino acids. In some cases, the peptide unit of K^1 has at least 20 amino acids. In some cases, the peptide unit of K^1 has at most 20 amino acids. In some cases, the peptide unit of K^1 has 20 amino acids. In some cases, the peptide unit of K^1 has at most 30 amino acids. In some cases, the peptide unit of K^1 has at least 30 amino acids. In some cases, K^1 is a peptide unit selected from a glycine and two adjacent sarcosines. In some cases K^1 is a

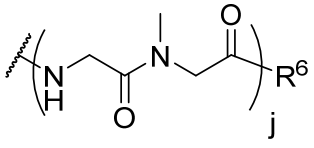
peptide unit selected from a glycine and three adjacent sarcosines. In some cases, K^1 is a peptide unit selected from a glyicine and four adjacent sarcosines. In some cases, when a peptide unit includes adjacent sarcosines, there is at least one other amino acid present. In some cases, K^1 includes a glycine and two adjacent sarcosines. In some cases, K^1 includes a glycine and three adjacent sarcosines. In some cases, K^1 includes a glycine and four adjacent sarcosines. In some cases, K^1 is a peptide unit selected from a glycine and two adjacent sarcosines. In some cases K^1 is a peptide unit selected from a glycine and three adjacent sarcosines. In some cases, K^1 is a peptide unit selected from a glyicine and four adjacent sarcosines. In some cases, K^1 includes 2 glycines and 8 sarcosines. In some cases, K^1 includes 3 glycines and 8 sarcosines. In some cases, K^1 includes 4 glycines and 7 sarcosines. In some cases, K^1 includes 3 glycines and 7 sarcosines. In some cases, K^1 includes 3 glycines and 6 sarcosines. In some cases, K^1 includes 3 glycines and 5 sarcosines. In some cases, K^1 includes 3 glycines and 4 sarcosines. In some cases, K^1 includes 3 glycines and 3 sarcosines. In some cases, K^1 includes 3 glycines and 9 sarcosines. In some cases, K^1 includes 3 glycines and 10 sarcosines. In some cases, K^1 includes 5 glycines and 5 sarcosines. In some cases, K^1 includes 4 glycines and 4 sarcosines. In some cases, K^1 includes 4 glycines and 5 sarcosines. In some cases, K^1 includes 5 glycines and 4 sarcosines. In some cases, K^1 has at most 9 sarcosines. In some cases, K^1 has at most 8 sarcosines. In some cases, K^1 has at most 7 sarcosines. In some cases, K^1 has at most 6 sarcosines. In some cases, K^1 has at most 5 sarcosines. In some cases, K^1 has at most 4 sarcosines. In some cases, K^1 has at most 3 sarcosines. In some cases, K^1 has at most 2 sarcosines. In some cases, K^1 has at most 1 sarcosine. In some cases, K^1 has at most 9 glycines. In some cases, K^1 has at most 8 glycines. In some cases, K^1 has at most 7 glycines. In some cases, K^1 has at most 6 glycines. In some cases, K^1 has at most 5 glycines. In some cases, K^1 has at most 4 glycines. In some cases, K^1 has at most 3 glycines. In some cases, K^1 has at most 2 glycines. In some cases, K^1 has at most 1 glycine. In some cases, the amino acids of K^1 is selected from a group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, sarcosine, serine, threonine, tryptophan, tyrosine, valine, citrulline, and β-Alanine. In some cases, the amino acids of K^1 is selected from a group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, citrulline, and β-Alanine. In some cases, the amino acids of K^1 is selected from a group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, citrulline, and β-Alanine. In some cases, the amino acids of K^1 is selected from a group consisting of glycine,

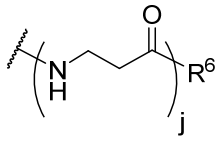
sarcosine, proline, serine, alanine, and β-Alanine. In some cases, the amino acids of K^1 is selected from a group consisting of glycine, proline, serine, alanine, and β-Alanine. In some cases, the amino acids of K^1 is selected from a group consisting of proline, serine, alanine, and β-Alanine. In some cases, the amino acids of K^1 includes at least one glycine and at least one other amino acid. In some cases, the amino acids of K^1 includes at least one glycine and at least one sarcosine. In some cases, the amino acids of K^1 includes at least one glycine and at least one other amino acid selected from proline, serine, alanine, and β-Alanine. In some cases, the amino acids of K^1 is selected from a group consisting of glycine, proline, serine, alanine, and β-Alanine. In some cases, K^1 includes at least one glycine. In some cases, K^1 includes at least one proline. In some cases, K^1 includes at least one serine. In some cases, K^1 includes at least one alanine. In some cases, K^1 includes at least one β-Alanine.

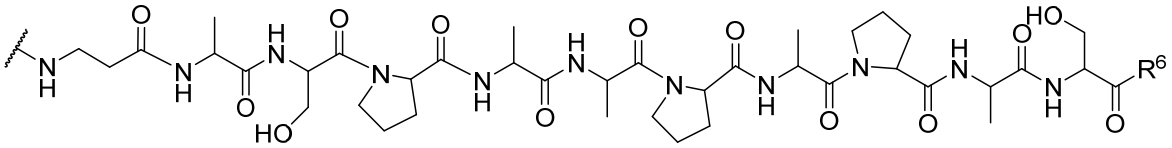
[00169] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), the peptide unit of K^1 has a terminus unit. In some cases, K^1 is selected from

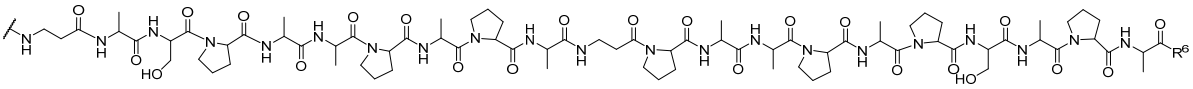

(SEQ ID NO: 16),


(SEQ ID NO: 17),

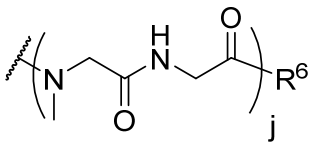

(SEQ ID NO: 18),

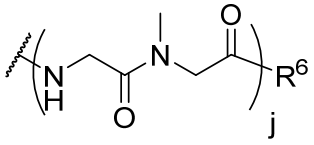

(SEQ ID NO: 19),

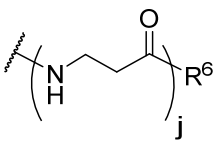

(SEQ ID NO: 9),


(SEQ ID NO: 10),

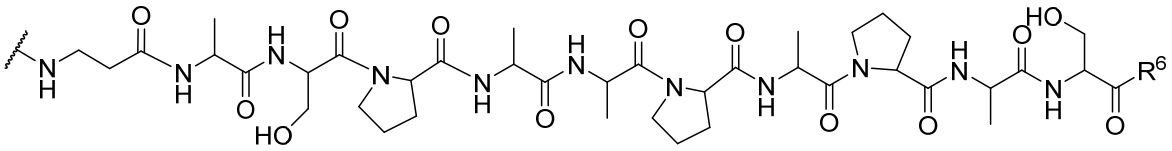
wherein the terminus unit is represented by R^6, and each j is selected from 1 to 30. In some cases, K^1 is selected from


(SEQ ID NO: 17),

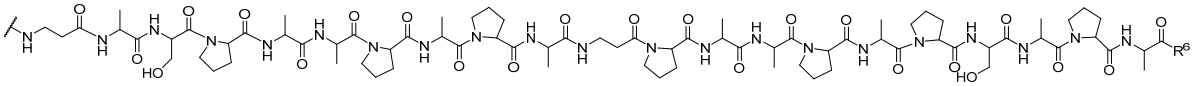


(SEQ ID NO: 18), 

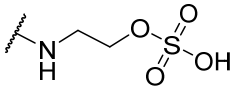
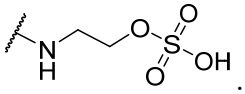
(SEQ ID NO: 19),

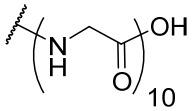
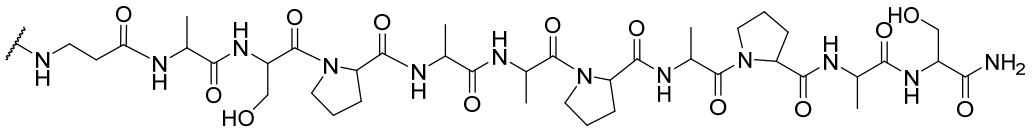


(SEQ ID NO: 9),

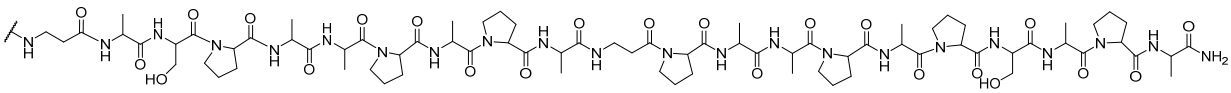


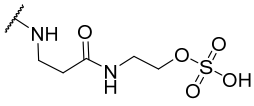
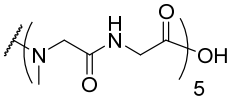
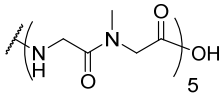
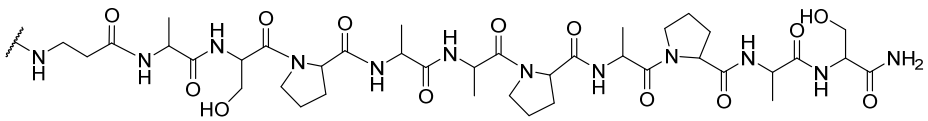
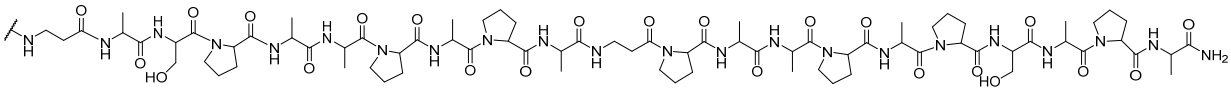
(SEQ ID NO: 10),

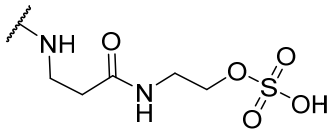
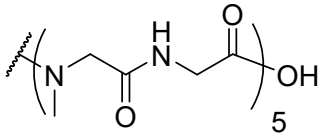
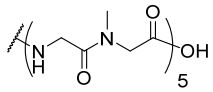
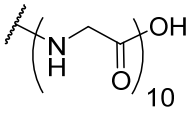
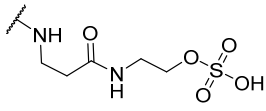
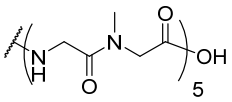
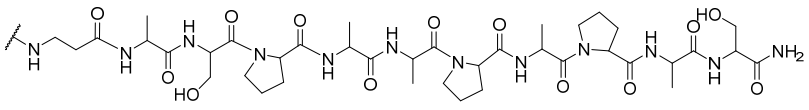
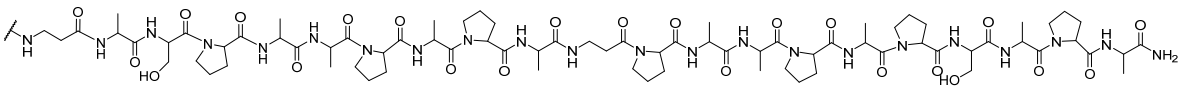
wherein the terminus unit is represented by R^6, and each j is selected from 1 to 30. In some cases, j is 1. In some cases, j is 3. In some cases, j is 5. In some cases, j is 10. In some cases, j is 20. In some cases, R^6 is selected from $-OR^7$ and $-NHR^7$, wherein R^7 is selected from hydrogen; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle. In some cases, R^6 is selected from -OH, $-NH_2$, and . In some cases, R^6 is -OH. In some cases, R^6 is $-NH_2$. In some cases, R^6 is .

[00170] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), K^1 is selected from  (SEQ ID NO: 7), 

(SEQ ID NO: 9),

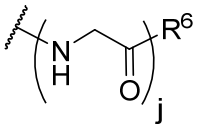
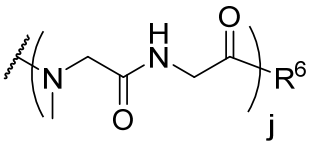


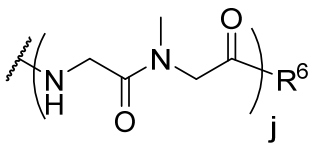
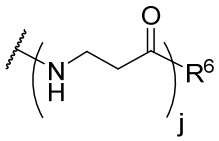
(SEQ ID NO: 10), ,  (SEQ ID NO: 20), and  (SEQ ID NO: 8). In some cases, K^1 is selected from  (SEQ ID NO: 9), 

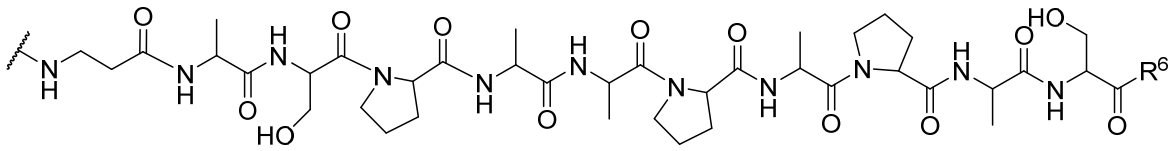
(SEQ ID NO: 10), ,  (SEQ ID NO: 20), and  (SEQ ID NO: 8). In some cases, K^1 is selected from  (SEQ ID NO: 7). In some cases, K^1 is selected from . In some cases, K^1 is selected from  (SEQ ID NO: 8). In some cases, K^1 is selected from  (SEQ ID NO: 9). In some cases, K^1 is selected from 

(SEQ ID NO: 10).

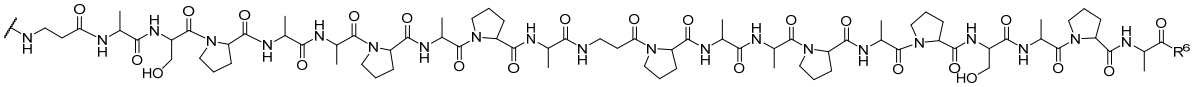
[00171] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), the peptide unit of K^1 has a terminus unit. In

some cases, K^1 is selected from  (SEQ ID NO: 16), 

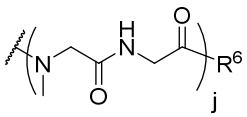
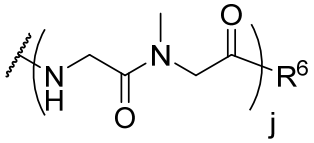
(SEQ ID NO: 17),  (SEQ ID NO: 18),  (SEQ ID NO: 19),

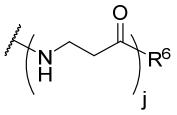


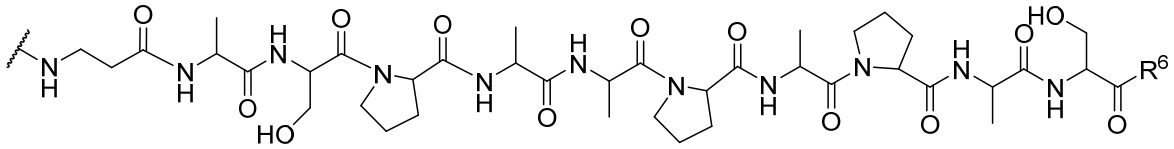
(SEQ ID NO: 9),



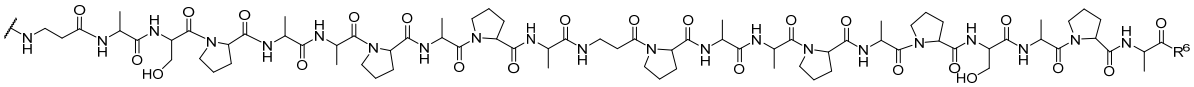
(SEQ ID NO: 10),

wherein the terminus unit is represented by R^6, and each j is selected from 1 to 30. In some cases, K^1 is selected from  (SEQ ID NO: 17), 

(SEQ ID NO: 18),  (SEQ ID NO: 19),

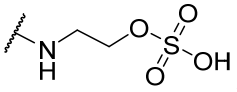
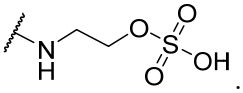


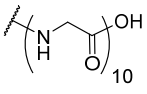
(SEQ ID NO: 9),

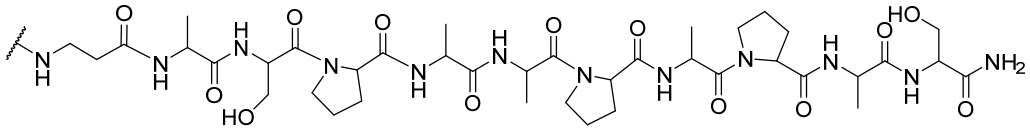


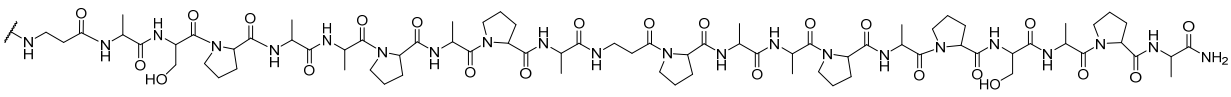
(SEQ ID NO: 10),

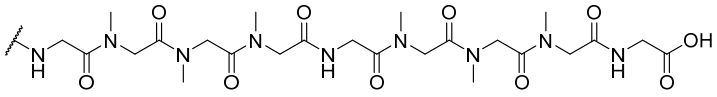
wherein the terminus unit is represented by R^6, and each j is selected from 1 to 30. In some cases, j is 1. In some cases, j is 3. In some cases, j is 5. In some cases, j is 10. In some cases, j is 20. In some cases, R^6 is selected from $-OR^7$ and $-NHR^7$, wherein R^7 is selected from hydrogen; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, -O-

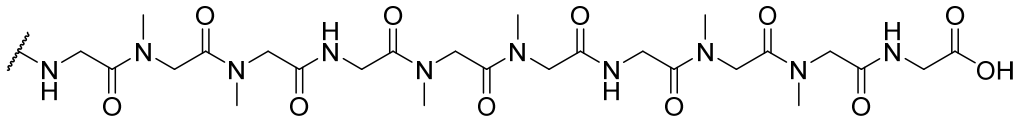
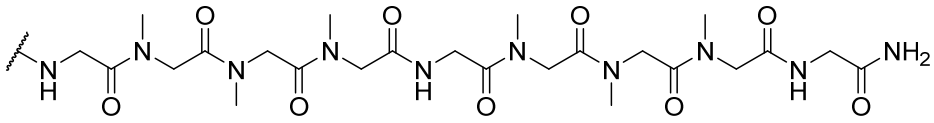
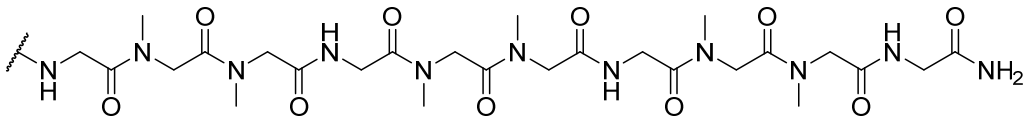
$S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle. In some cases, R^6 is selected from -OH, $-NH_2$, and . In some cases, R^6 is -OH. In some cases, R^6 is $-NH_2$. In some cases, R^6 is .

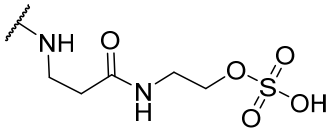
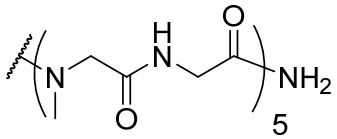
In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), K^1 is selected from  (SEQ ID NO: 7),

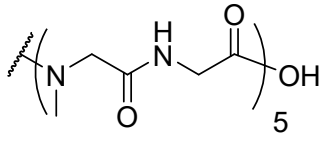
 (SEQ ID NO: 9),

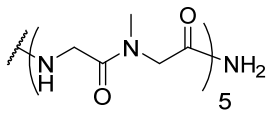
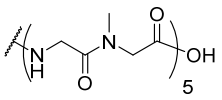


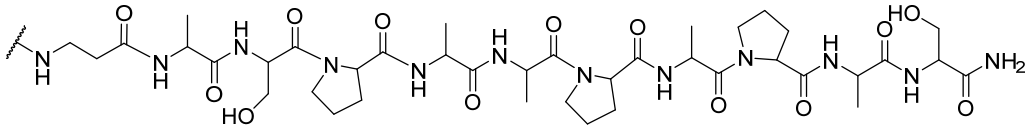
(SEQ ID NO: 10)  (SEQ ID NO: 11),

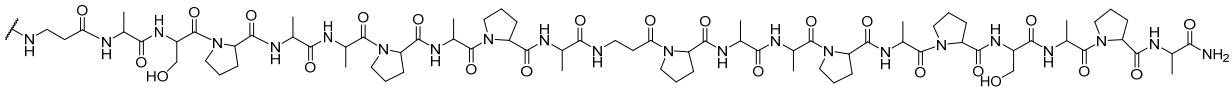
 (SEQ ID NO: 12),  (SEQ ID NO: 11), 

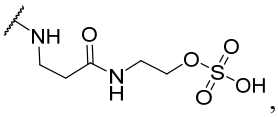
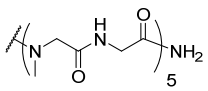
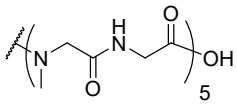
(SEQ ID NO: 12), ,  (SEQ ID NO: 20),

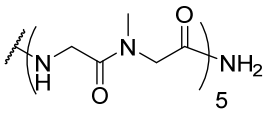
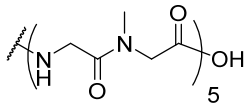
 (SEQ ID NO: 20),

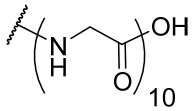
 (SEQ ID NO: 8), and  (SEQ ID NO: 8). In some cases, K^1 is selected from

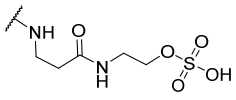
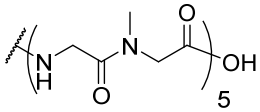
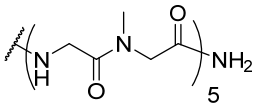
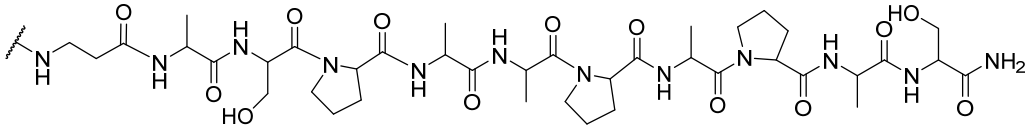
 (SEQ ID NO: 9),

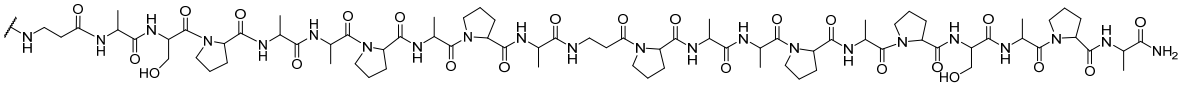


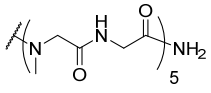
(SEQ ID NO: 10), ,  (SEQ ID NO: 20), 

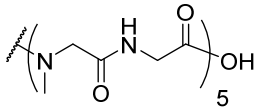
(SEQ ID NO: 20),  (SEQ ID NO: 8),and  (SEQ ID NO: 8).

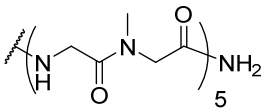
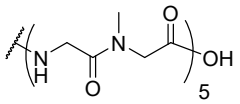
In some cases, K^1 is selected from  (SEQ ID NO: 7). In some cases, K^1 is selected from

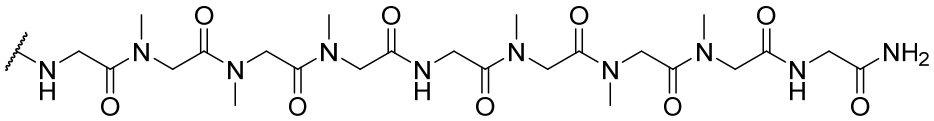
. In some cases, K^1 is selected from  (SEQ ID NO: 8). In some cases, K^1 is selected from  (SEQ ID NO: 8). In some cases, K^1 is selected from  (SEQ ID NO: 9). In some cases, K^1 is selected from

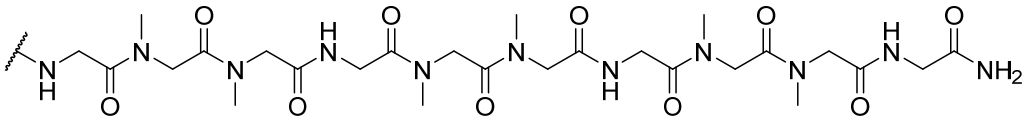
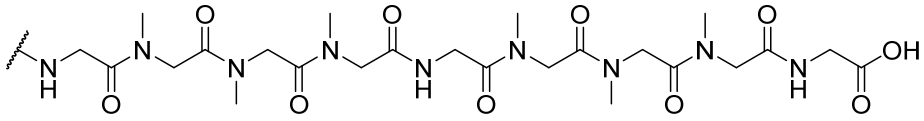
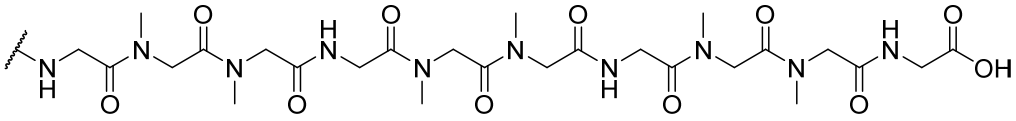


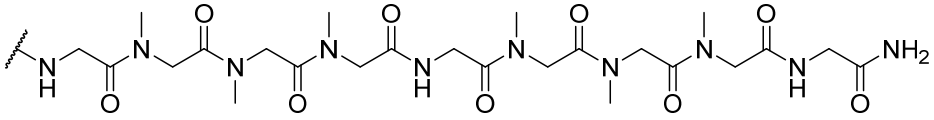
(SEQ ID NO: 10). In some cases, K^1 is selected from  (SEQ ID NO: 20),

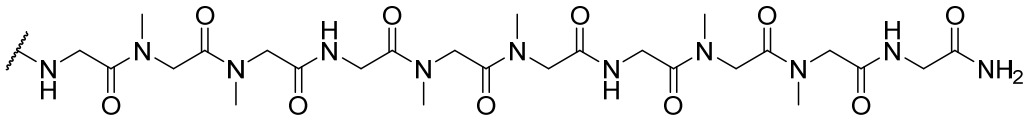
 (SEQ ID NO: 20),

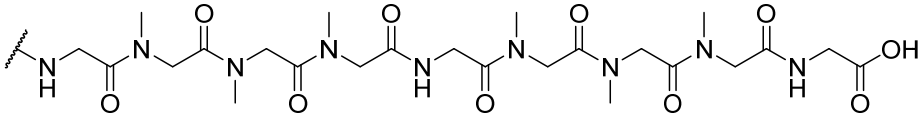
 (SEQ ID NO: 8),  (SEQ ID NO: 8),

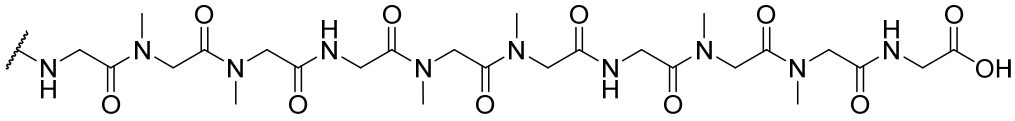
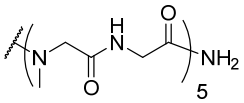
 (SEQ ID NO: 11),

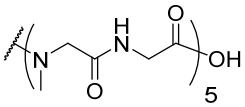
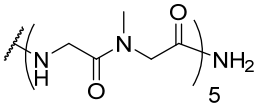
 (SEQ ID NO: 12),  (SEQ ID NO: 11) and  (SEQ ID NO: 12). In some cases, K^1 is selected from

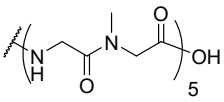
 (SEQ ID NO: 11)

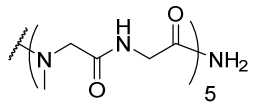
and  (SEQ ID NO: 12). In some cases, K^1 is selected from

 (SEQ ID NO: 11)

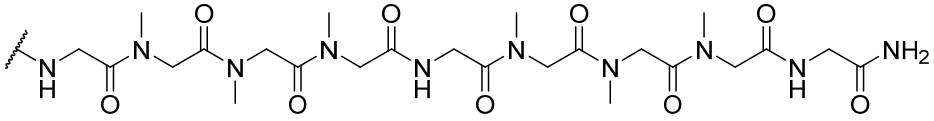
and  (SEQ ID NO: 12). In some cases, K^1 is selected from  (SEQ ID NO: 20),

 (SEQ ID NO: 20),  (SEQ ID NO: 8), and

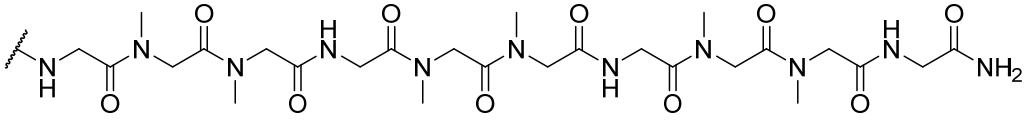
 (SEQ ID NO: 8).In some cases, K^1 is selected from



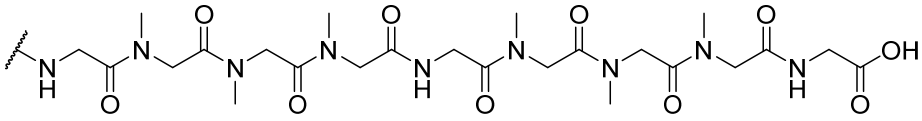
(SEQ ID NO: 20). In some cases, K^1 is selected from



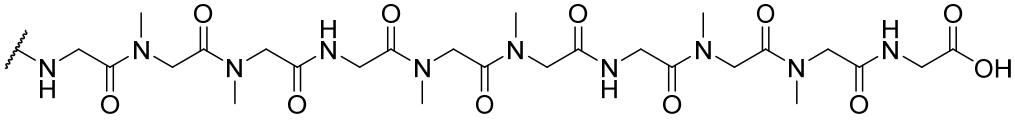
(SEQ ID NO: 11). In some cases, K^1 is selected from



(SEQ ID NO: 12). In some cases, K^1 is selected from



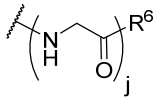
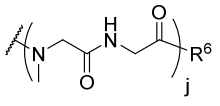
(SEQ ID NO: 11). In some cases, K^1 is selected from

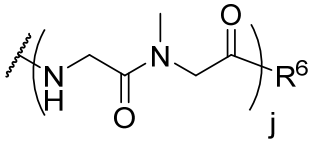
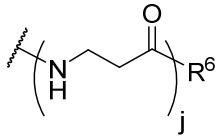


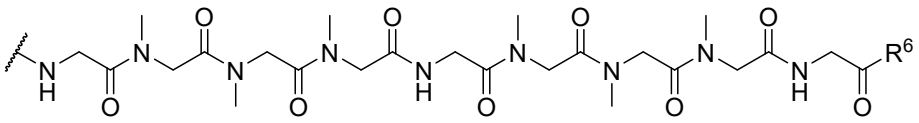
(SEQ ID NO: 12).

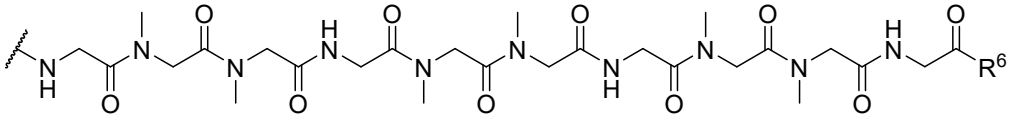
[00172] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), the K^1 is selected from a peptide unit. wherein the peptide unit has a terminal -NH_2. In some cases, K^1 is selected from a peptide unit. wherein the peptide unit has a terminal -OH. In some cases, K^1 is selected from a peptide. wherein the peptide has a terminal -NH_2. In some cases, K^1 is selected from a peptide, wherein the peptide has a terminal -OH.

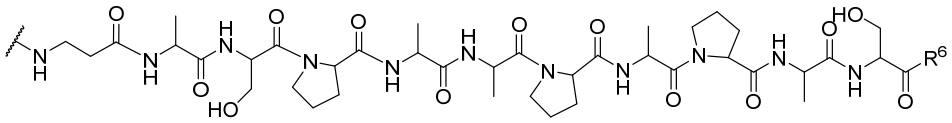
[00173] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), the peptide unit of K^1 has a terminus unit. In

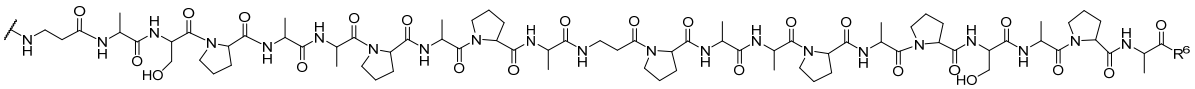
some cases, K^1 is selected from  (SEQ ID NO: 16),  (SEQ ID NO: 17),

 (SEQ ID NO: 18),  (SEQ ID NO: 19),

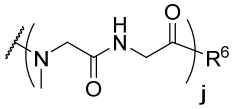
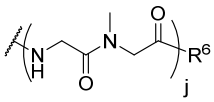
 (SEQ ID NO: 11),

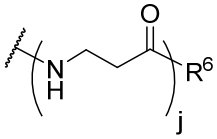
 (SEQ ID NO: 12),

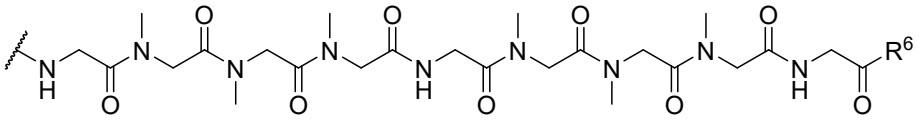
 (SEQ ID NO: 9),

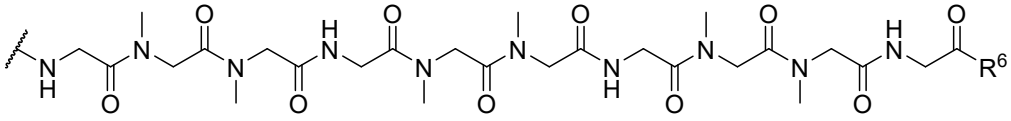


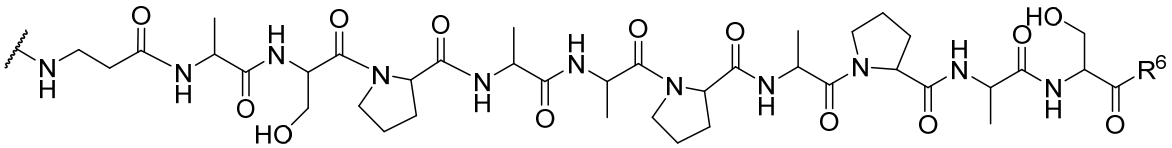
(SEQ ID NO: 10),

wherein the terminus unit is represented by R^6, and each j is selected from 1 to 30. In some cases, K^1 is selected from  (SEQ ID NO: 17),  (SEQ ID NO: 18),

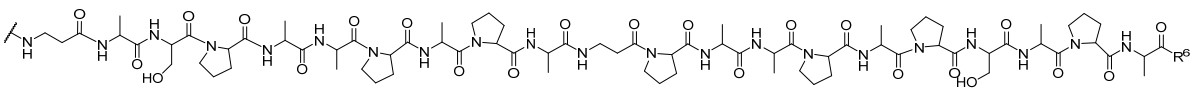
 (SEQ ID NO: 19),

 (SEQ ID NO: 11),

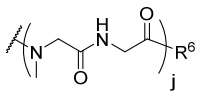
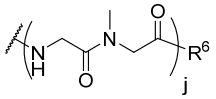
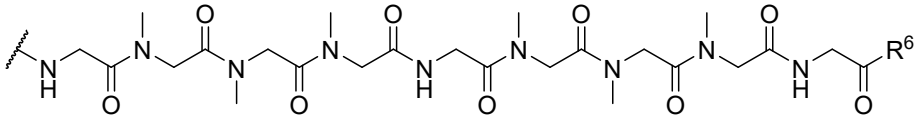
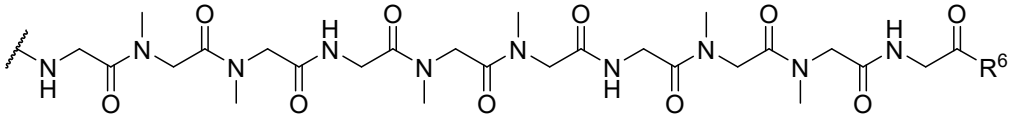
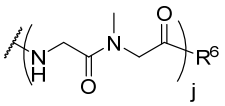
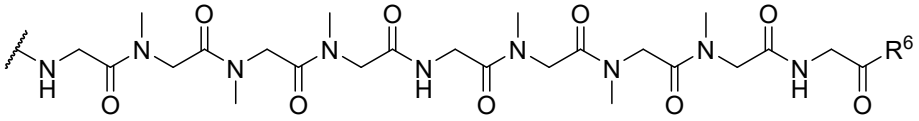
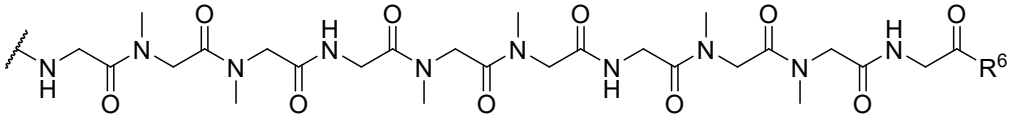
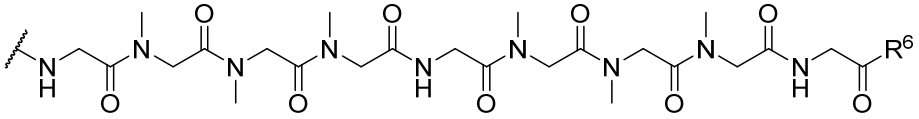
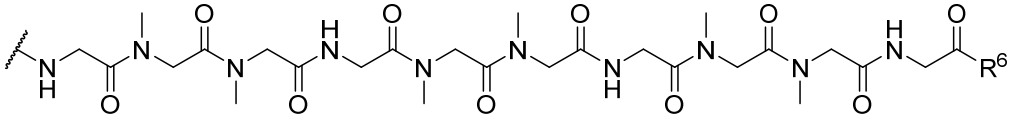
 (SEQ ID NO: 12),



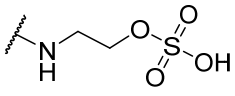
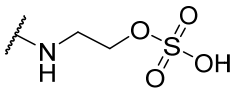
(SEQ ID NO: 9),

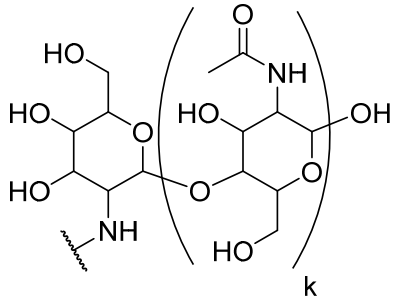
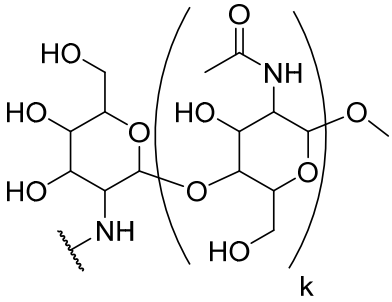


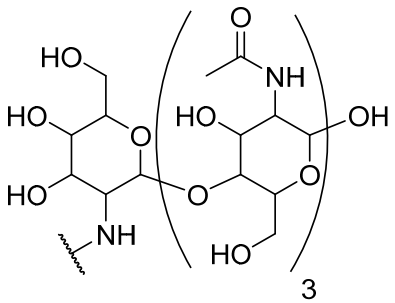
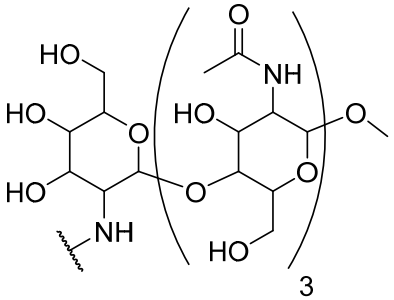
(SEQ ID NO: 10),

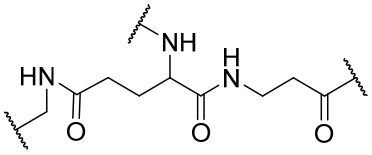
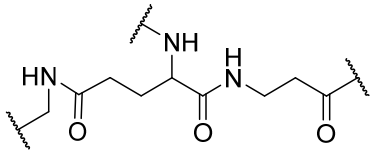
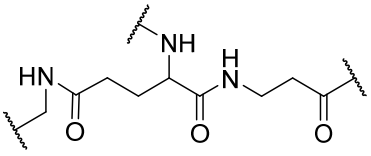
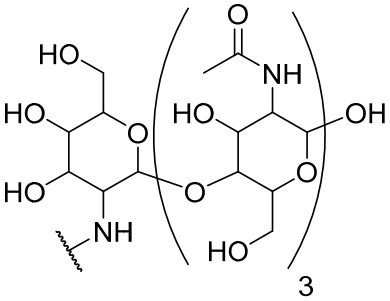
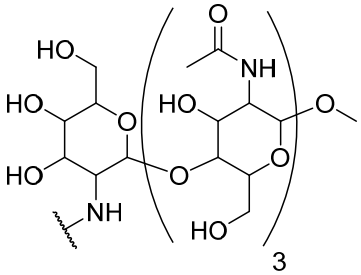
wherein the terminus unit is represented by R^6, and each j is selected from 1 to 30. In some cases, K^1 is selected from  (SEQ ID NO: 17),  (SEQ ID NO: 18),  (SEQ ID NO: 11),  (SEQ ID NO: 12), In some cases, K^1 is selected from  (SEQ ID NO: 18),  (SEQ ID NO: 11),  (SEQ ID NO: 12), In some cases, K^1 is selected from  (SEQ ID NO: 11),  (SEQ ID NO: 12),

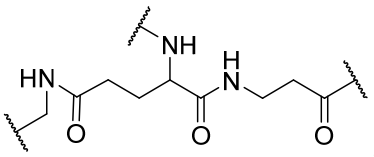
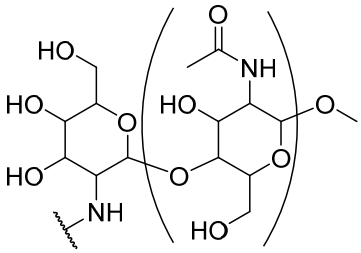
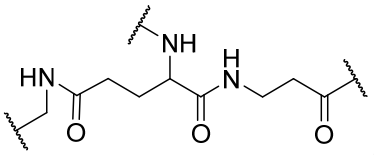
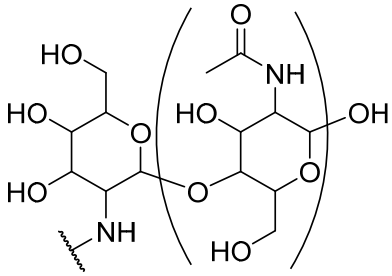
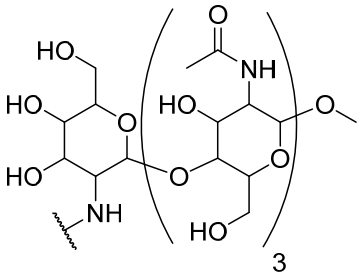
wherein the terminus unit is represented by R^6, and each j is selected from 1 to 30. In some cases, j is 1. In some cases, j is 3. In some cases, j is 5. In some cases, j is 10. In some cases, j is 20. In some cases, R^6 is selected from $-OR^7$ and $-NHR^7$, wherein R^7 is selected from hydrogen; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3-

to 10-membered heterocycle. In some cases, R^6 is selected from -OH, $-NH_2$, and . In some cases, R^6 is -OH. In some cases, R^6 is $-NH_2$. In some cases, R^6 is .

[00174] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-D), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), each K^1 is selected from: an oligosaccharide. In some cases, each K^1 is selected from: , wherein k is selected from 2 to 10. In some cases, each K^1 is selected from: , wherein k is selected from 2 to 10. In some cases, k is 2. In some cases, k is 3. In some cases, k is 4. In some cases, k is 5. In

some cases, k is 6. In some cases, each K^1 is selected from: . In some cases, each K^1 is selected from: .

[00175] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), S^1 is represented by . In some cases, S^1 is , and K^1 is an oligosaccharide. In some cases, S^1 is , and K^1 is selected from:  and . In some cases, S^1 is

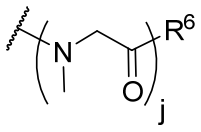
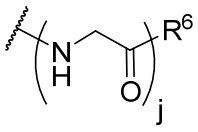
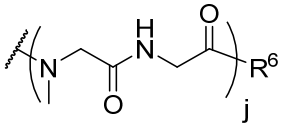

, and K^1 is 
. In some cases, S^1 is 
, and K^1 is 
. In some cases, K^1 is 
.

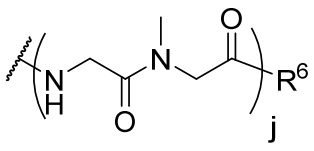
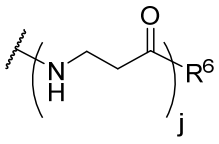
[00176] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (Ia), Formula (Ib), Formula (II-A), Formula (II-B), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (XX), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), K^2 is selected from a peptide unit. In some cases, the peptide unit is a residue. In some cases, the peptide unit of K^2 has 1 to 50 amino acids. In some cases, the peptide unit of K^2 has 1 to 20 amino acids. In some cases, the peptide unit of K^2 has 1 to 10 amino acids. In some cases, the peptide unit of K^2 has 2 to 50 amino acids. In some cases, the peptide unit of K^2 has 2 to 40 amino acids. In some cases, the peptide unit of K^2 has 2 to 30 amino acids. In some cases, the peptide unit of K^2 has 2 to 20 amino acids. In some cases, the peptide unit of K^2 has 2 to 10 amino acids. In some cases, the peptide unit of K^2 has 5 to 10 amino acids. In some cases, the peptide unit of K^2 has at least 1 amino acid. In some cases, the peptide unit of K^2 has 1 amino acid. In some cases, the peptide unit of K^2 has at least 2 amino acids. In some cases, the peptide unit of K^2 has at least 5 amino acids. In some cases, the peptide unit of K^2 has at least 8 amino acids. In some cases, the peptide unit of K^2 has at least 10 amino acids. In some cases, the peptide unit of K^2 has at most 10 amino acids. In some cases, the peptide unit of K^2 has 10 amino acids. In some cases, the peptide unit of K^2 has at least 12

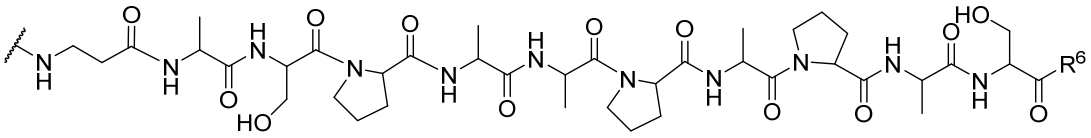
amino acids. In some cases, the peptide unit of K^2 has at most 12 amino acids. In some cases, the peptide unit of K^2 has at least 20 amino acids. In some cases, the peptide unit of K^2 has at most 20 amino acids. In some cases, the peptide unit of K^2 has 20 amino acids. In some cases, the peptide unit of K^2 has at most 30 amino acids. In some cases, the peptide unit of K^2 has at least 30 amino acids. In some cases, the amino acids of K^2 are selected from a group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, sarcosine, serine, threonine, tryptophan, tyrosine, valine, citrulline, and β-Alanine. In some cases, the amino acids of K^2 are selected from a group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, citrulline, and β-Alanine. In some cases, the amino acids of K^2 are selected from a group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, citrulline, and β-Alanine. In some cases, the amino acids of K^2 are selected from a group consisting of glycine, sarcosine, proline, serine, alanine, and β-Alanine. In some cases, the amino acids of K^2 are selected from a group consisting of sarcosine, proline, serine, alanine, and β-Alanine. In some cases, the amino acids of K^2 are selected from a group consisting of glycine, proline, serine, alanine, and β-Alanine. In some cases, the amino acids of K^2 are selected from a group consisting of glycine, proline, serine, alanine, and β-Alanine. In some cases, K^2 includes at least one glycine. In some cases, K^2 includes at least one proline. In some cases, K^2 includes at least one serine. In some cases, K^2 includes at least one alanine. In some cases, K^2 includes at least one β-Alanine. In some cases, K^2 is a polysarcosine. In some cases, K^2 is a polysarcosine with ten repeating sarcosine units. In some cases, the amino acids of K^2 includes at least one glycine and at least one amino acid. In some cases, the amino acids of K^2 includes at least one glycine and at least one amino acid selected from sarcosine, proline, serine, alanine, and β-Alanine.

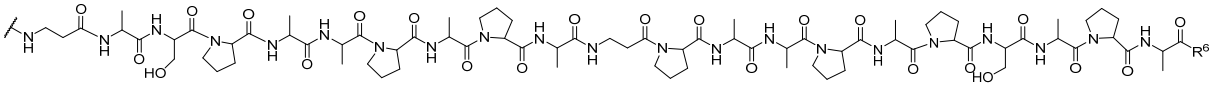
[00177] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-AA), Formula (I-AB), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-C), Formula (II-CA), Formula (II-D), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), or Formula (A-2), K^2 K^2 is not a polysarcosine. In some cases, K^2includes adjacent sarcosines. In some cases, when K^2includes a sarcosine, there is at least one other amino acid present. In some cases, when K^2 includes adjacent sarcosines, there is at least one other amino acid present. In some cases, when a peptide unit includes a sarcosine, there is at least one other amino acid present. In some cases, when a

peptide unit includes adjacent sarcosines, there is at least one other amino acid present. In some cases, K^2 includes a glycine and two adjacent sarcosines. In some cases, K^2 includes a glycine and three adjacent sarcosines. In some cases, K^2 includes a glycine and four adjacent sarcosines. In some cases, K^2 is a peptide unit selected from a glycine and two adjacent sarcosines. In some cases K^2 is a peptide unit selected from a glycine and three adjacent sarcosines. In some cases, K^2 is a peptide unit selected from a glyicine and four adjacent sarcosines. In some cases, K^2 includes 2 glycines and 8 sarcosines. In some cases, K^2 includes 3 glycines and 8 sarcosines. In some cases, K^2 includes 4 glycines and 7 sarcosines. In some cases, K^2 includes 3 glycines and 7 sarcosines. In some cases, K^2 includes 3 glycines and 6 sarcosines. In some cases, K^2 includes 3 glycines and 5 sarcosines. In some cases, K^2 includes 3 glycines and 4 sarcosines. In some cases, K^2 includes 3 glycines and 3 sarcosines. In some cases, K^2 includes 3 glycines and 9 sarcosines. In some cases, K^2 includes 3 glycines and 10 sarcosines. In some cases, K^2 includes 5 glycines and 5 sarcosines. In some cases, K^2 includes 4 glycines and 4 sarcosines. In some cases, K^2 includes 4 glycines and 5 sarcosines. In some cases, K^2 includes 5 glycines and 4 sarcosines. In some cases, K^2 has at most 9 sarcosines. In some cases, K^2 has at most 8 sarcosines. In some cases, K^2 has at most 7 sarcosines. In some cases, K^2 has at most 6 sarcosines. In some cases, K^2 has at most 5 sarcosines. In some cases, K^2 has at most 4 sarcosines. In some cases, K^2 has at most 3 sarcosines. In some cases, K^2 has at most 2 sarcosines. In some cases, K^2 has at most 1 sarcosine. In some cases, K^2 has at most 9 glycines. In some cases, K^2 has at most 8 glycines. In some cases, K^2 has at most 7 glycines. In some cases, K^2 has at most 6 glycines. In some cases, K^2 has at most 5 glycines. In some cases, K^2 has at most 4 glycines. In some cases, K^2 has at most 3 glycines. In some cases, K^2 has at most 2 glycines. In some cases, K^2 has at most 1 glycine.

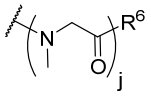
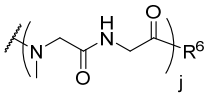
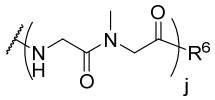
[00178] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (Ia), Formula (Ib), Formula (II-A), Formula (II-B), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (XX), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab),Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), the peptide unit of K^2 has a terminus unit. In some cases, K^2 is selected from  (SEQ ID NO: 21),  (SEQ ID NO: 16),  (SEQ ID NO: 17),

 (SEQ ID NO: 18),  (SEQ ID NO: 19),

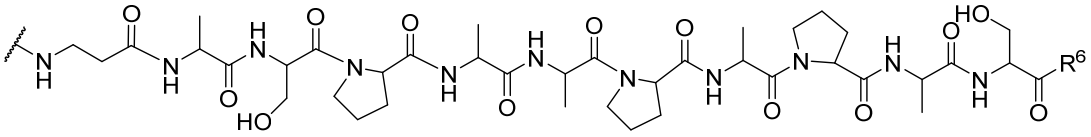
 (SEQ ID NO: 9),

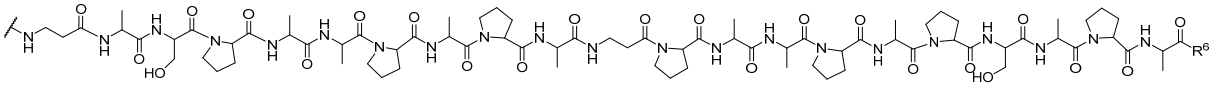


(SEQ ID NO: 10),

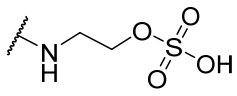
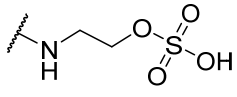
wherein the terminus unit is represented by R^6, and each j is selected from 1 to 30. In some cases, K^2 is selected from  (SEQ ID NO: 21),  (SEQ ID NO: 17), 

(SEQ ID NO: 18),

 (SEQ ID NO: 9),

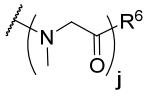
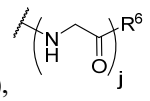
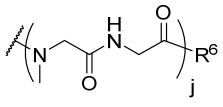


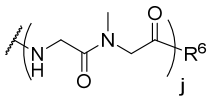
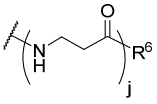
(SEQ ID NO: 10),

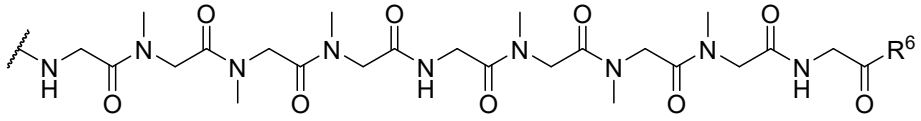
wherein the terminus unit is represented by R^6, and each j is selected from 1 to 30. In some cases, j is 1. In some cases, j is 3. In some cases, j is 5. In some cases, j is 10. In some cases, j is 20. In some cases, R^6 is selected from $-OR^7$ and $-NHR^7$, wherein R^7 is selected from hydrogen; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle. In some cases, R^6 is selected from -OH, $-NH_2$, and . In some cases, R^6 is -OH. In some cases, R^6 is $-NH_2$. In some cases, R^6 is .

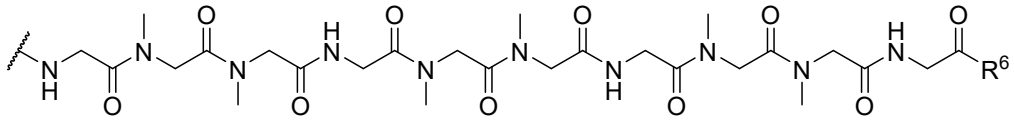
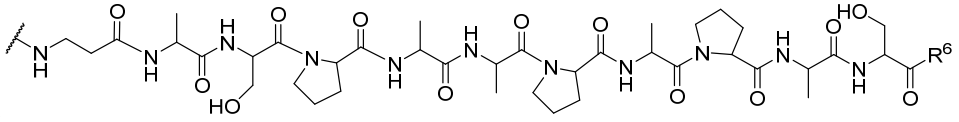
[00179] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (Ia), Formula (Ib), Formula (II-A), Formula (II-B), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (XX),

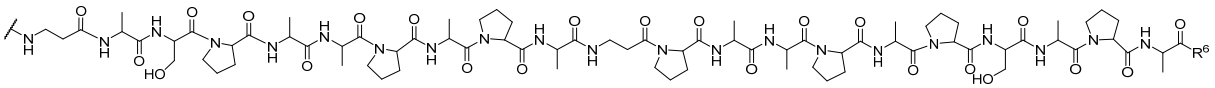
Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab),Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), the peptide unit of K^2 has a terminus unit. In some cases, K^2 is selected from

 (SEQ ID NO: 21),  (SEQ ID NO: 16),  (SEQ ID NO: 17),

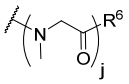
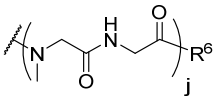
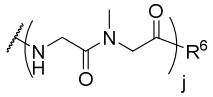
 (SEQ ID NO: 18),  (SEQ ID NO: 19),

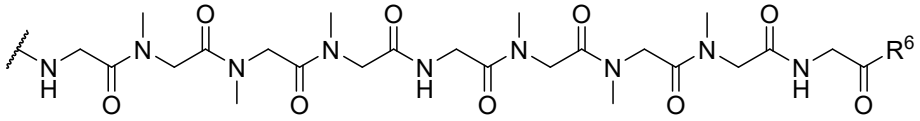
 (SEQ ID NO: 11),

 (SEQ ID NO: 12),  (SEQ ID NO: 9),

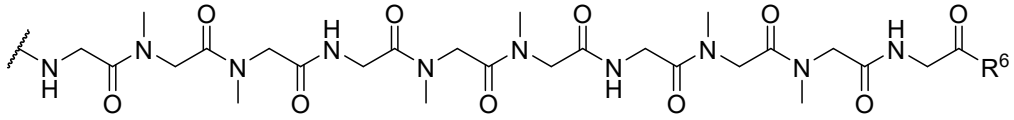


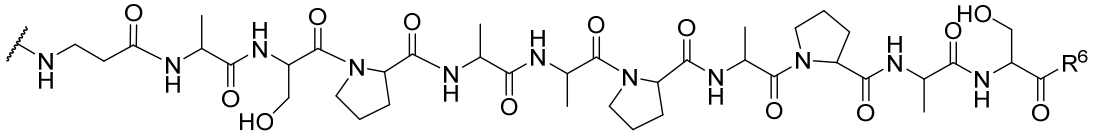
(SEQ ID NO: 10),

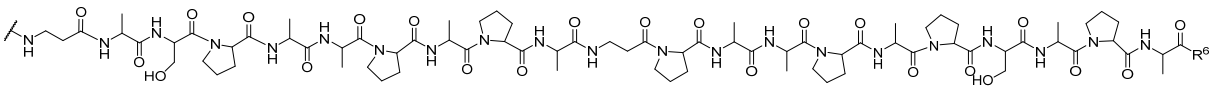
wherein the terminus unit is represented by R^6, and each j is selected from 1 to 30. In some cases, K^2 is selected from  (SEQ ID NO: 21),  (SEQ ID NO: 17), 

 (SEQ ID NO: 18),

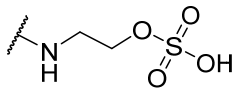
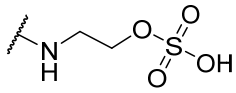
(SEQ ID NO: 11),

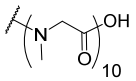
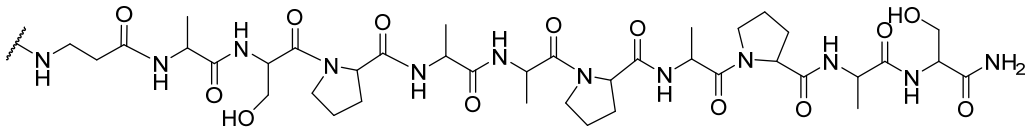
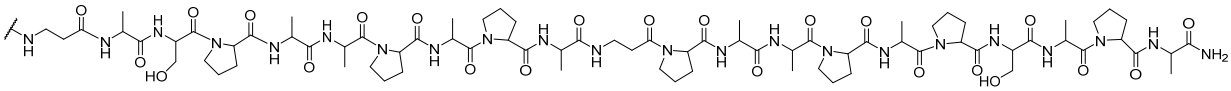
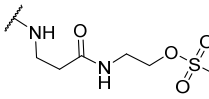
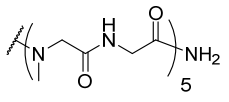
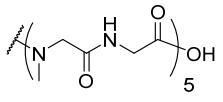
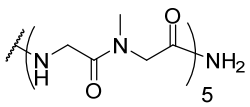
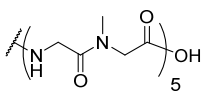
 (SEQ ID NO: 12),

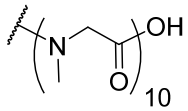
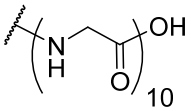
 (SEQ ID NO: 9),

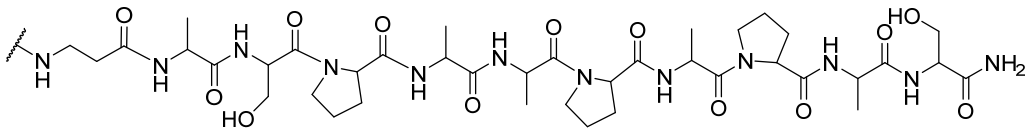


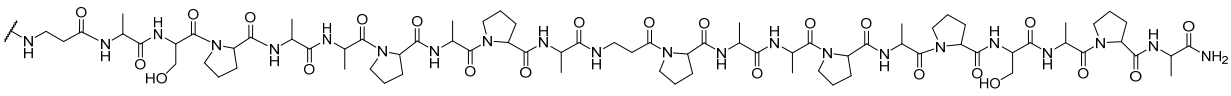
(SEQ ID NO: 10),

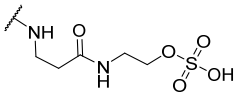
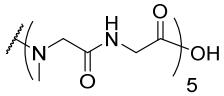
wherein the terminus unit is represented by R^6, and each j is selected from 1 to 30. In some cases, j is 1. In some cases, j is 3. In some cases, j is 5. In some cases, j is 10. In some cases, j is 20. In some cases, R^6 is selected from $-OR^7$ and $-NHR^7$, wherein R^7 is selected from hydrogen; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle. In some cases, R^6 is selected from -OH, $-NH_2$, and . In some cases, R^6 is -OH. In some cases, R^6 is $-NH_2$. In some cases, R^6 is .

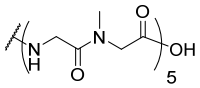
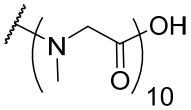
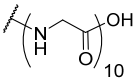
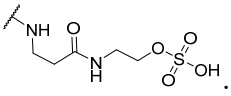
[00180] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (Ia), Formula (Ib), Formula (II-A), Formula (II-B), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (XX), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), K^2 is selected from  (SEQ ID NO: 13),  (SEQ ID NO: 9),  (SEQ ID NO: 10), ,  (SEQ ID NO: 20),  (SEQ ID NO: 20),  (SEQ ID NO: 8), and  (SEQ ID NO: 8). In some cases, K^2 is selected from

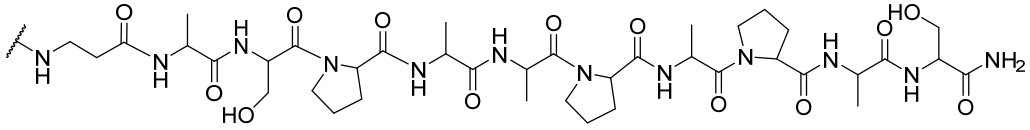
 (SEQ ID NO: 13),  (SEQ ID NO: 7),

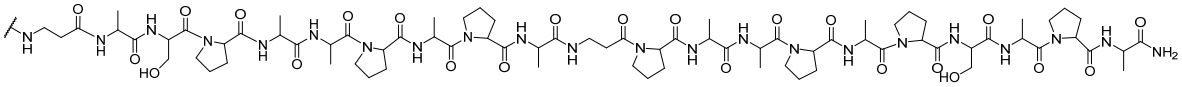
 (SEQ ID NO: 9),



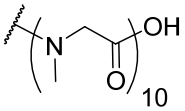
(SEQ ID NO: 10), ,  (SEQ ID NO: 20), and

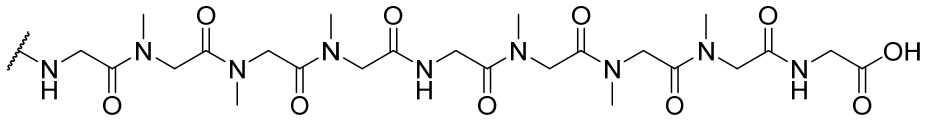
 (SEQ ID NO: 8). In some cases, K^2 is selected from  (SEQ ID NO: 13). In some cases, K^2 is selected from  (SEQ ID NO: 7). In some cases, K^2 is selected from . In some cases, K^2 is selected from

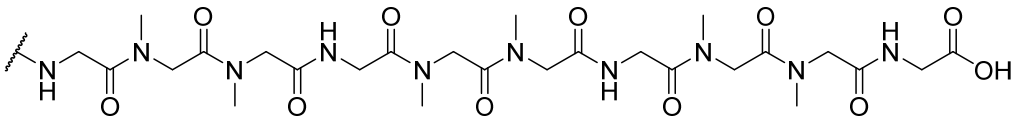
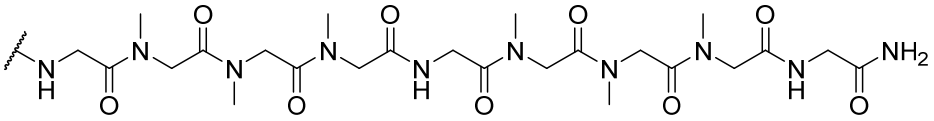
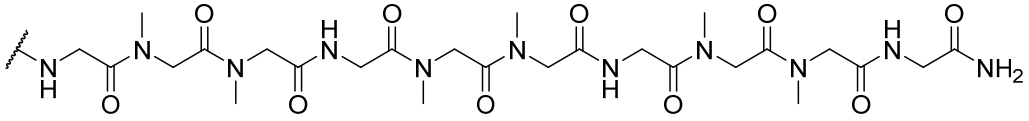
 (SEQ ID NO: 9). In some cases, K^2 is selected from



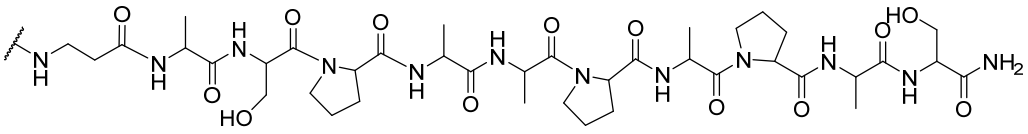
(SEQ ID NO: 10).

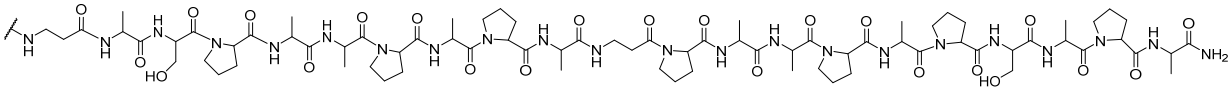
[00181] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (Ia), Formula (Ib), Formula (II-A), Formula (II-B), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (XX), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), K^2 is selected from  (SEQ ID NO: 13),

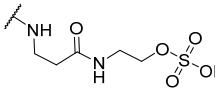
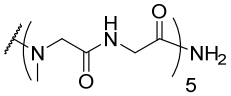
 (SEQ ID NO: 11),

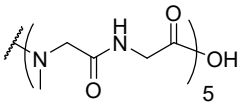
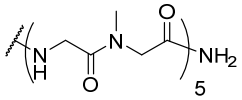
 (SEQ ID NO: 12),  (SEQ ID NO: 11), 

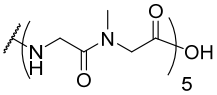
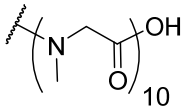
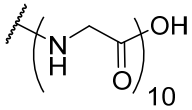
(SEQ ID NO: 12),

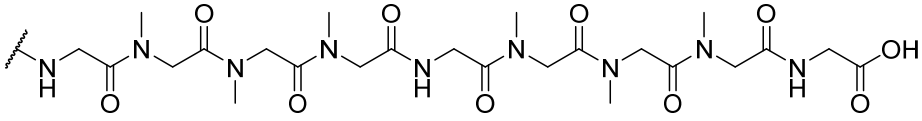
 (SEQ ID NO: 9),

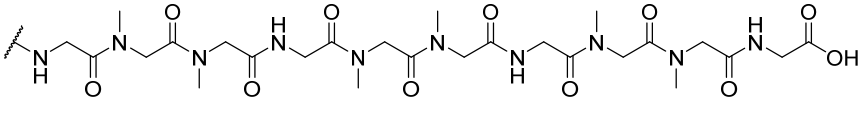


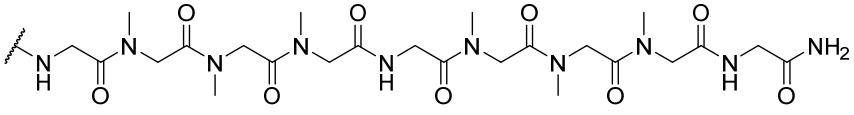
(SEQ ID NO: 10), ,  (SEQ ID NO: 20),

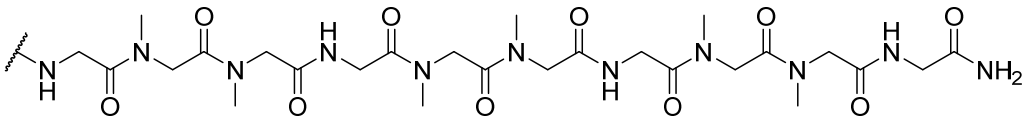
 (SEQ ID NO: 20),  (SEQ ID NO: 8), and

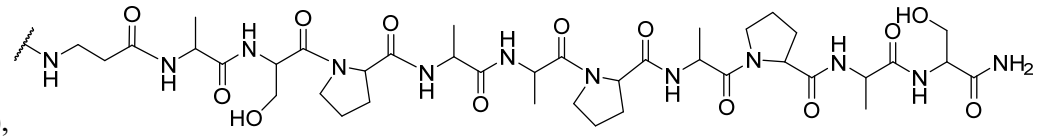
 (SEQ ID NO: 8). In some cases, K^2 is selected from  (SEQ ID NO: 13),  (SEQ ID NO: 7),

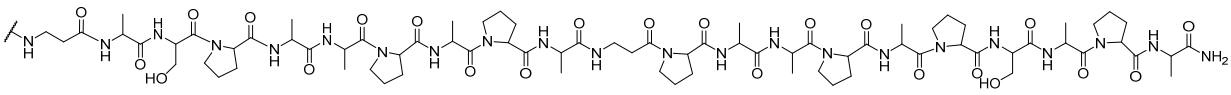
 (SEQ ID NO: 11),

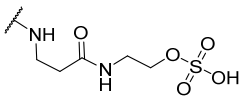
 (SEQ ID NO: 12),

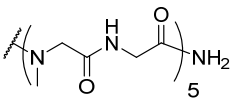
 (SEQ ID NO: 11),

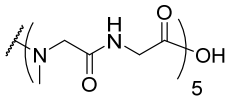

(SEQ ID NO: 12),

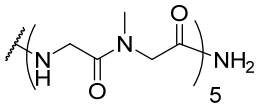

(SEQ ID NO: 9),

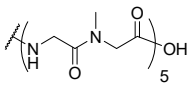

(SEQ ID NO: 10),

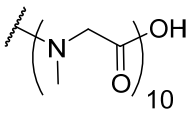

,

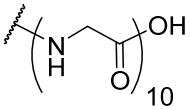

(SEQ ID NO: 20),

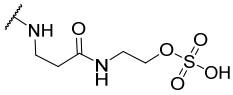

(SEQ ID NO: 20),

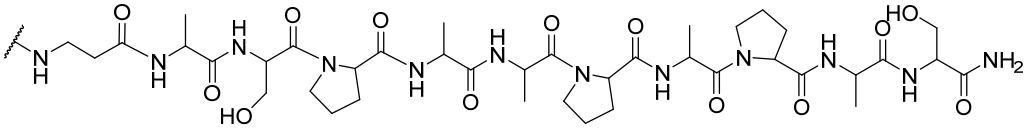

(SEQ ID NO: 8), and

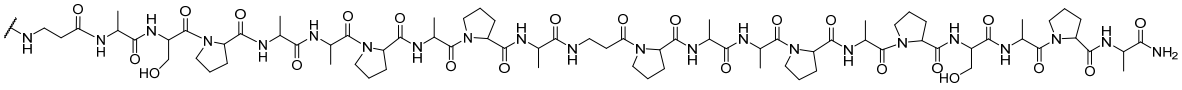

(SEQ ID NO: 8). In some cases, K^2 is selected from

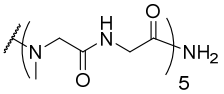

(SEQ ID NO: 13). In some cases, K^2 is selected from

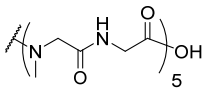

(SEQ ID NO: 7). In some cases, K^2 is selected from

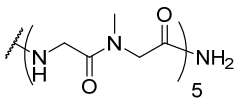

. In some cases, K^2 is selected from

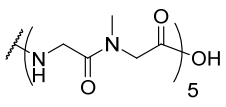

(SEQ ID NO: 9). In some cases, K^2 is selected from

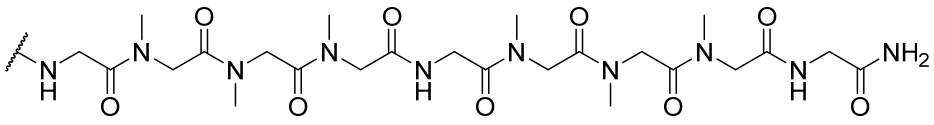
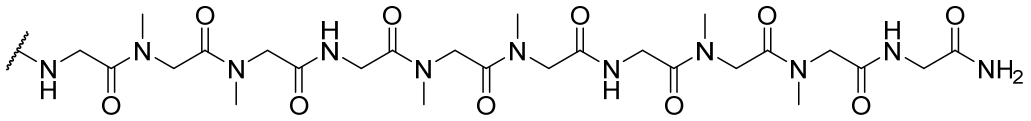

(SEQ ID NO: 10). In some cases, K^2 is selected from

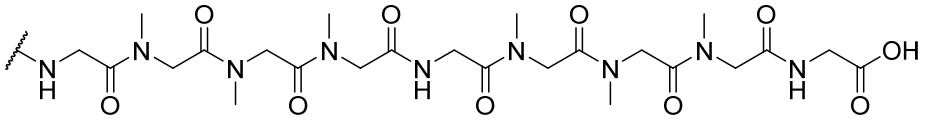

(SEQ ID NO: 20),

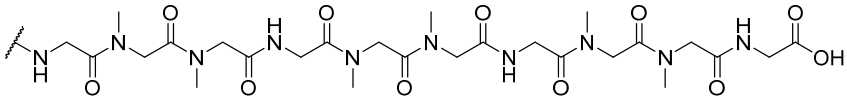

(SEQ ID NO: 20),


(SEQ ID NO: 8),

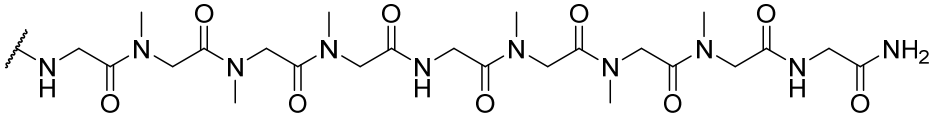

(SEQ ID NO: 8),

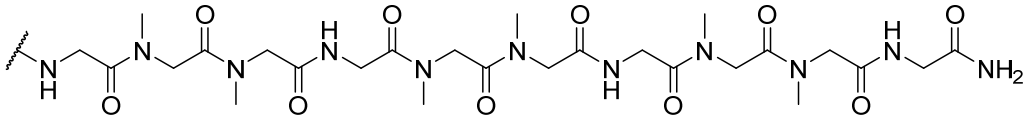
 (SEQ ID NO: 11), 

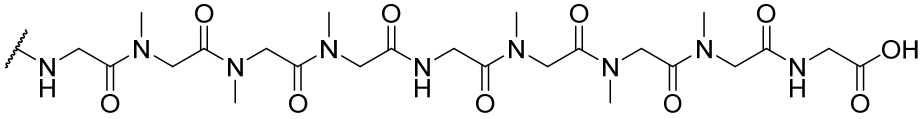
(SEQ ID NO: 12), 

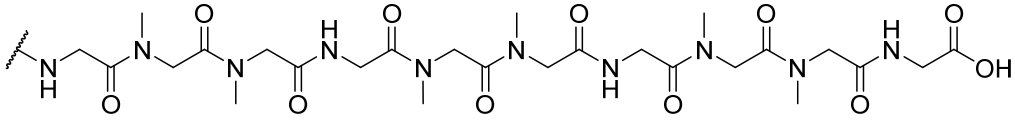
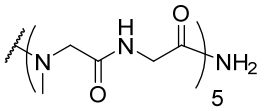
(SEQ ID NO: 11) and  (SEQ ID NO: 12).

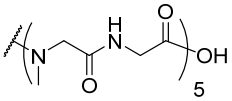
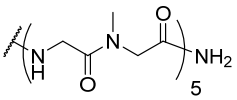
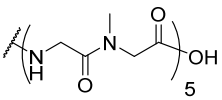
In some cases, K^2 is selected from

 (SEQ ID NO: 11)

and  (SEQ ID NO: 12). In some cases, K^2 is selected from

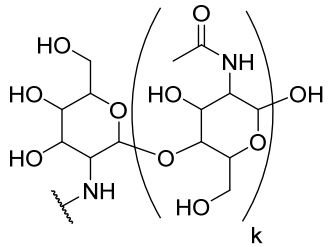
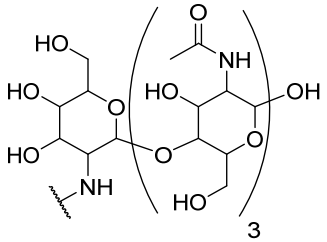
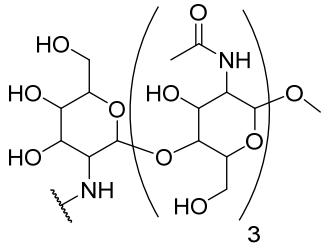
 (SEQ ID NO: 11)

and  (SEQ ID NO: 12). In some cases, K^2 is selected from  (SEQ ID NO: 20),

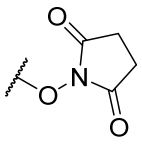
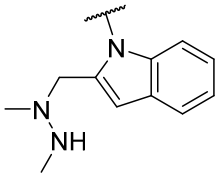
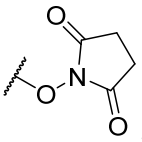
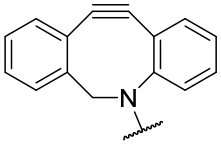
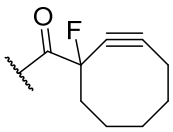
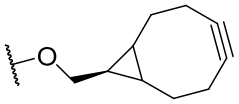
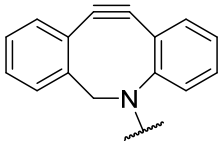
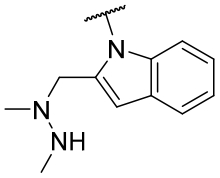
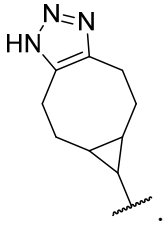
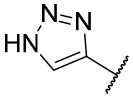
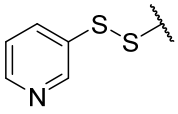
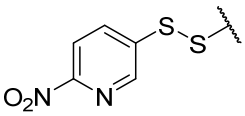
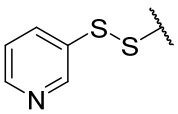
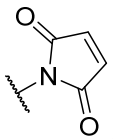
 (SEQ ID NO: 20),  (SEQ ID NO: 8), and 

(SEQ ID NO: 8).

[00182] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (Ia), Formula (Ib), Formula (II-A), Formula (II-B), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (X), Formula (XIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-3), Formula (A-4),

Formula (A-5), or Formula (A-6), each K^2 is selected from: an oligosaccharide. In some cases, each K^2 is selected from:  , wherein k is selected from 2 to 10. In some cases, k is 2. In some cases, k is 3. In some cases, k is 4. In some cases, k is 5. In some cases, k is 6. In some cases, each K^2 is selected from:  . In some cases, each K^2 is selected from:  .

[00183] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (II-A), Formula (II-B), Formula (II-C), or Formula (II-D), M^1 is a group which can react with a Targeting Unit to form a connector unit. In some cases, a group that can react with a Targeting Unit to form a connector unit refers to any chemical moiety that is being reactive for covalently binding a Targeting Unit (e.g., antibody, ligand, antigen-binding fragment). In some cases, it may react with a thiol group present on a Targeting Unit. In some cases, it may react with a thiol group present on an antibody or antigen-binding fragment thereof. In some cases, it may react with a thiol group present on a ligand. In some cases, the chemical moieties that are being reactive for covalently binding a ligand includes: carboxylic acid; primary amine; secondary amine; tertiary amine; hydroxyl; halogen; activated ester such as N-hydroxysuccinimide ester, perfluorinated esters, nitrophenyl esters, aza-benzotriazole and benzotriazole activated ester, acylureas; alkynyl; alkenyl; azide; isocyanate; isothiocyanate; aldehyde; thiol- reactive moieties such as maleimide, halomaleimides, haloacetyls, pyridyl disulfides; thiol; acrylate; mesylate; tosylate; triflate, hydroxylamine; chlorosulfonyl; boronic acid - $B(OR')_2$ derivatives wherein R' is hydrogen or alkyl group. In some cases, M^1 is selected from maleimide, halogen, COOH,


, azide, , activated  group , , OH, SH, activated disulfide group, NH_2, and -ONH_2. In some cases, M^1 is maleimide. In some cases, M^1 is halogen. In some cases, M^1 is COOH. In some cases, M^1 is . In some cases, M^1 is azide. In some cases, M^1 is . In some cases, the activated group of M^1 is selected from , , and . In some cases, M^1 is . In some cases, M^1 is . In some cases, M^1 is . In some cases, M^1 is . In some cases, M^1 is OH. In some cases, M^1 is SH. In some cases, the activated disulfide group of M^1 is selected from  and . In some cases, M^1 is . In some cases, M^1 is NH_2. In some cases, M^1 is -ONH_2. In some cases, M^1 is suitable for click reaction (e.g., cyclic alkyne, azide). In some cases, M^1 is .

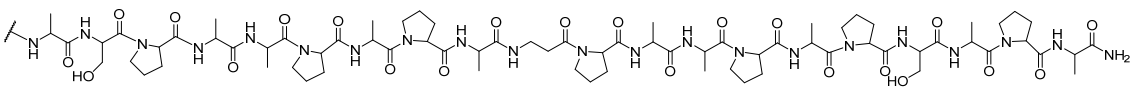
[00184] In some embodiments, for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-CA), Formula (II-D), Formula (II-E), Formula (II-F), Formula (II-G), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula

(A-2), Formula (A-3), Formula (A-4), Formula (A-5), Formula (A-6), K^1 is a hydrophilic spacer. In some cases, K^1 is selected from polyethylene glycol units, cyclodextrin units, polyamides, hydrophilic peptides, polysaccharides and dendrimers. In some cases, K^1 is selected from polyamides, hydrophilic peptides, and polysaccharides. In some cases, K^1 is selected from hydrophilic peptides and polysaccharides. In some cases, K^1 is selected from hydrophilic peptides. In some cases, K^1 is selected from polysaccharides. In some cases, cases K^1 is a half-life promoting substituent. In some cases, the half-life promoting substituent increases the half-life of the drug. In some cases, the half-life promoting substituent increases the half-life of the conjugate.

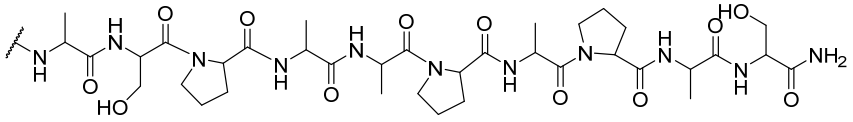
[00185] In some embodiments, for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (Ia), Formula (Ib), Formula (II-A), Formula (II-B), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (XX), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-3), Formula (A-4), Formula (A-5), Formula (A-6), K^2 is a hydrophilic spacer. In some cases, K^2 is selected from polyethylene glycol units, cyclodextrin units, polyamides, hydrophilic peptides, polysaccharides and dendrimers. In some cases, K^2 is selected from polyamides, hydrophilic peptides, and polysaccharides. In some cases, K^2 is selected from hydrophilic peptides and polysaccharides. In some cases, K^2 is selected from hydrophilic peptides. In some cases, K^2 is selected from polysaccharides. In some cases, cases K^2 is a half-life promoting substituent. In some cases, the half-life promoting substituent increases the half-life of the drug. In some cases, the half-life promoting substituent increases the half-life of the conjugate. In some cases, p is 1.

[00186] In some embodiments, for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (Ia), Formula (Ib), Formula (II-A), Formula (II-B), Formula (II-E), Formula (II-F), or for a conjugate or salt of Formula (XX), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-3), Formula (A-4), Formula (A-5), Formula (A-6), K^2 includes PASylation. In some cases, PASylation is a peptide comprising proline, alanine, and serine. In some cases, PASylation is a peptide consisting of only proline, alanine, and serine. In some cases, K^2 includes PASylation of less than PAS100. For example, PAS100 refers to a peptide having 100 amino acids, wherein the amino acids are selected from proline, alanine, and serine. In some cases, K^2 includes PASylation of less than PAS50. In some cases, K^2 includes PASylation of less than PAS25. In some cases, K^2 includes PASylation of more than PAS5. In some cases, K^2 includes PASylation of more than PAS9. In some cases, K^2 includes PASylation of more than PAS15. In some cases, K^2 includes PASylation of PAS5 to PAS25. In some cases, K^2 includes PASylation of PAS10 to PAS20. In some cases, K^2 includes PASylation of PAS10. In some cases, K^2 includes PASylation of PAS20. In some cases, K^2 includes a beta-alanine that

links the PASylation to the drug-linker. In some cases, PASylation is used to extend the plasma half-life. In some cases, PASylation is used to increase solubility. In some cases, PASylation is used to increase solubility without generating secondary structures. In some cases, PASylation is



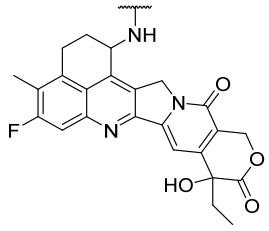
(SEQ ID NO: 14) In some cases, PASylation is



(SEQ ID NO: 15) .

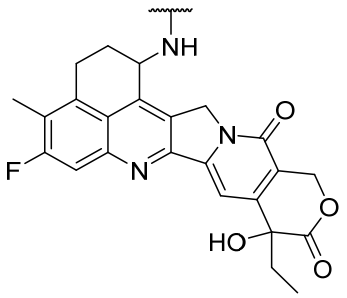
[00187] In some embodiments, for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb),Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-D), Formula (II-E), or Formula (II-F), Formula (II-G), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), D is drug unit. In some cases, D includes a spacer. In some cases, the spacer is a divalent moiety that covalently attaches the drug to the linker. In some cases, the spacer is a divalent moiety that covalently attaches the drug to the rest of the molecule. In some cases, D does not include a spacer. In some cases, the spacer can be selected from the group consisting of –C_1-C_{10} alkylene-, –C_1-C_{10} heteroalkylene-, -C_3-C_8 carbocyclo-, -O-(C_1 C_8 alkyl)-, -arylene-, –C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, –C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_3-C_8 heterocyclo-, –C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -(C_3-C_8 heterocyclo)–C_1-C_{10} alkylene-, –C_1-C_{10} alkylene-C(=O)-, –C_1-C_{10} heteroalkylene-C(=O)-, -C_3-C_8 carbocyclo-C(=O)-, -O-(C_1-C_8 alkyl)-C(=O)-, -arylene-C(=O)-, -C_1-C_{10} alkylene-arylene-C(=O)-, -arylene-C_1-C_{10} alkylene-C(=O)-, -C_1- C_{10} alkylene-(C_3-C_8carbocyclo)-C(=O)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-C(=O)-, - C_3-C_8 heterocyclo-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8heterocyclo)-C(=O)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-NH-, -C_1-C_{10} heteroalkylene-NH-, -C_3-C_8 carbocyclo-NH-, -O-(C_1-C_8 alkyl)-NH-, -arylene-NH-, -C_1-C_{10} alkylene- arylene-NH-, -arylene-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-NH-, - (C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-NH-, -C_3-C_8heterocyclo-NH-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-NH-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-S-, - C_1-C_{10} heteroalkylene-S -, -C_3-C_8carbocyclo-S -, -O-(C_1-C_8 alkyl)-)-S-, -arylene-S-, -C_1-C_{10} alkylene-arylene-S-, -arylene-C_1-C_{10} alkylene-S-, -C_1-C_{10} alkylene-(C_3- C_8 carbocyclo)-S-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-S-, -C_3-C_8 heterocyclo-S-, -C_1- C_{10} alkylene-(C_3-C_8 heterocyclo)-S-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-S-, –C_1-C_{10} alkylene-O-C(=O)-, -C_3-

C_8 carbocyclo-O-C(=O)-, -O-(C_1-C_8 alkyl)-O-C(=O)-, -arylene- O-C(=O)-, -C_1-C_{10} alkylene-arylene-O-C(=O)-, -arylene-C_1-C_{10} alkylene-O-C(=O)-, -C_1- C_{10} alkylene-(C_3-C_8carbocyclo)-O-C(=O)-,-(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-O-C(=O)-, -C_3-C_8 heterocyclo-O-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8heterocyclo)-O-C(=O)-, and -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-O-C(=O)-. In some cases, the spacer can be selected from the group consisting of –C_1-C_{10} alkylene-, and -C_1-C_{10} alkylene-NH-. In some cases, the drug unit is only a drug.

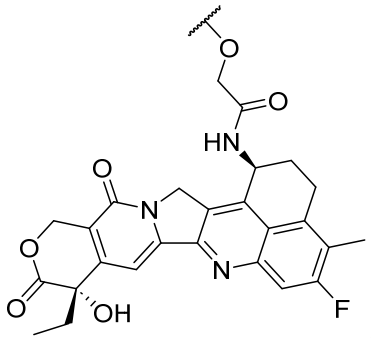
[00188] In some embodiments, for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb),Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-D), Formula (II-E), or Formula (II-F), Formula (II-G), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), D is selected from a Drug unit. In some cases, the Drug unit comprises a drug. In some cases, the Drug unit is a drug. In some cases, the Drug unit is a drug and a spacer. In some cases, D is selected from a drug. In some cases, D is a selected from a cytotoxic agent, an immune modulatory agent, a nucleic acid, a growth inhibitory agent, a PROTAC, a toxin, a radioactive isotope and a chelating ligand. In some cases, D is a selected from a cytotoxic agent, and an immune modulatory agent. In some cases, D is selected from exatecan and monomethyl auristatin E (MMAE). In some cases, D is a camptothecin. In some cases, D is exatecan. In some cases, D is 

. In some cases, D is SN-38. In some cases, D is selected from MMAF and MMAE. In some cases, the cytotoxic agent is selected from the group consisting of an auristatin, a maytansinoid, a camptothecin, a duocarmycin, and a calicheamicin. In some cases, a cytotoxic agent is an agent that has a cytotoxic effect on a cell. In some cases, cytotoxic agents include, for example, tubulin disrupting agents, topoisomerase inhibitors, DNA minor groove binders, and DNA alkylating agents. In some cases, tubulin disrupting agents include, for example, auristatins, dolastatins, tubulysins, colchicines, vinca alkaloids, taxanes, cryptophycins, maytansinoids, hemiasterlins, as well as other tubulin disrupting agents. In some cases, auristatins are derivatives of the natural product dolastatin 10. In some cases, auristatins are selected from MMAE (N-methylvaline-valine-dolaisoleuine-dolaproine-norephedrine (SEQ ID NO: 22)), MMAF (N-methylvaline-valine-dolaisoleuine-dolaproine-phenylalanine (SEQ ID NO: 23)) and AFP. In some

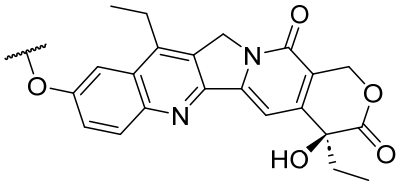
cases, a cytotoxic agent can be a topoisomerase inhibitor. In some cases, a drug is an immune modulatory agent, such as a TLR7 and/or TLR8 agonist. In some cases, an immune modulatory agent is a STING agonist. In some cases, a drug is a radioactive atom. In some cases, a drug is a proteolysis targeted chimera (PROTAC). In some cases, the drug is selected from exatecan, MMAE, MMAF, duocarmycin, SN-38, and dxd. In some cases, the drug is selected from MMAE, MMAF, duocarmycin, SN-38, and dxd. In some cases, the drug is



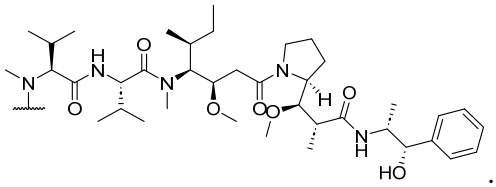
. In some cases, the drug is



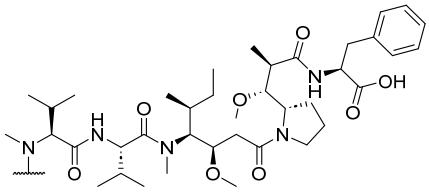
. In some cases, the drug is



. In some cases, the drug is



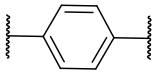
. (SEQ ID NO: 22) In some cases, the drug is



(SEQ ID NO: 23).

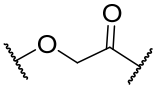
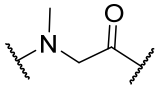
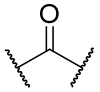
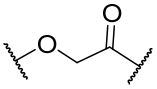
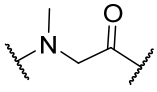
[00189] In some embodiments, for a Linker or salt of Formula (III) or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), or a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), S^3 is selected from a spacer. In some cases, the spacer is a divalent moiety that covalently binds two components of the conjugate or Drug-Linker. In some cases, S^3 is present. In some cases, S^3 is absent. In some cases, the spacer is selected from: alkylene, heteroalkylene (an alkylene having one or more alkylene units replaced by at least one heteroatom selected from Si, N, O and S, with the

appropriate valency); polyether such as polyalkylene glycol and typically polyethylene glycol; one or more natural or non-natural aminoacids such as glycine, alanine, proline, valine, N-methylglycine; C_3-C_8 heterocyclo; C_3-C_8 carbocyclo; arylene, and any combination thereof. In some cases, a spacer is a divalent linear alkylene group. In some cases, the spacer can be selected from the group consisting of –C_1-C_{10} alkylene-, –C_1-C_{10} heteroalkylene-, -C_3-C_8 carbocyclo-, -O-(C_1 C_8 alkyl)-, -arylene-, –C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, –C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_3-C_8 heterocyclo-, –C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -(C_3-C_8 heterocyclo)–C_1-C_{10} alkylene-, –C_1-C_{10} alkylene-C(=O)-, –C_1- C_{10} heteroalkylene-C(=O)-, -C_3-C_8 carbocyclo-C(=O)-, -O-(C_1-C_8 alkyl)-C(=O)-, -arylene-C(=O)-, -C_1-C_{10} alkylene-arylene-C(=O)-, -arylene-C_1-C_{10} alkylene-C(=O)-, -C_1- C_{10} alkylene-(C_3-C_8carbocyclo)-C(=O)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-C(=O)-, - C_3-C_8 heterocyclo-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8heterocyclo)-C(=O)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-NH-, -C_1-C_{10} heteroalkylene-NH-, -C_3-C_8 carbocyclo-NH-, -O-(C_1-C_8 alkyl)-NH-, -arylene-NH-, -C_1-C_{10} alkylene- arylene-NH-, -arylene-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-NH-, - (C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-NH-, -C_3-C_8heterocyclo-NH-, -C_1-C_{10} alkylene-(C_3- C_8 heterocyclo)-NH-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-S-, - C_1-C_{10} heteroalkylene-S -, -C_3-C_8carbocyclo-S -, -O-(C_1-C_8 alkyl)-)-S -, -arylene-S-, -C_1- C_{10} alkylene-arylene-S-, -arylene-C_1-C_{10} alkylene-S-, -C_1-C_{10} alkylene-(C_3- C_8 carbocyclo)-S-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-S-, -C_3-C_8 heterocyclo-S-, -C_1- C_{10} alkylene-(C_3-C_8 heterocyclo)-S-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-S-, –C_1-C_{10} alkylene-O-C(=O)-, -C_3-C_8 carbocyclo-O-C(=O)-, -O-(C_1-C_8 alkyl)-O-C(=O)-, -arylene- O-C(=O)-, -C_1-C_{10} alkylene-arylene-O-C(=O)-, -arylene-C_1-C_{10} alkylene-O-C(=O)-, -C_1- C_{10} alkylene-(C_3-C_8carbocyclo)-O-C(=O)-,-(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-O-C(=O)-, -C_3-C_8 heterocyclo-O-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8heterocyclo)-O-C(=O)-, and -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-O-C(=O)-. In some cases, S^3 is optionally substituted with one or more of the substituents selected from (i) halogen, -OR^{30}, -$N(R^{30})_2$, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -O-$S(O)_2R^{30}$, -$S(O)_2R^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, and -CN; (ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{30}, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -O-$S(O)_2OR^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle; and (iii) C_{3-10} carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{30}, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -

$OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl. In some cases, S^3 is optionally substituted with one or more of the substituents selected from (i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-O-S(O)_2R^{30}$, $-S(O)_2R^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN. In some cases, S^3 is unsubstituted. In some cases, S^3 is substituted. In some cases, S^3 is a phenylene. In some cases, S^3 is .

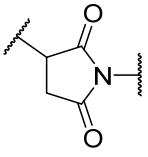
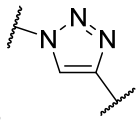
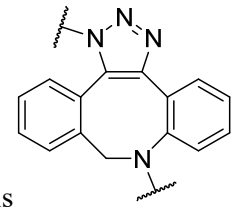
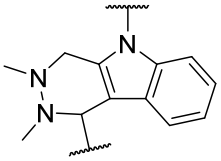
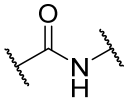
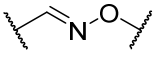
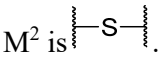
[00190] In some embodiments, for a Linker or salt of Formula (III) or for a Drug-Linker or salt of Formula (X), Formula (XIII), Formula (I), Formula (Ia), Formula (Ib), Formula (II-A), Formula (II-B), Formula (II-E), Formula (II-F), Formula (II-G), or a conjugate or salt of Formula (XX), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), S^4 is selected from (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, 5- to 6-membered heterocyclene, or $–P(O)(R^{20})_2–$. In some cases, S^4 is selected from (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, –O–, –C(O)–. In some cases, S^4 is selected from (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, –O–, and –C(O)–. In some cases, S^4 is selected from: (i) an optionally substituted C_8-C_{12} alkylene wherein one or more alkylene units of the C_8-C_{12} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, –O–, and –C(O)–. In some cases, S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, $–S(O)_2–$, or $–P(O)(R^{20})_2–$. In some cases, S^4 is selected from: (i) an optionally substituted C_6-C_{10} alkylene wherein one or more alkylene units of the C_6-C_{10} alkylene are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, or –C(O)–. In some cases, S^4 is an optionally substituted C_1 alkylene. In some cases, S^4 is an optionally substituted C_2 alkylene. In some cases, S^4 is an optionally substituted C_3 alkylene. In some cases, S^4 is an optionally substituted C_4 alkylene. In some cases, S^4 is an optionally substituted C_5 alkylene. In some cases, S^4 is an optionally substituted C_6 alkylene. In some cases, S^4 is an optionally substituted C_7 alkylene. In some cases, S^4 is an optionally substituted

C_8 alkylene. In some cases, S^4 is an optionally substituted C_9 alkylene. In some cases, S^4 is an optionally substituted C_{10} alkylene. In some cases, S^4 is an optionally substituted C_{11} alkylene. In some cases, S^4 is an optionally substituted C_{12} alkylene. In some cases, S^4 is an optionally substituted C_{13} alkylene. In some cases, S^4 is an optionally substituted C_{14} alkylene. In some cases, S^4 is an optionally substituted C_{15} alkylene. In some cases, S^4 is an optionally substituted C_{16} alkylene. In some cases, S^4 is an optionally substituted C_{17} alkylene. In some cases, S^4 is an optionally substituted C_{18} alkylene. In some cases, S^4 is an optionally substituted C_{19} alkylene. In some cases, S^4 is an optionally substituted C_{20} alkylene. In some cases, the one or more alkylene units of the alkylene of S^4 are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, $–N(R^{20})S(O)_2–$, $–S(O)_2N(R^{20})–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, or $–P(O)(R^{20})_2–$. In some cases, the one or more alkylene units of the alkylene of S^4 are optionally and independently replaced by $–N(R^{20})–$, $–N(R^{20})C(O)–$, $–C(O)N(R^{20})–$, or $–C(O)–$. In some cases, the one or more alkylene units of the alkylene of S^4 are optionally and independently replaced by $–N(R^{20})–$. In some cases, the one or more alkylene units of the alkylene of S^4 are optionally and independently replaced by $–N(R^{20})C(O)–$. In some cases, the one or more alkylene units of the alkylene of S^4 are optionally and independently replaced by $–C(O)N(R^{20})–$. In some cases, the one or more alkylene units of the alkylene of S^4 are optionally and independently replaced by $–C(O)–$. In some cases, the one or more alkylene units of the alkylene of S^4 are optionally and independently replaced by $–O–$. In some cases, if an alkylene unit of the alkylene is replaced, the alkylene may be referred to as a resulting alkylene. In some cases, if two or more of the alkylene units of S^4 are replaced, the replaced alkylene units are not adjacent alkylene units. In some cases, if two or more of the alkylene units of S^4 are replaced, the adjacent alkylene units of the resulting alkylene are not replaced. In some cases, if two or more of the alkylene units of S^4 are replaced, the resulting alkylene has no repeating heteroatoms of adjacent alkylene units. In some cases, if two or more of the alkylene units of S^4 are replaced, the resulting alkylene has no repeating of the same heteroatoms of adjacent alkylene units. In some cases, if two or more of the alkylene units of S^4 are replaced, the resulting alkylene unit has no -N-N- or -O-O-. In some cases, if two or more of the alkylene units of S^4 are replaced, the resulting alkylene unit is a stable alkylene. In some cases, if two or more of the alkylene units of S^4 are replaced, the resulting alkylene unit is an unreactive alkylene. In some cases, the resulting alkylene has only 1 heteroatom. In some cases, the resulting alkylene has only 2 heteroatoms, wherein the 2 heteroatoms are different from each other. In some cases, the resulting alkylene has only 2 heteroatoms, wherein the 2 heteroatoms are not adjacent to each other. In some cases, the resulting alkylene has only 3 heteroatoms, wherein the 3 heteroatoms are not adjacent to each other. In some cases, the resulting alkylene

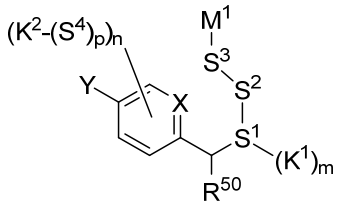
has only 4 heteroatoms, wherein the 4 heteroatoms are not adjacent to each other. In some cases, the alkylene has 0 replaced units. In some cases, the alkylene has 1 replaced unit. In some cases, the alkylene has 2 replaced units. In some cases, the alkylene has 1 replaced unit. In some cases, the alkylene has 3 replaced units. In some cases, the alkylene has 1 replaced unit. In some cases, the alkylene has 4 replaced units. In some cases, the alkylene has 1 replaced unit. In some cases, the alkylene has 5 replaced units. In some cases, the optional substituents on S^4, are independently selected at each occurrence from: (i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN; (ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{30}$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle. In some cases, the optional substituents on S^4, are independently selected at each occurrence from: (i) halogen, $-OR^{30}$, $-N(R^{30})_2$, $-SR^{30}$, $-N(R^{30})_2$, $-C(O)R^{30}$, $-C(O)N(R^{30})_2$, $-N(R^{30})C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)R^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-O-S(O)_2OR^{30}$, $-P(O)(OR^{30})_2$, $-OP(O)(OR^{30})_2$, $-NO_2$, =O, =S, $=N(R^{30})$, and -CN. In some cases, the optional substituents on S^4, are independently selected at each occurrence from: halogen, $-OR^{30}$, $-N(R^{30})_2$, =O, and -CN. In some cases, the optional substituents on S^4, are independently selected at each occurrence from: =O. In some cases, S^4 is selected from , , and . In some cases, S^4 is . In some cases, S^4 is . In some cases, S^4 is .

[00191] In some embodiments, for a Linker or salt of Formula (III), or for a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-D), or Formula (II-G), further includes attaching a Targeting Unit to M^1 to form a conjugate, wherein M^1 of the Drug-Linker reacts and forms a covalent bond to the Targeting Unit. In some cases, the Targeting unit is selected from an antibody or an antigen-binding portion thereof. In some cases, the conjugate has an average ratio of Drug-Linker to Targeting unit of about 1 to 10. In some cases, the Targeting unit is selected from an antibody or an antigen-binding portion thereof. In some cases,

the conjugate has an average ratio of Drug-Linker to Targeting unit of about 1 to 8. In some cases, the conjugate has an average ratio of Drug-Linker to Targeting unit of about 1 to 5. In some cases, the conjugate has an average ratio of Drug-Linker to Targeting unit of about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, or about 10. In some cases, the conjugate has an average ratio of Drug-Linker to Targeting unit (DAR) of about 8.

[00192] In some embodiments, for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-3), or Formula (A-4), M^2 is a connector unit. In some cases, the connector unit refers to a component that connects different parts of the conjugate together. In some cases, the connector unit can connect the Targeting Unit to S^3 (if present) or to S^2. In some cases, the connector unit forms a bond with a sulfur atom of a Targeting unit. In some cases, the connector unit forms a bond with a sulfur atom of a Targeting unit via a maleimide group. In some cases, the sulfur atom can be derived from, for example, a sulfhydryl group of a Targeting unit (e.g., a thiol group of an interchain disulfide bond). In some cases, M^2 is . In some cases, M^2 is . In some cases, M^2 is . In some cases, M^2 is . In some cases, M^2 is . In some cases, M^2 is . In some cases, M^2 is $-CH_2-C(O)NH-$. In some cases, M^2 is linked to the Targeting unit via a disulfide bond between a sulfur atom of M^2 and a sulfur atom of the Targeting unit. In some cases, M^2 is . In some cases, the connector unit forms a bond with a primary or secondary amino group of a Targeting unit. In some cases, M^2 is linked to the Targeting unit via a cystine of the Targeting unit.

[00193] In an aspect, the present disclosure provides a Linker of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt thereof, wherein;

n is selected from 0 and 1;

m is selected from 0 and 1;

wherein at least n or m is 1;

p is selected from 0 and 1;

X is selected from CH and N;

Y is a -O-T^1 and -NH-T^2;

T^1 is a sugar cleavable unit;

T^2 is peptide cleavable unit;

S^1 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^2 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–; (ii) optionally substituted C_3-C_{30} alkenylene, wherein one or more alkenylene units of the C_3-C_{30} alkenylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R^{20})$_2$–; (iii) one or more amino acid(s); (iv) one or more N-substituted amino acid(s); (v) optionally substituted polyether; (vi) optionally substituted C_3-C_{10} carbocyclene; (vii) optionally substituted 5- to 10-membered heterocyclene;

S^3 is selected from a spacer, wherein the spacer is preferably phenylene, wherein S^3 is present or absent;

S^4 is selected from: (i) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –N(R^{20})–, –N(R^{20})C(O)–, –C(O)N(R^{20})–, –N(R^{20})S(O)$_2$–, – S(O)$_2$N(R^{20})–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, 5- to 6-membered heterocyclene, or –P(O)(R^{20})$_2$–;

wherein the optional substituents on M^1, K^1, K^2, S^1, S^2, S^3, and S^4, are independently selected at each occurrence from:

(iv) halogen, -OR^{30}, -$N(R^{30})_2$, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -$S(O)_2OR^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, and -CN;

(ii) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{30}, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -$S(O)_2OR^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle; and

(iii) C_{3-10} carbocycle and 3- to 10-membered heterocycle each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{30}, -SR^{30}, -$N(R^{30})_2$, -$C(O)R^{30}$, -$C(O)N(R^{30})_2$, -$N(R^{30})C(O)R^{30}$, -$C(O)OR^{30}$, -$OC(O)R^{30}$, -$S(O)R^{30}$, -$S(O)_2R^{30}$, -$P(O)(OR^{30})_2$, -$OP(O)(OR^{30})_2$, -NO_2, =O, =S, =$N(R^{30})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

M^1 is a group which can react with a ligand to form a connector unit;

K^1 is selected from:

(iv) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, or –$P(O)(R^{20})_2$–;

(iii) an oligosaccharide; and

(iv) a polyether; wherein when X is CH, D is exatecan or MMAE, m is 1, n is 0, and K^1 is a polysarcosine, the polysarcosine contains 2-9 sarcosines (SEQ ID NO: 5) or 13-30 sarcosines (SEQ ID NO: 6);

K^2 is selected from:

(iv) a peptide unit,

(ii) an optionally substituted C_1-C_{30} alkylene wherein one or more alkylene units of the C_1-C_{30} alkylene are optionally and independently replaced by –$N(R^{20})$–, –$N(R^{20})C(O)$–, –$C(O)N(R^{20})$–, –$N(R^{20})S(O)_2$–, – $S(O)_2N(R^{20})$–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –$S(O)_2$–, or –$P(O)(R^{20})_2$–;

(iii) an oligosaccharide; and

(iv) a polyether;

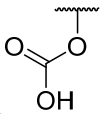
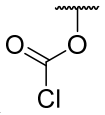
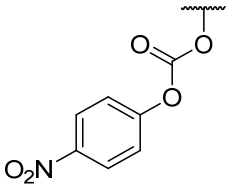
each R^{20} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -NO_2, -NH_2, -

$N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

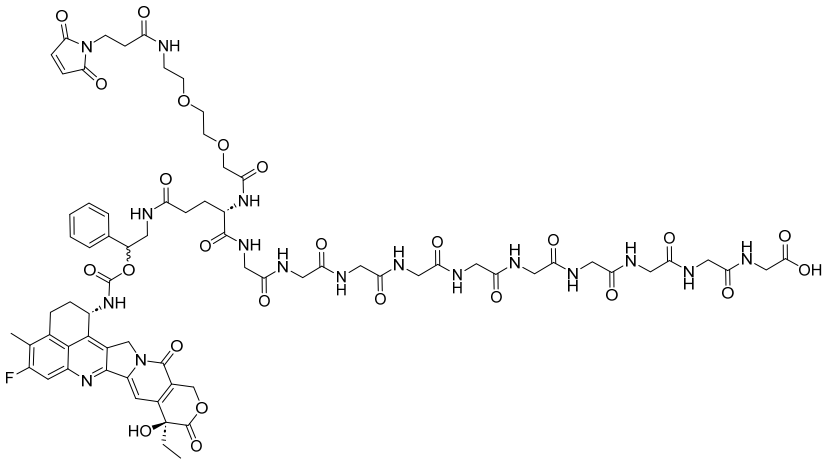
each R^{30} is independently selected from hydrogen; and C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, oxo, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

R^{50} is selected from a substituent capable of reacting with a nucleophilic group on a Drug unit.

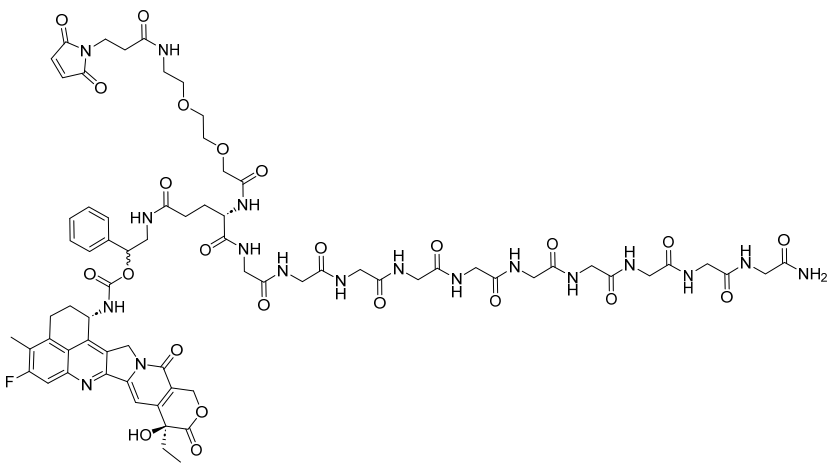
[00194] In some embodiments, for a linker of Formula (III), R^{50} is selected from a substituent capable of reacting with a nucleophilic group on a Drug. In some cases, the nucleophilic group on the Drug contains a nitrogen. In some cases, the nucleophilic group on the Drug contains an oxygen.

[00195] In some embodiments, for a linker of Formula (III), R^{50} is selected from . In some cases, R^{50} is selected from -OH. In some cases, R^{50} is selected from . In some cases, R^{50} is selected from .

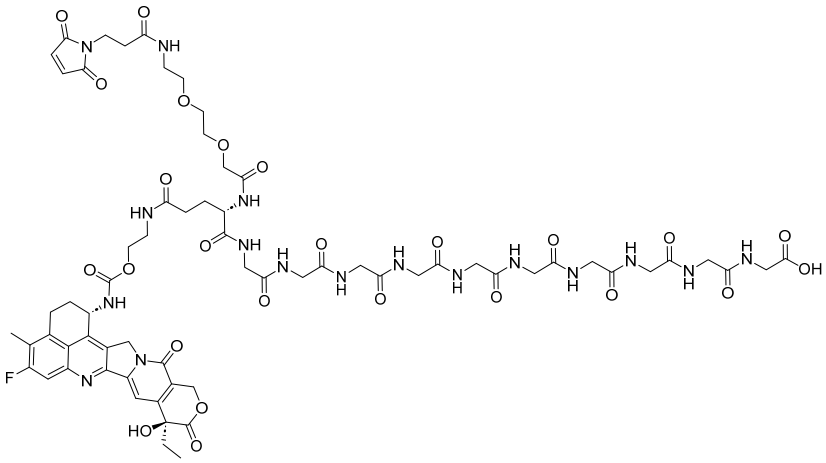
[00196] In some embodiments, a Drug-Linker of Formula (X) is selected from:



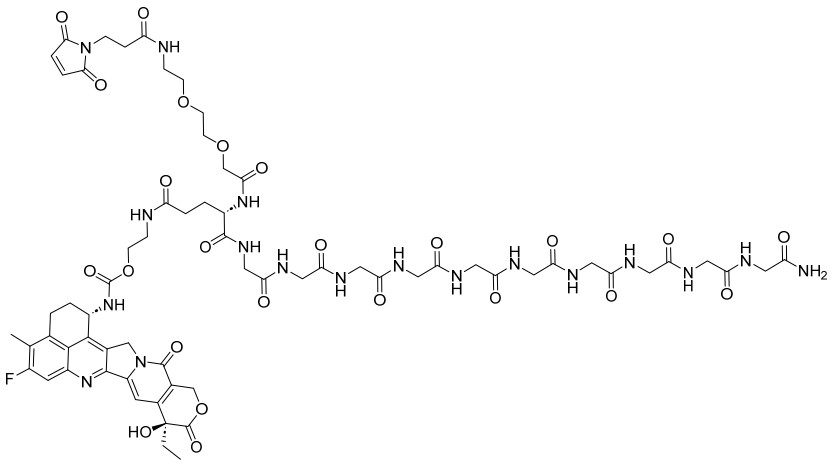
(SEQ ID NO: 24);



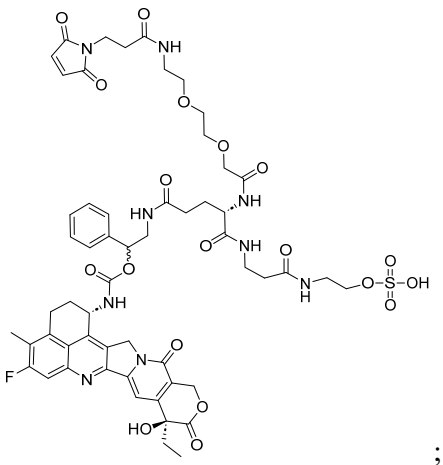
(SEQ ID NO: 24);



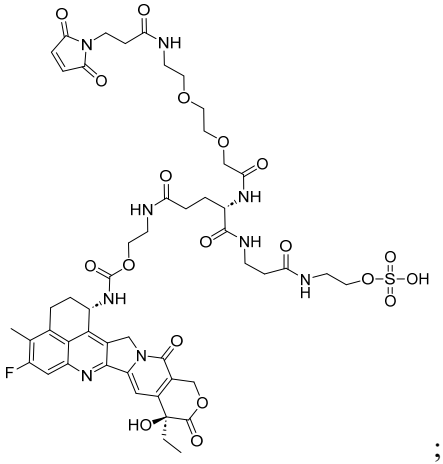
(SEQ ID NO: 24);



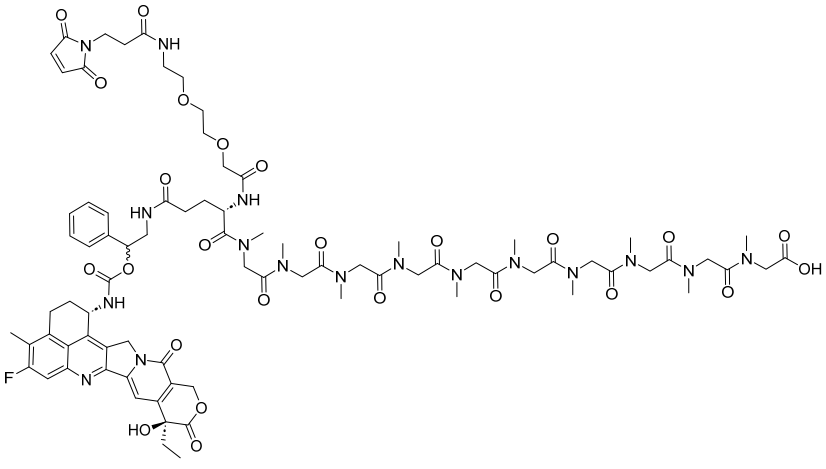
(SEQ ID NO: 24);



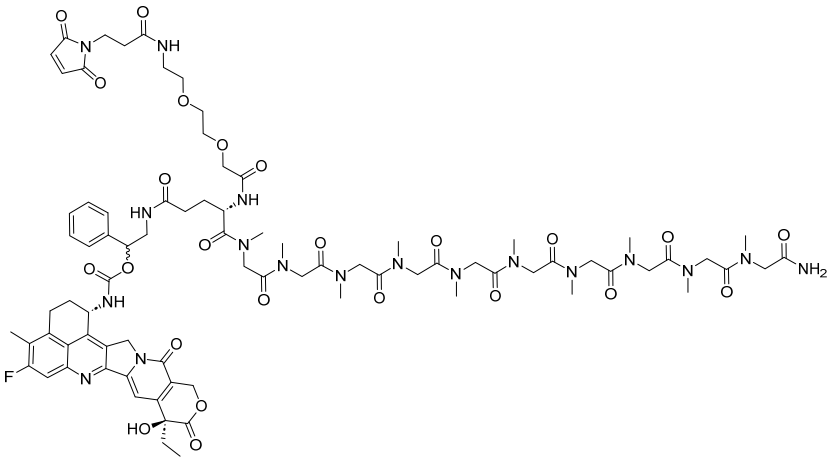
;



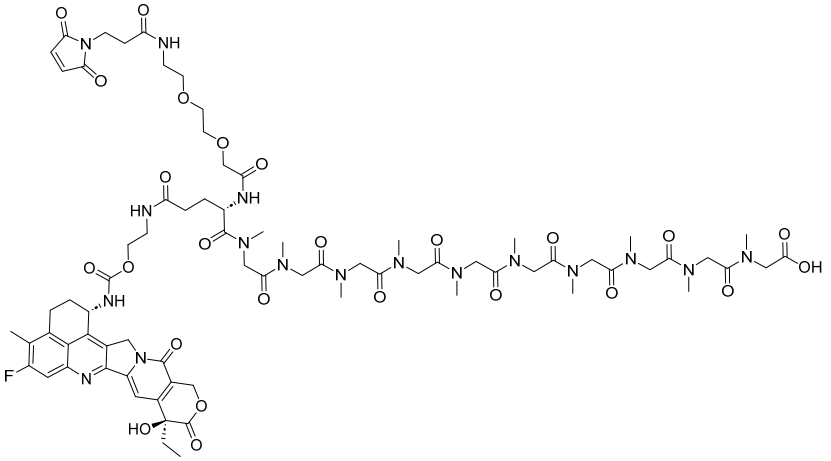
;



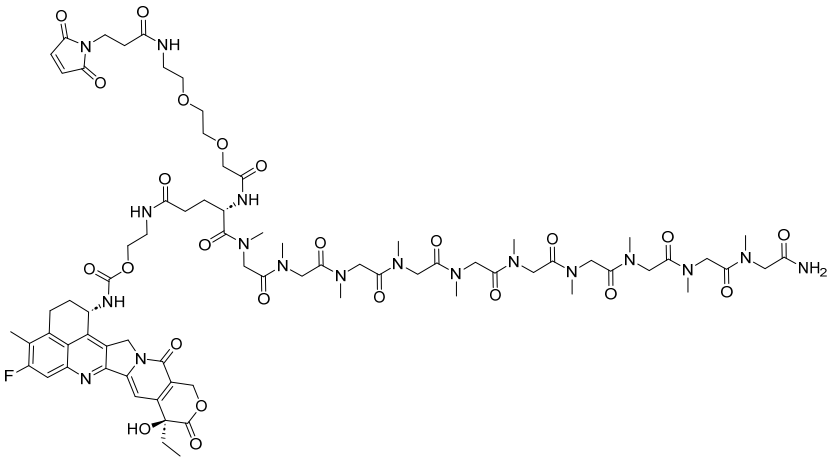
(SEQ ID NO: 25);



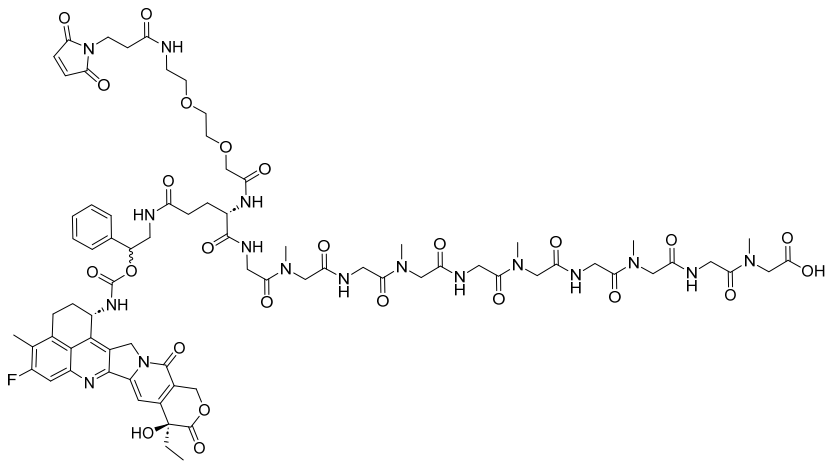
(SEQ ID NO: 25);



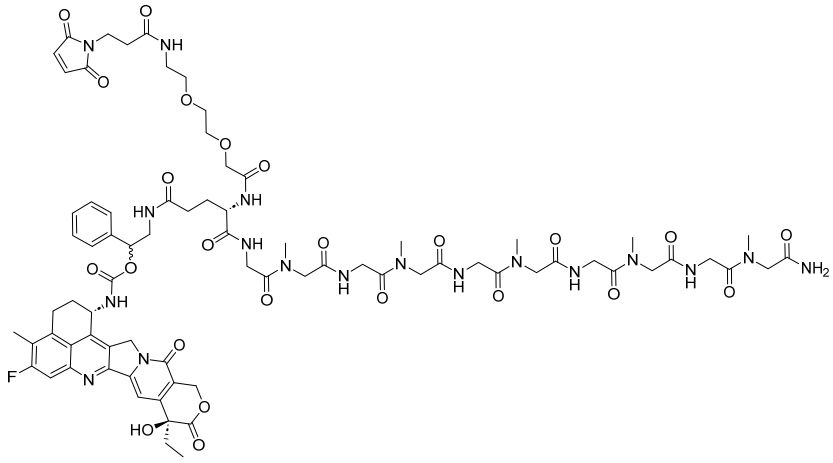
(SEQ ID NO: 25);



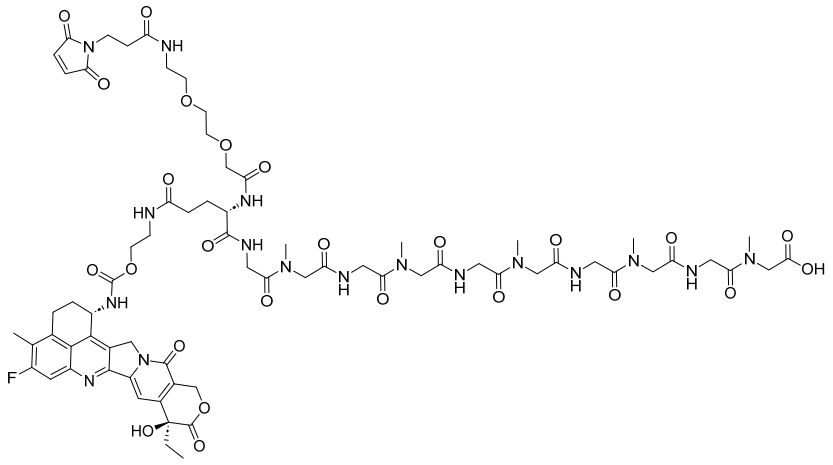
(SEQ ID NO: 25);



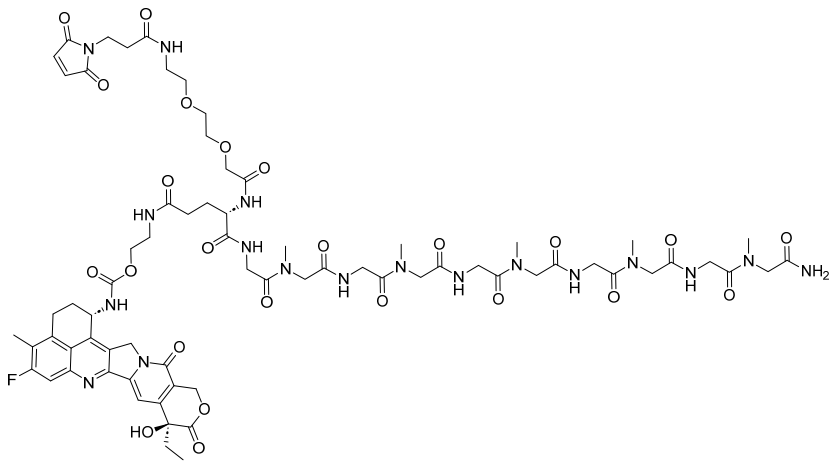
(SEQ ID NO: 26);



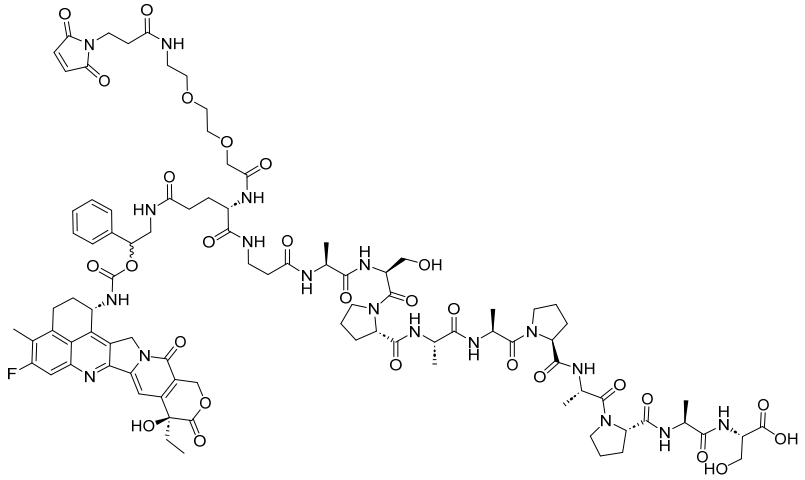
(SEQ ID NO: 26);



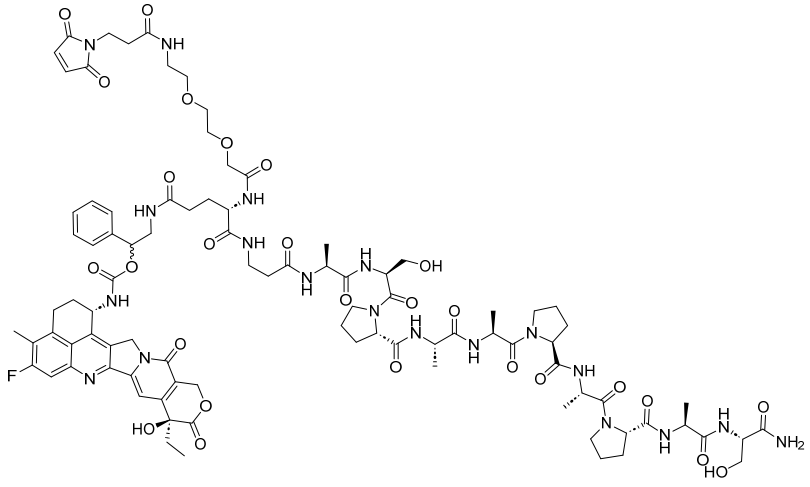
(SEQ ID NO: 26);



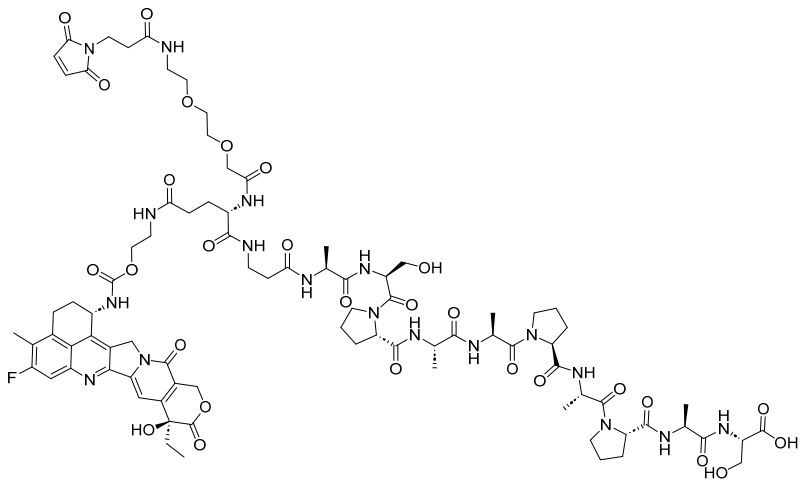
(SEQ ID NO: 26);



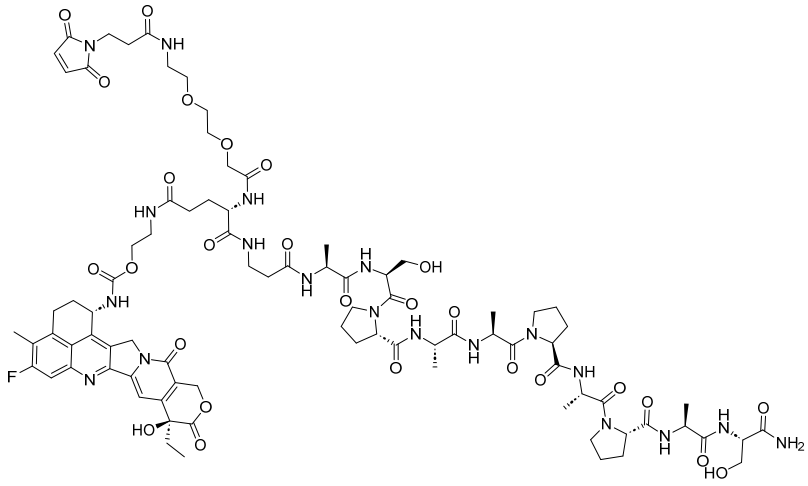
(SEQ ID NO: 27);



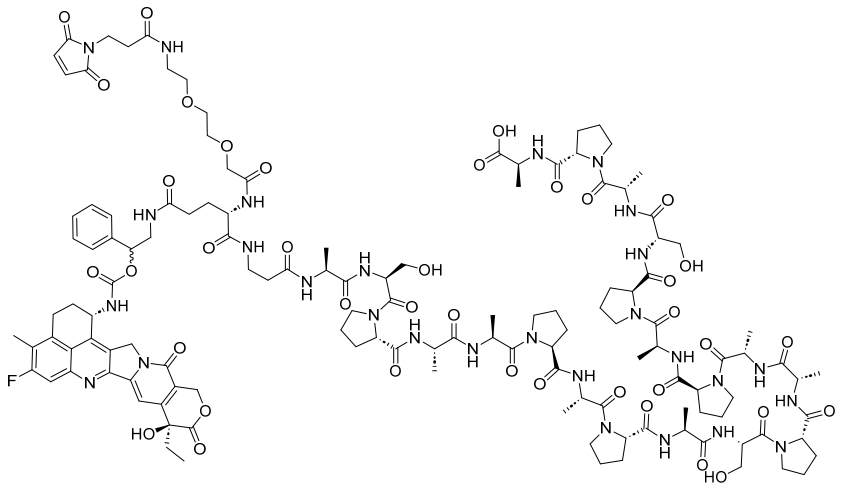
(SEQ ID NO: 27);



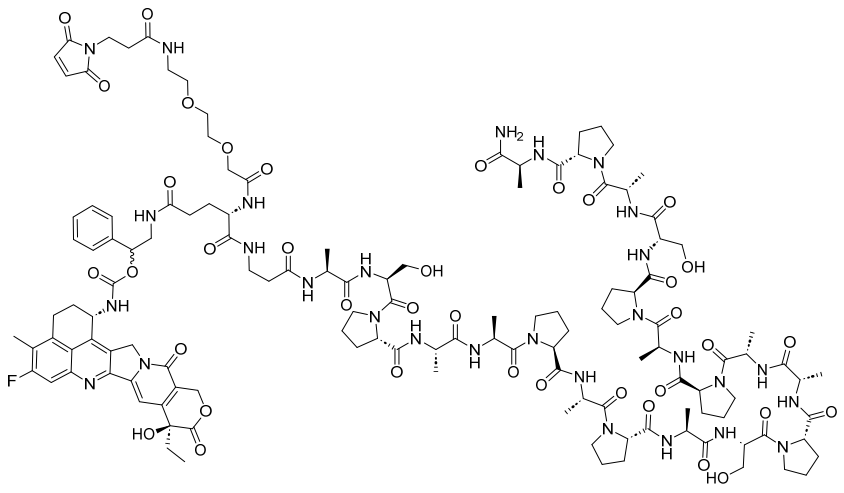
(SEQ ID NO: 27);



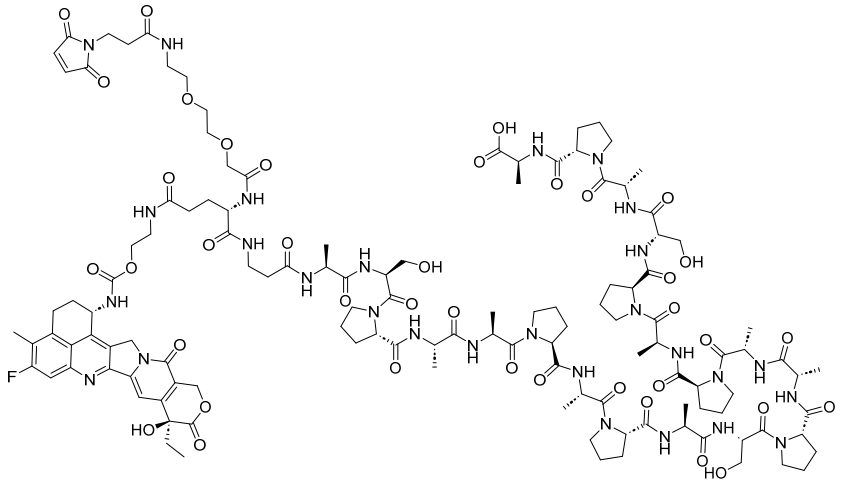
(SEQ ID NO: 27);



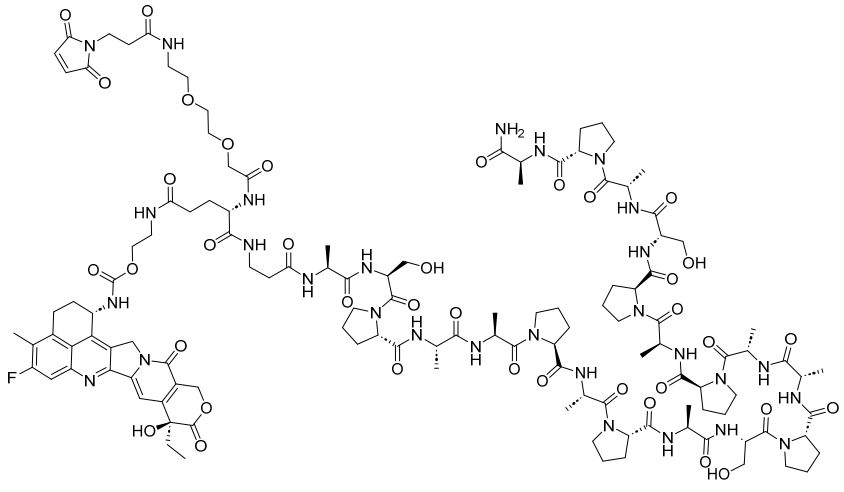
(SEQ ID NO: 28);



(SEQ ID NO: 28);

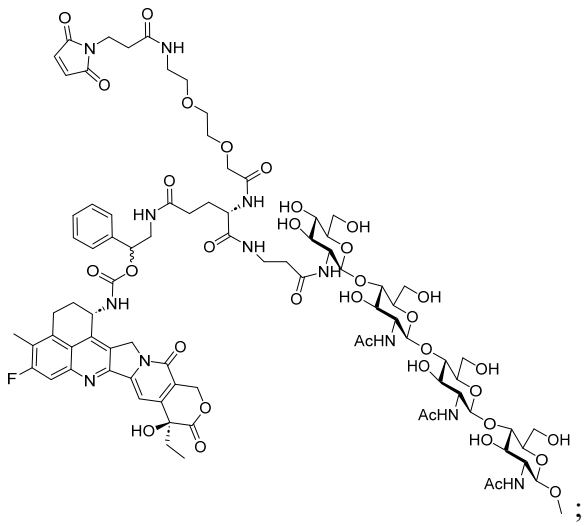


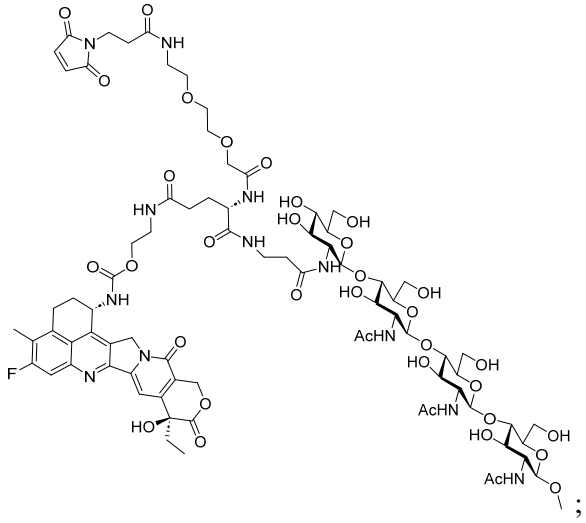
(SEQ ID NO: 28);

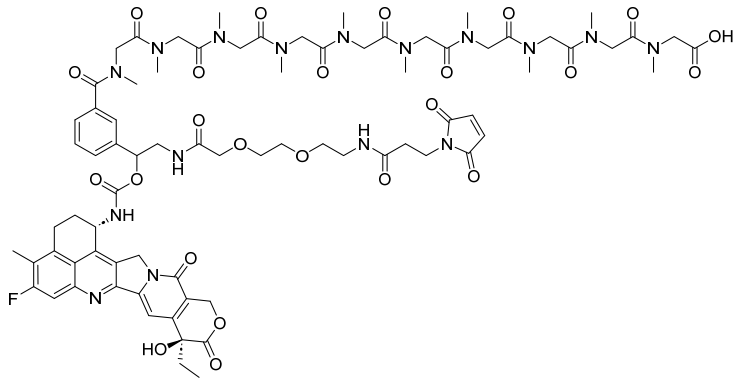


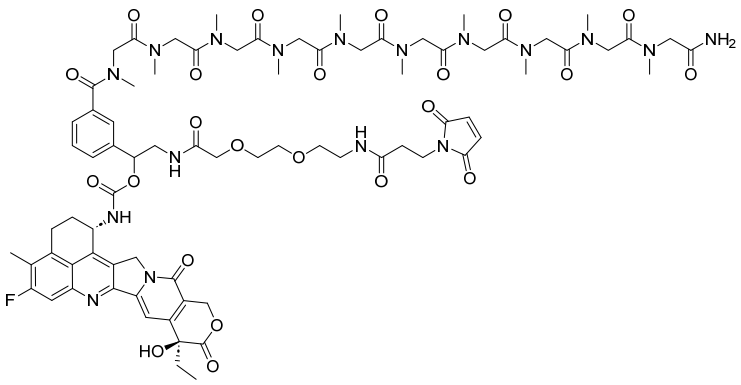
(SEQ ID NO: 28);

;

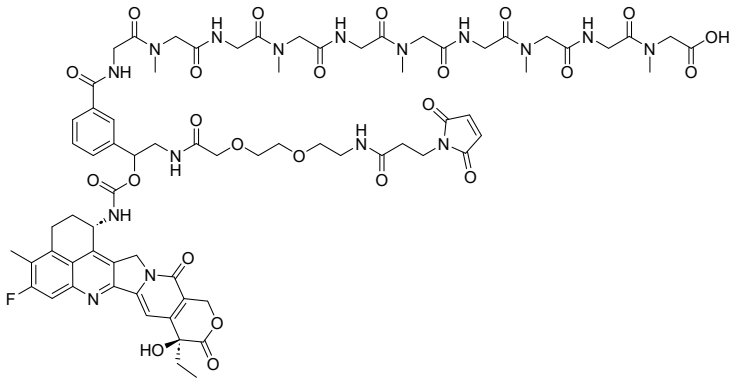

;


;

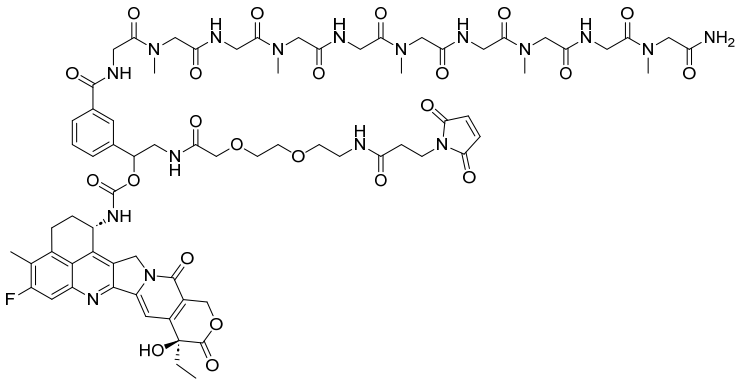

(SEQ ID NO: 29);



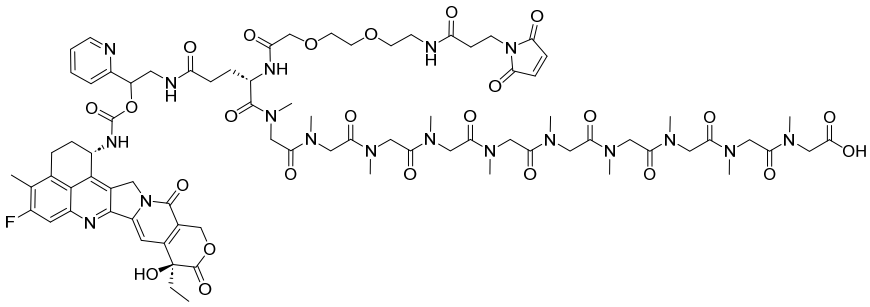
(SEQ ID NO: 29);



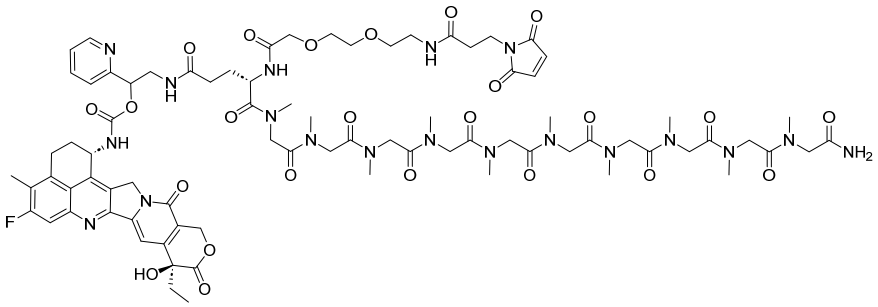
(SEQ ID NO: 30);



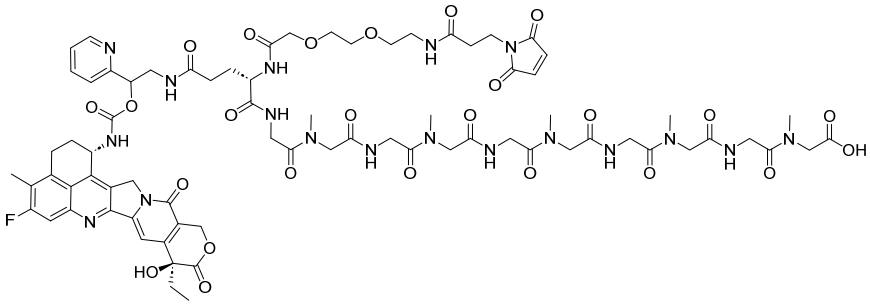
(SEQ ID NO: 30);



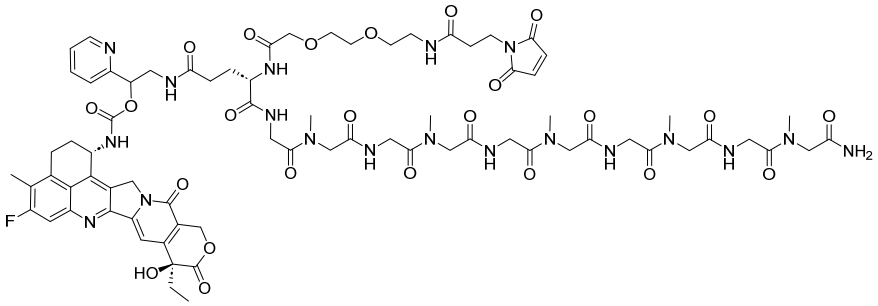
(SEQ ID NO: 25);



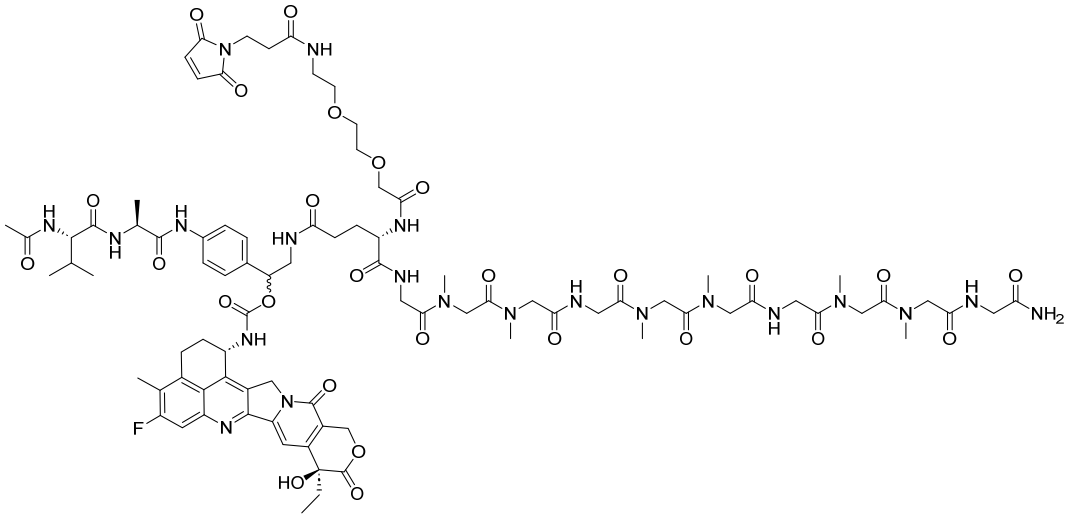
(SEQ ID NO: 25);



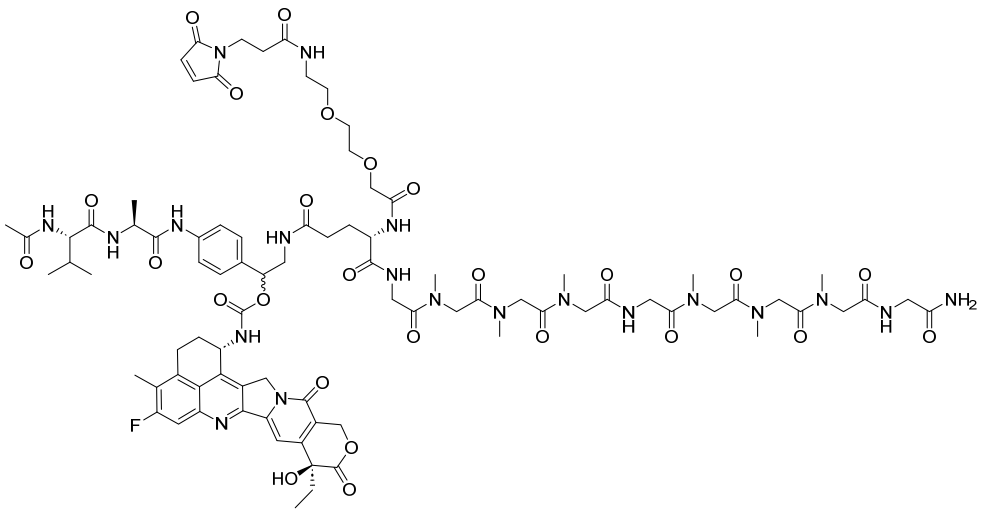
(SEQ ID NO: 26);



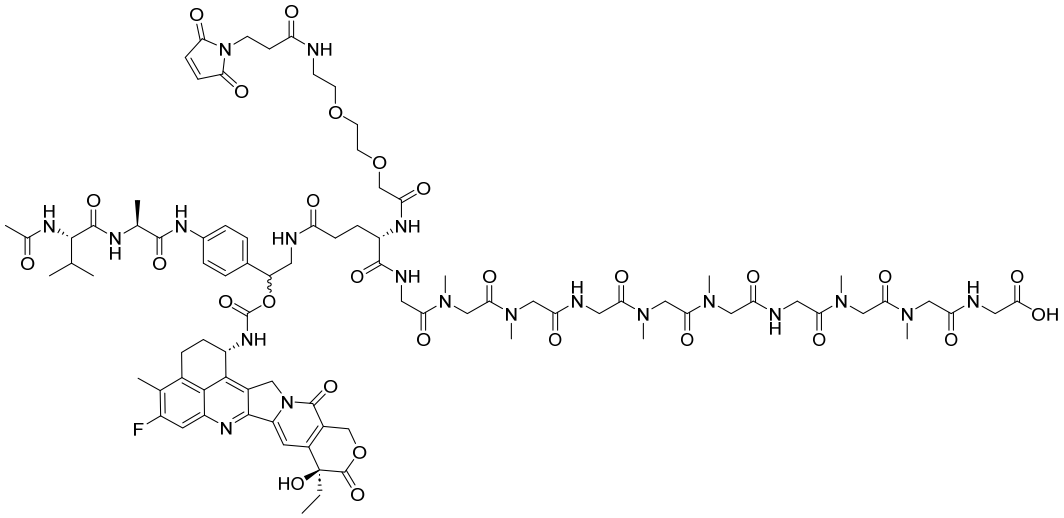
(SEQ ID NO: 26)



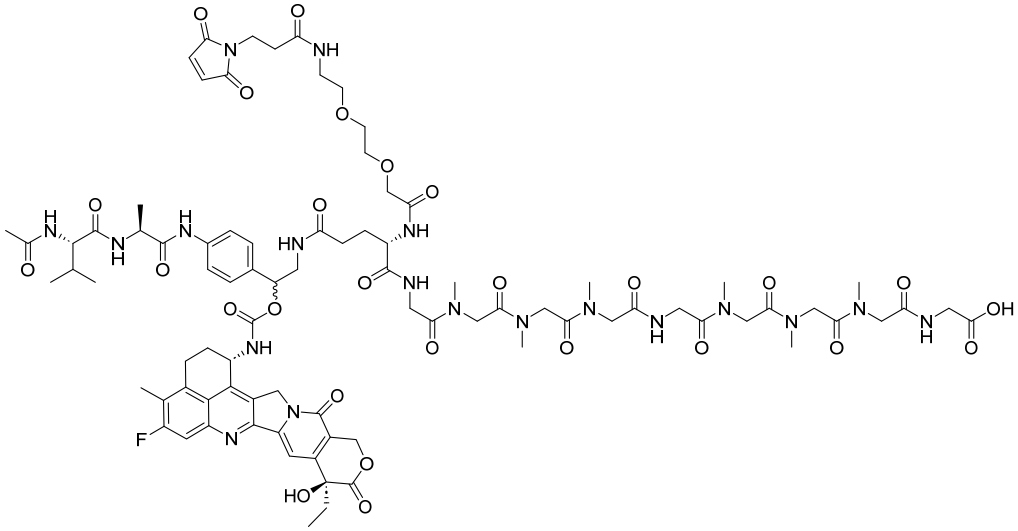
(SEQ ID NO: 31);



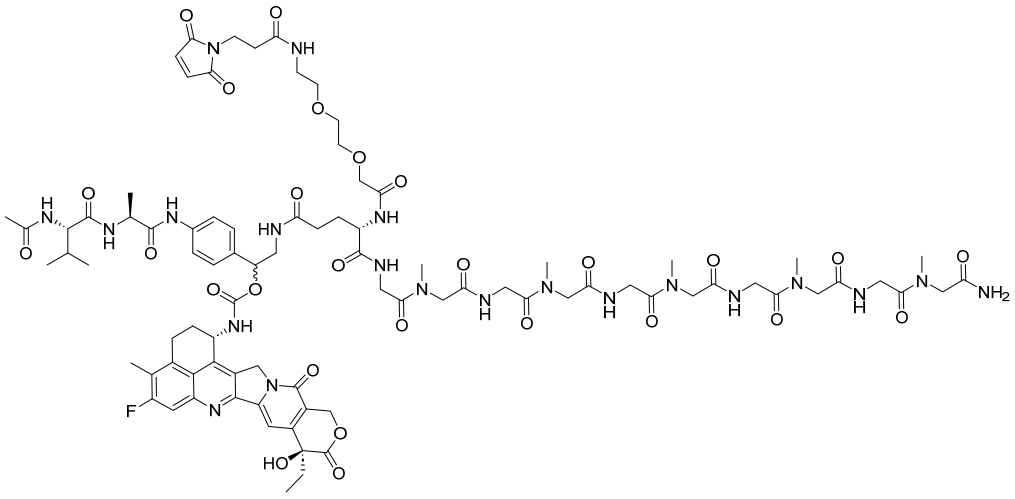
(SEQ ID NO: 32);



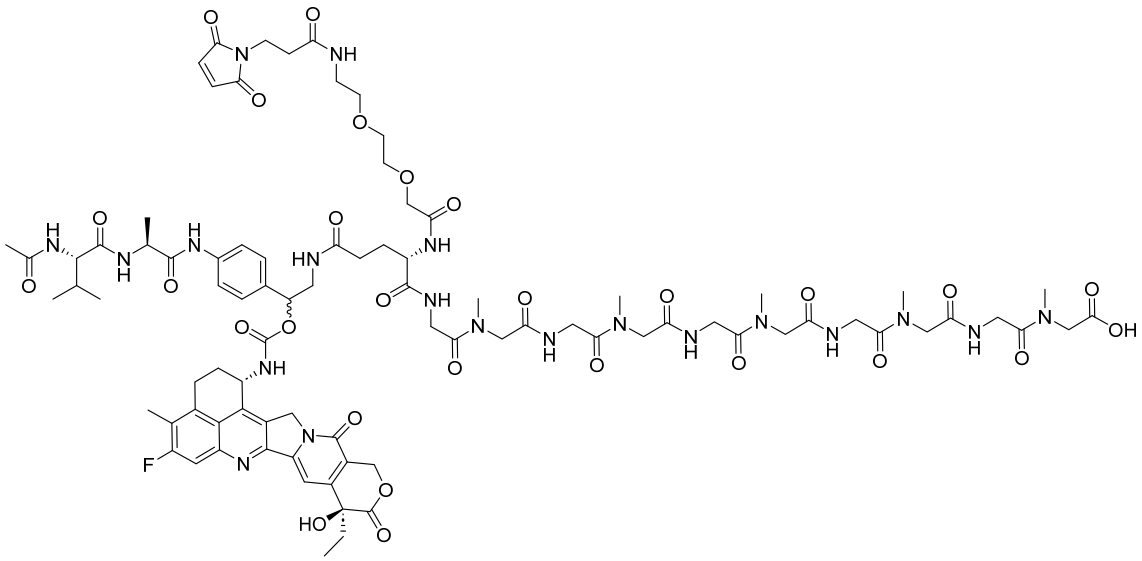
(SEQ ID NO: 31);



(SEQ ID NO: 32);

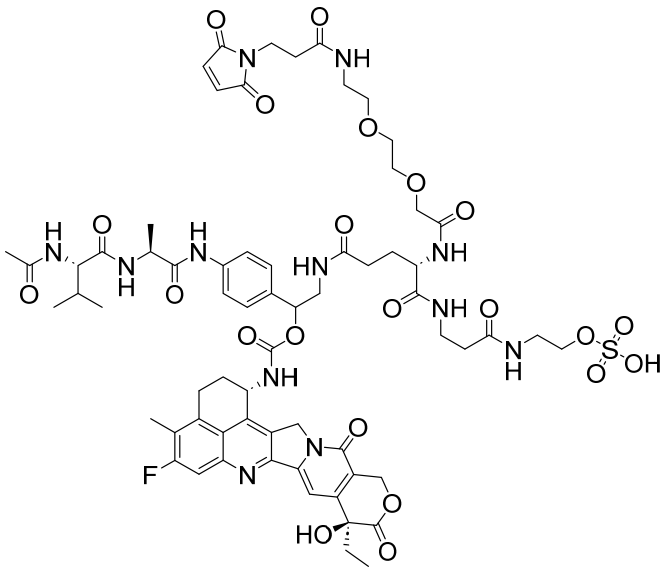


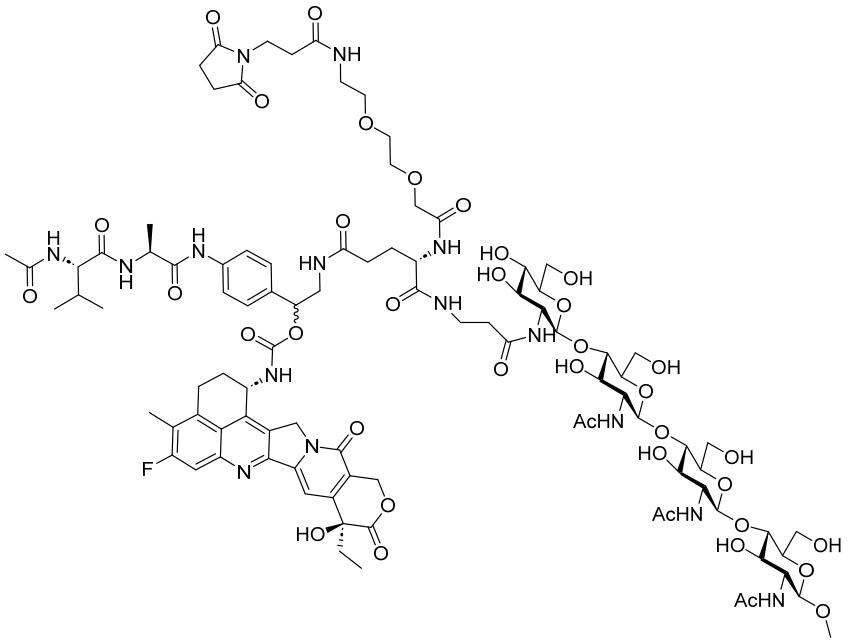
(SEQ ID NO: 26); and

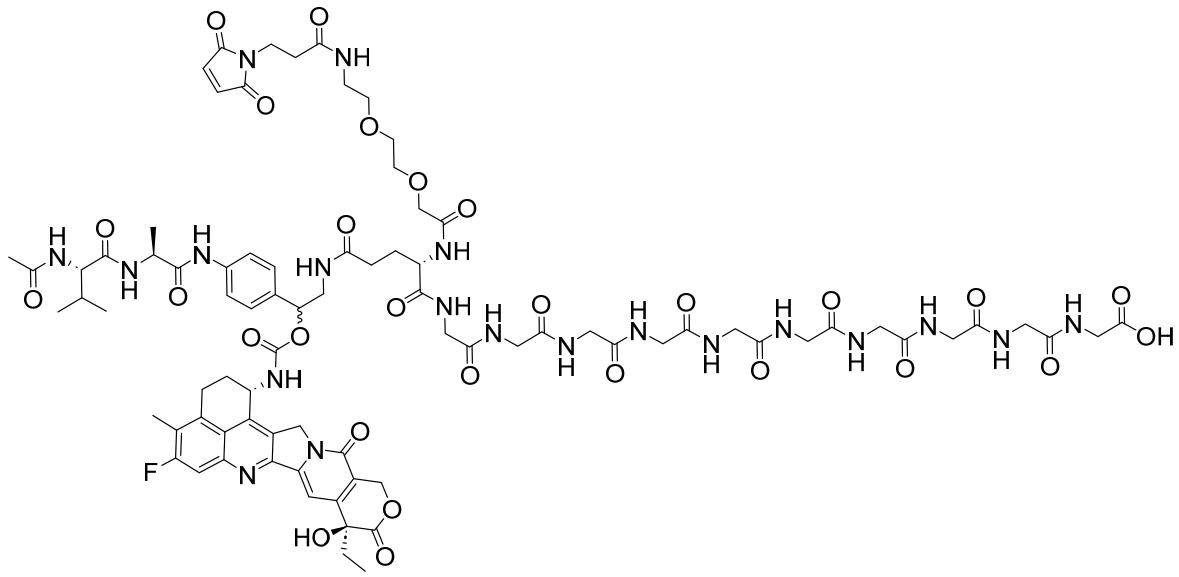


(SEQ ID NO: 26).

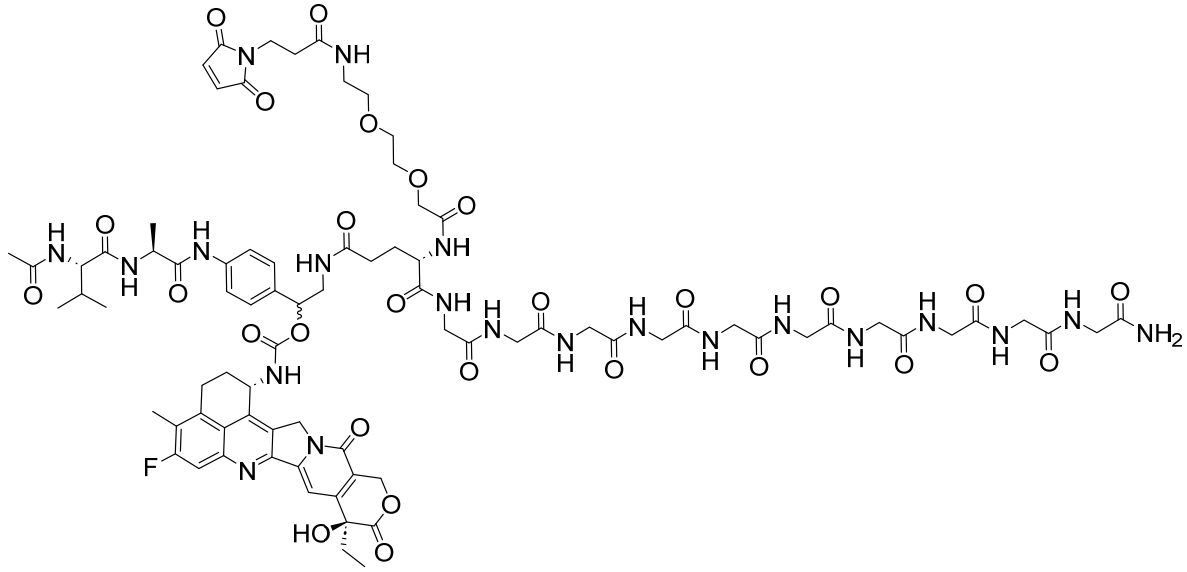
[00197] In some embodiments, a Drug-Linker of Formula (X) is selected from:



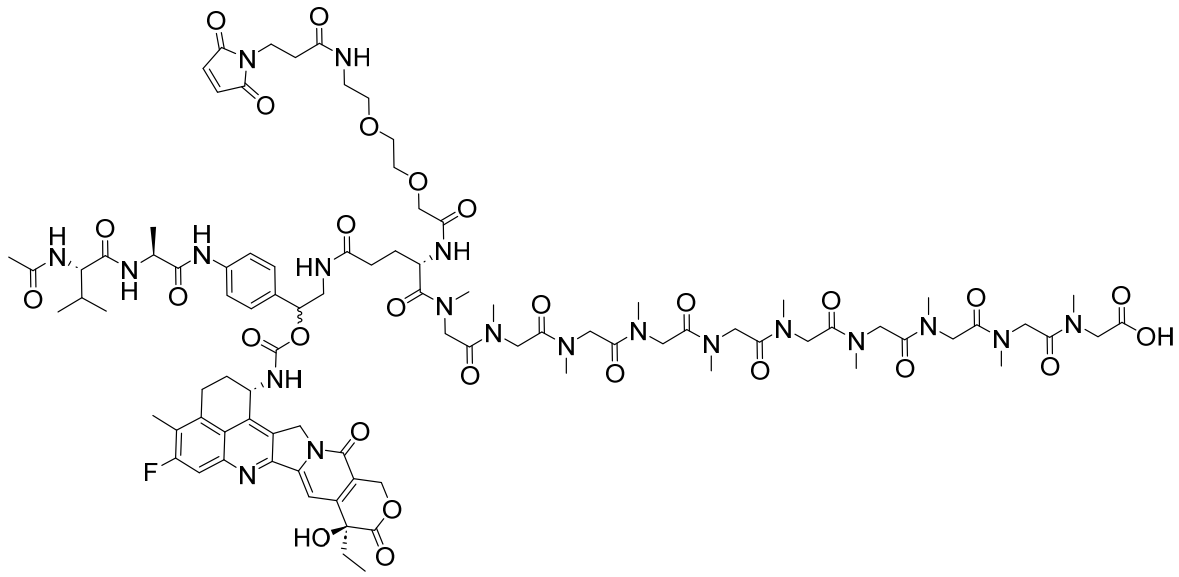




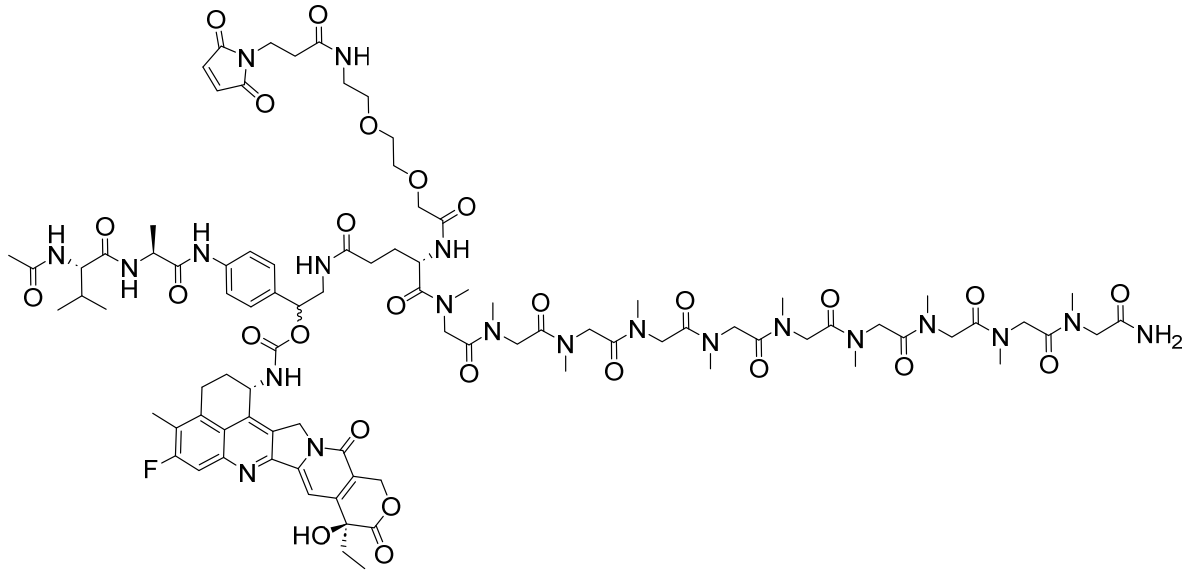
(SEQ ID NO: 24),



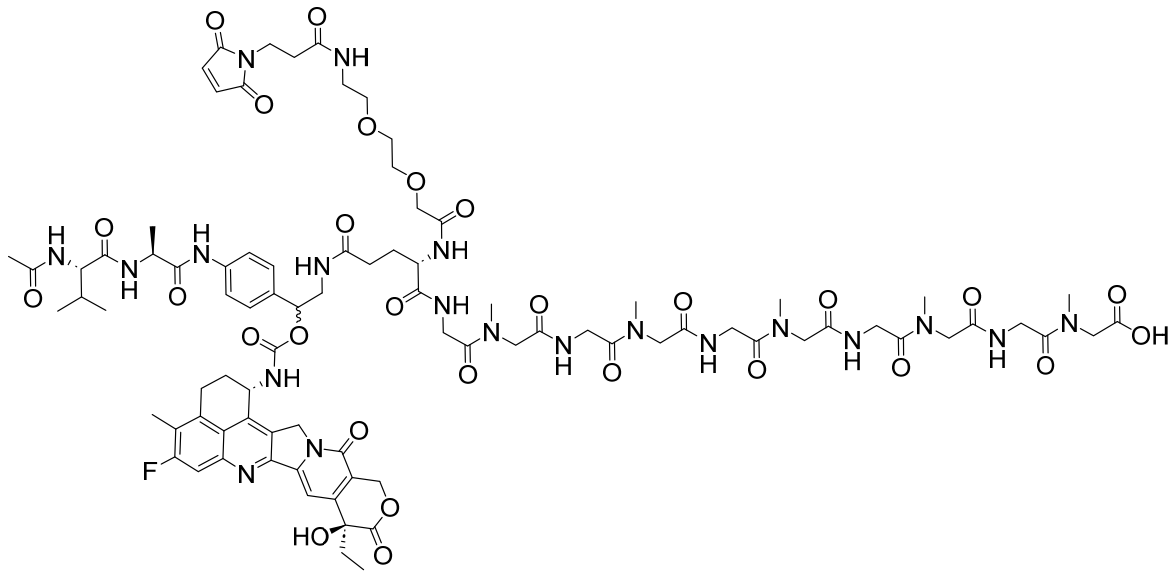
(SEQ ID NO: 24),



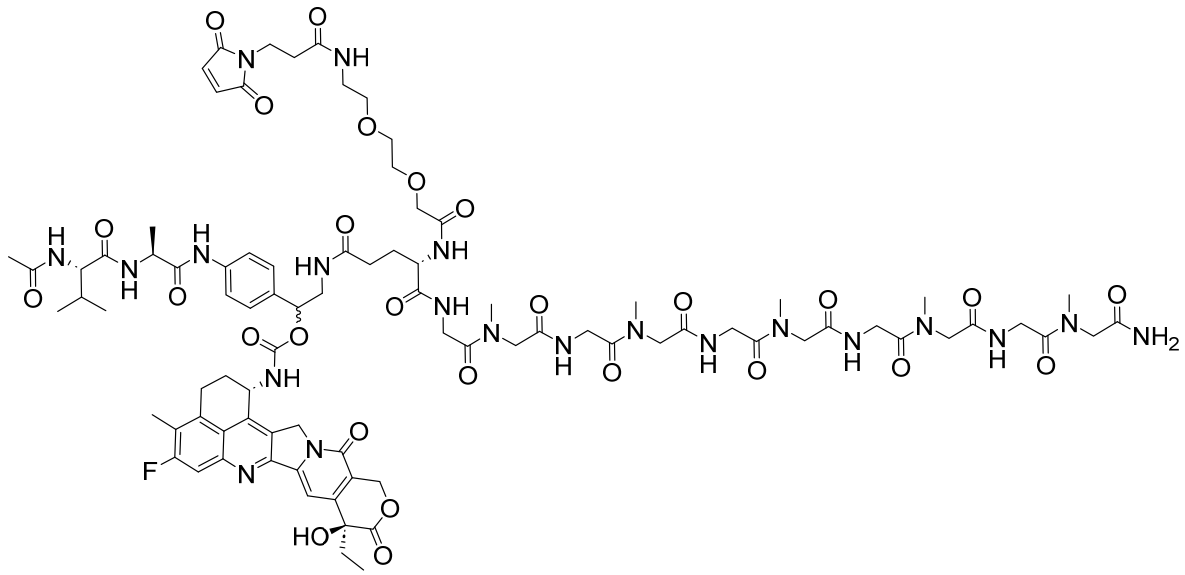
(SEQ ID NO: 25),



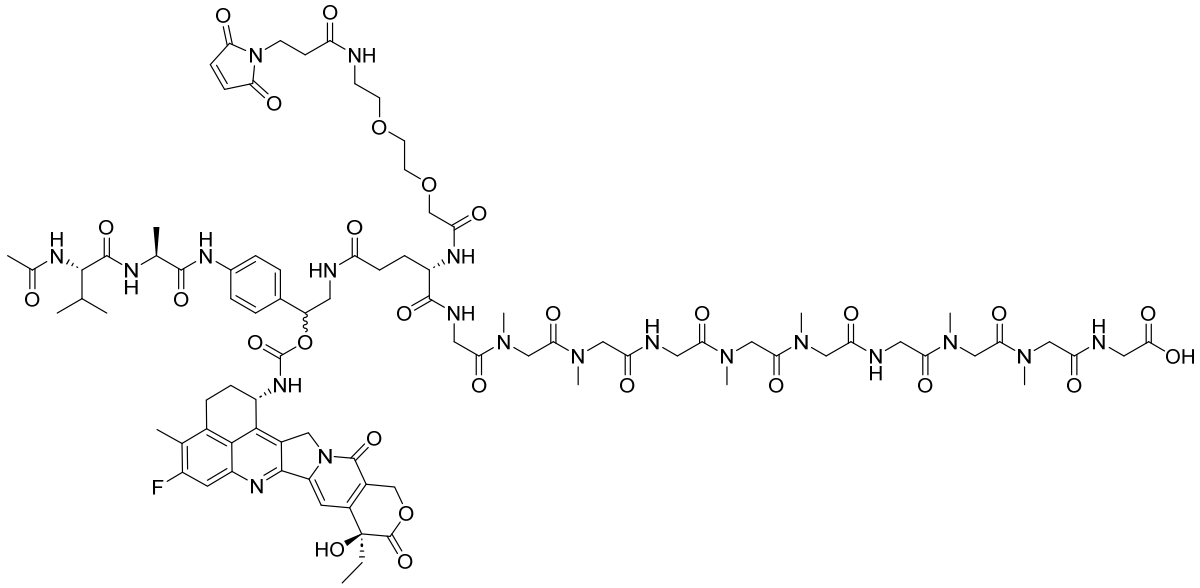
(SEQ ID NO: 25),



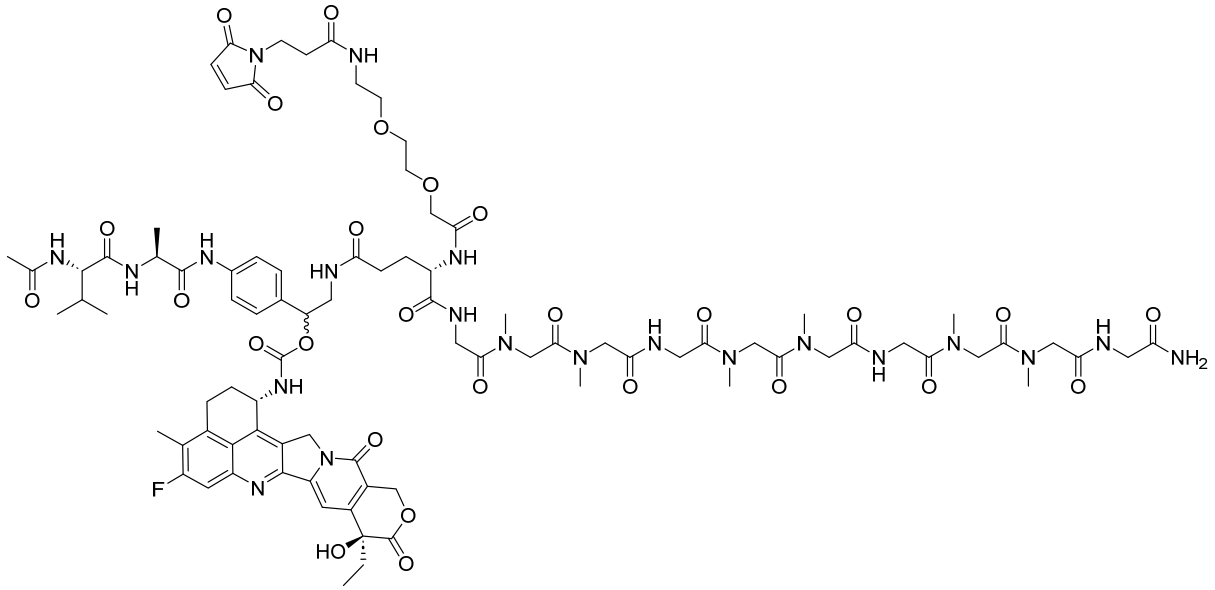
(SEQ ID NO: 26),



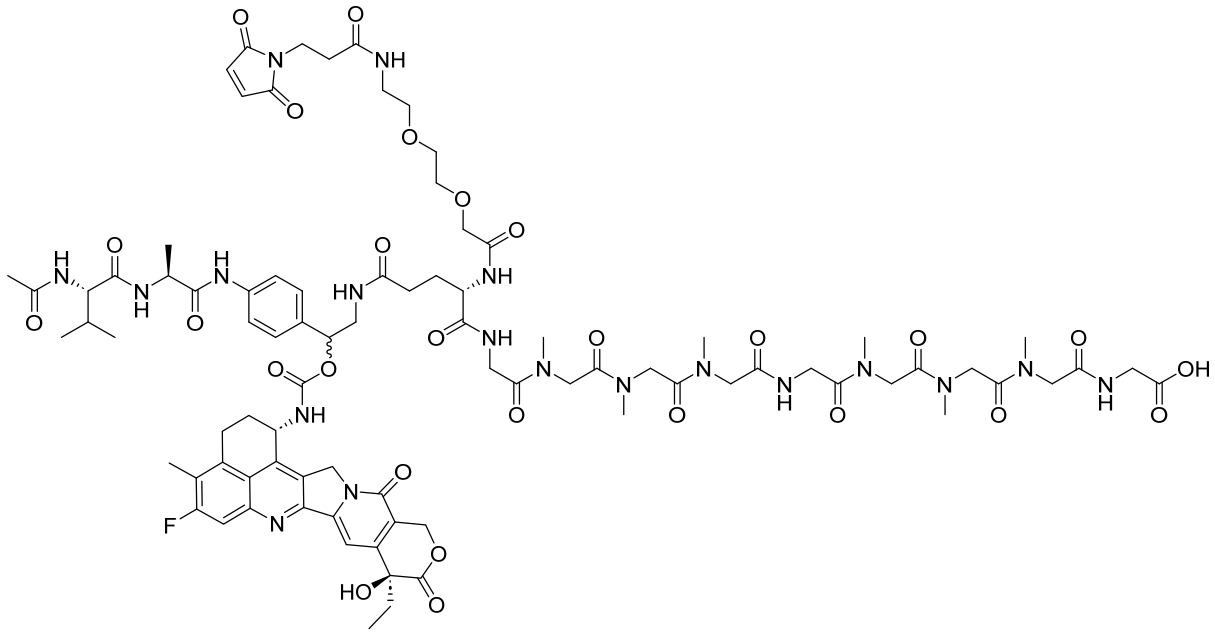
(SEQ ID NO: 26),



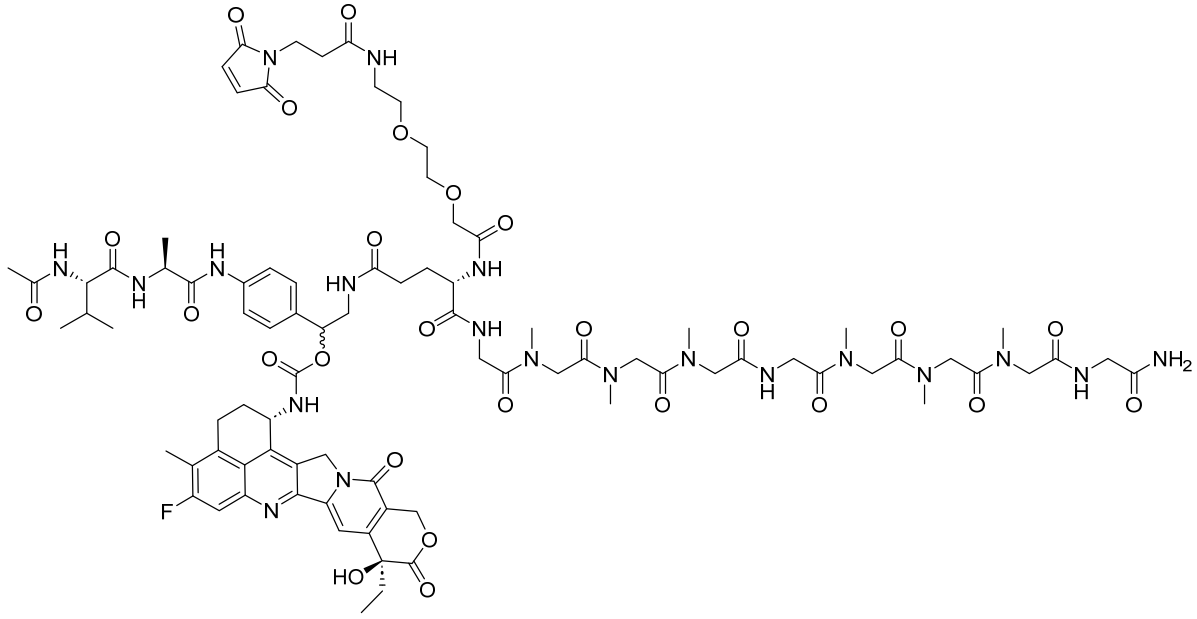
(SEQ ID NO: 31),



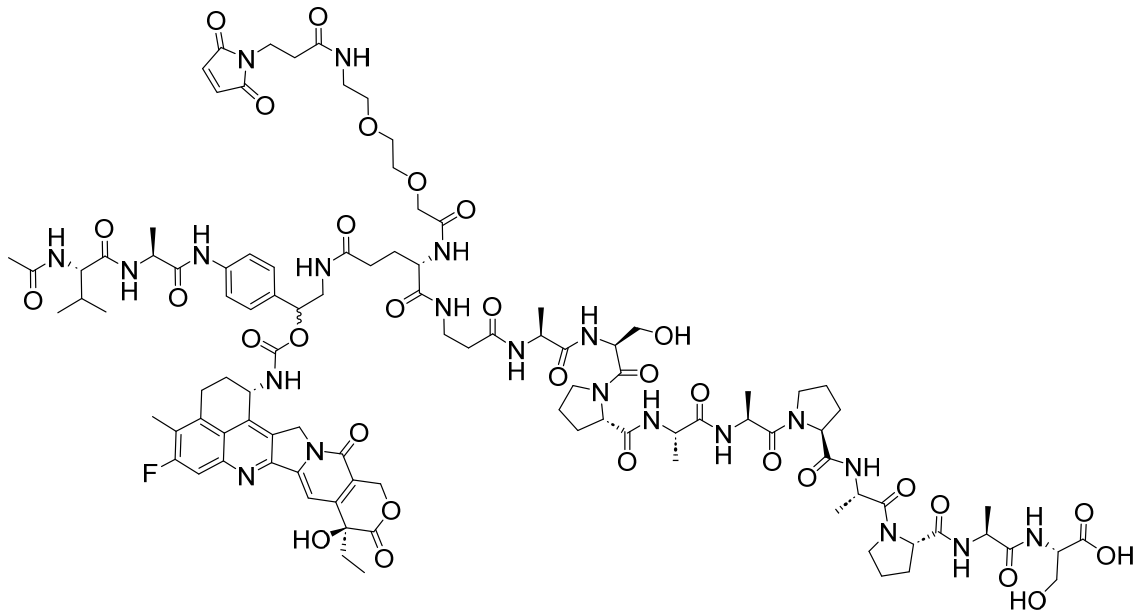
(SEQ ID NO: 31),



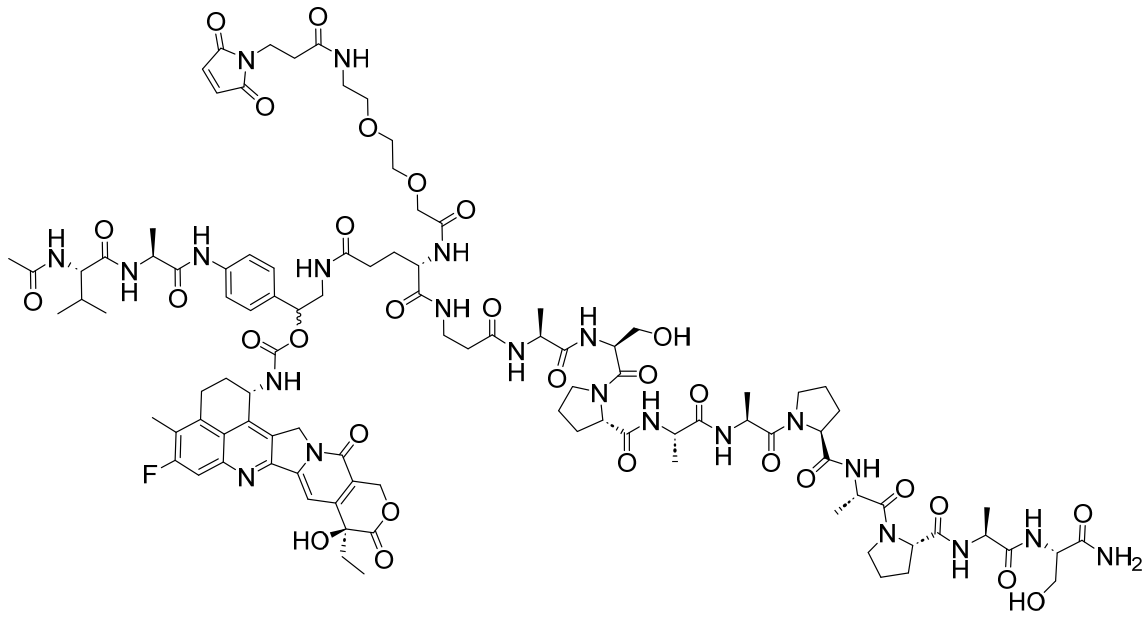
(SEQ ID NO: 32),



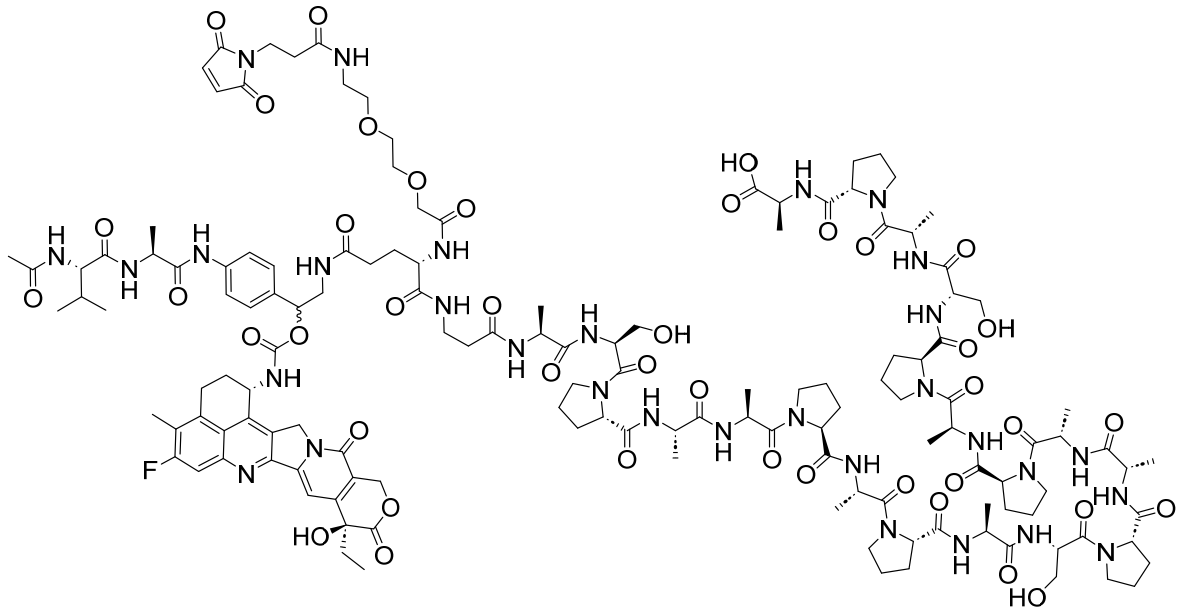
(SEQ ID NO: 32),



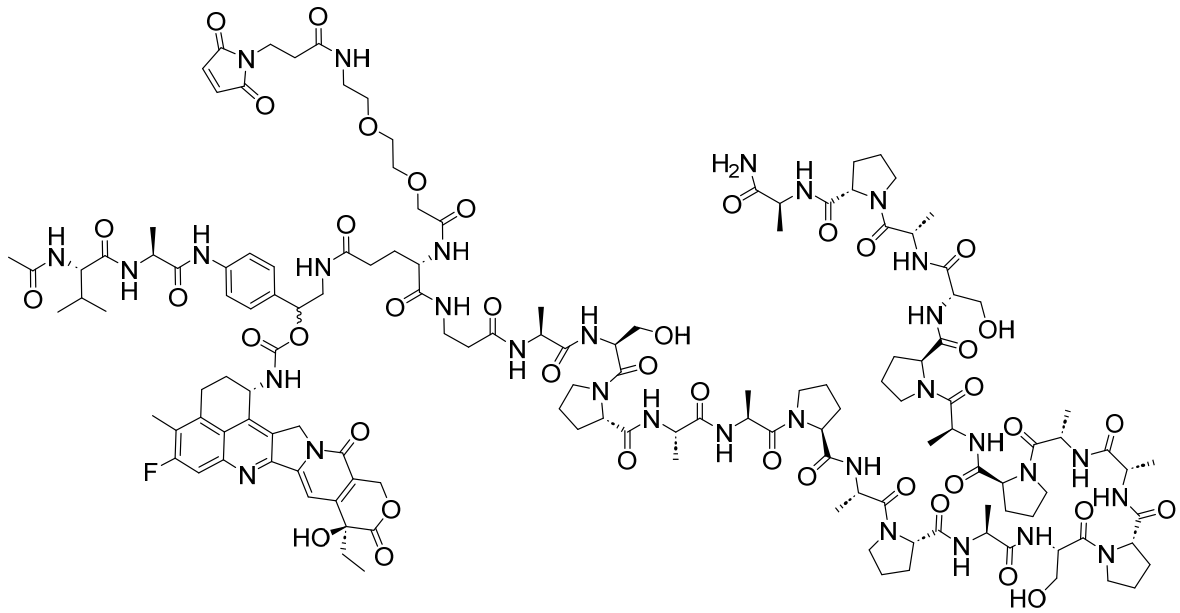
(SEQ ID NO: 27),



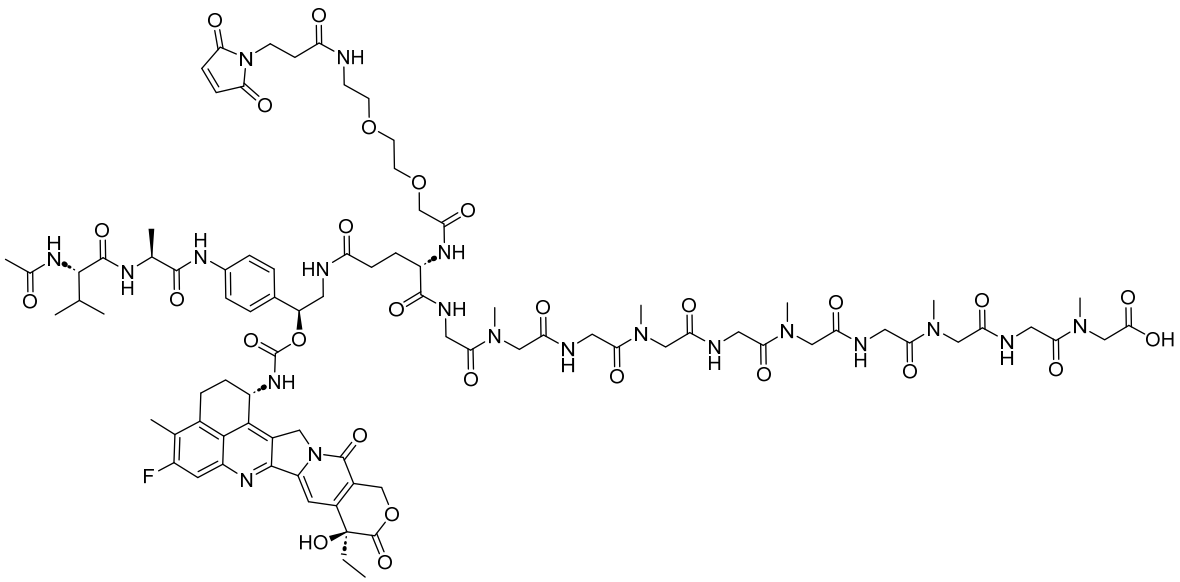
(SEQ ID NO: 27),



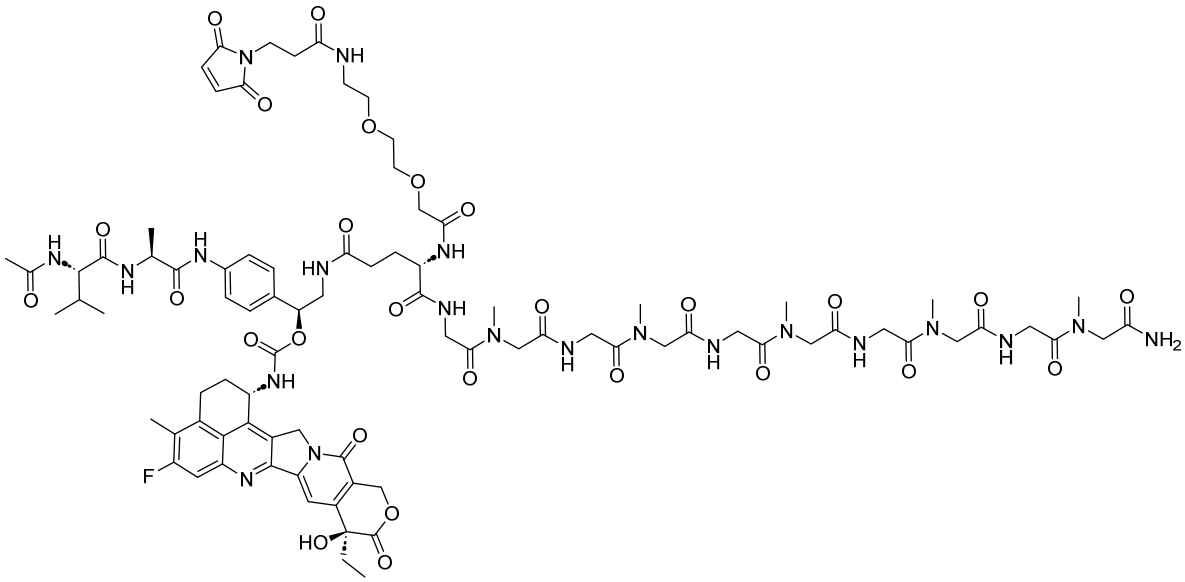
(SEQ ID NO: 28),



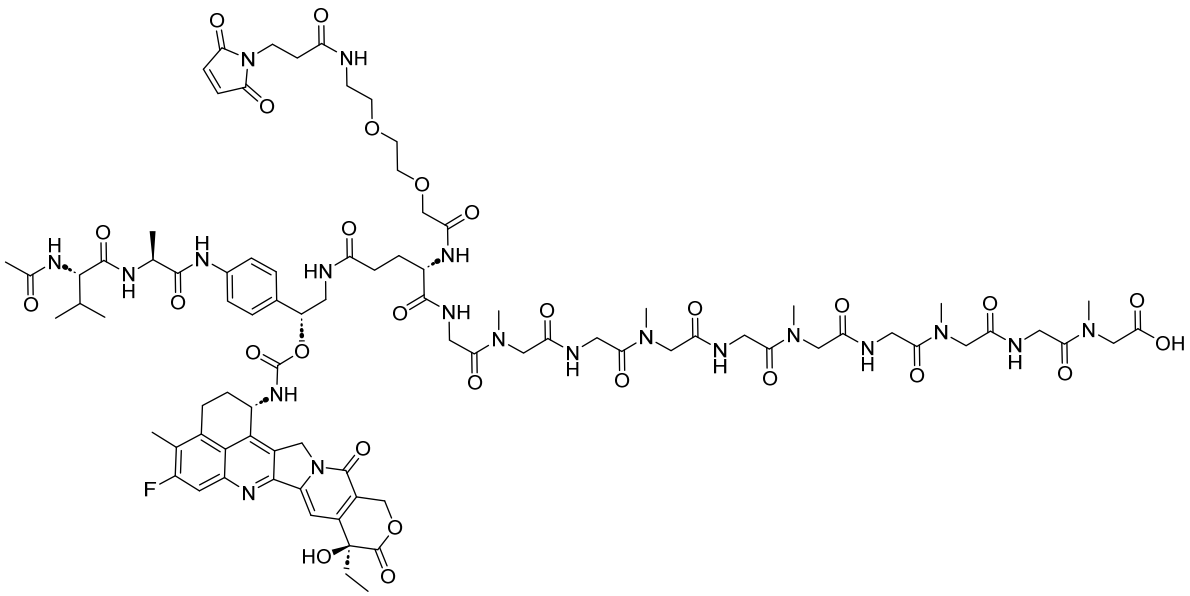
(SEQ ID NO: 28),



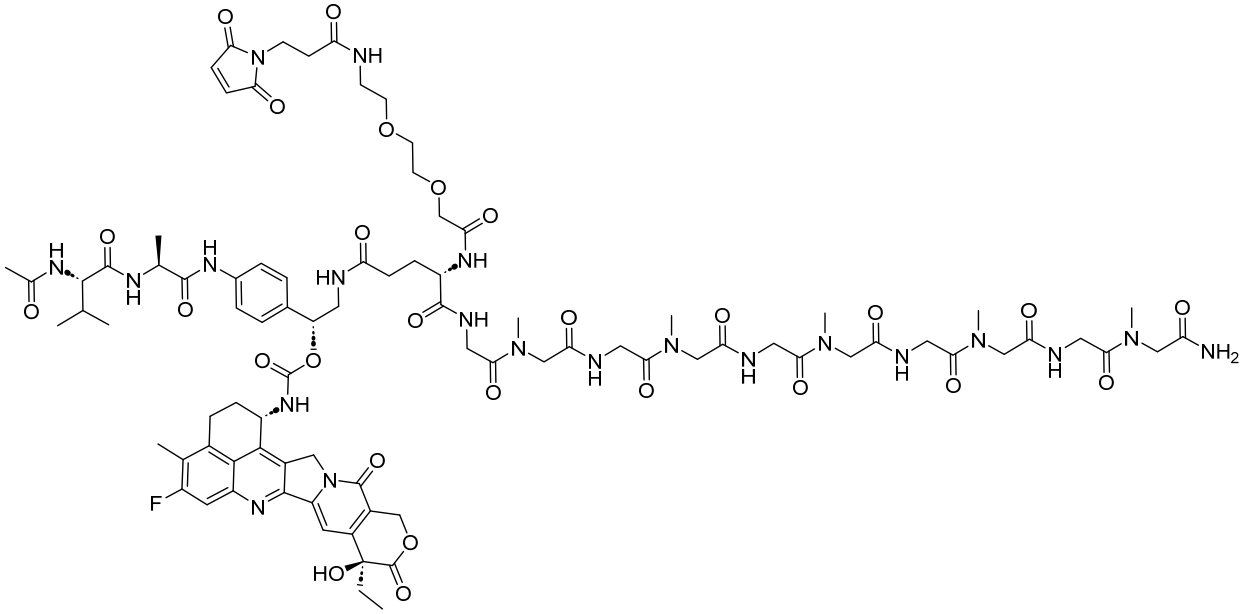
(SEQ ID NO: 26),



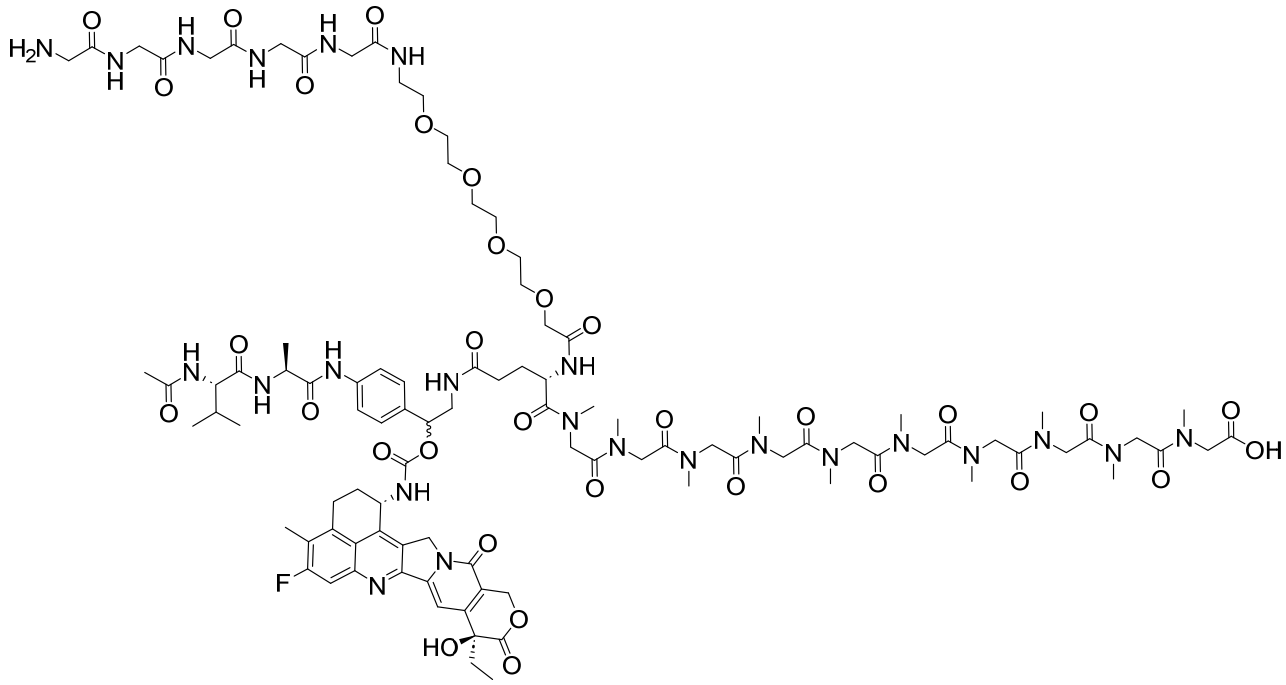
(SEQ ID NO: 26),



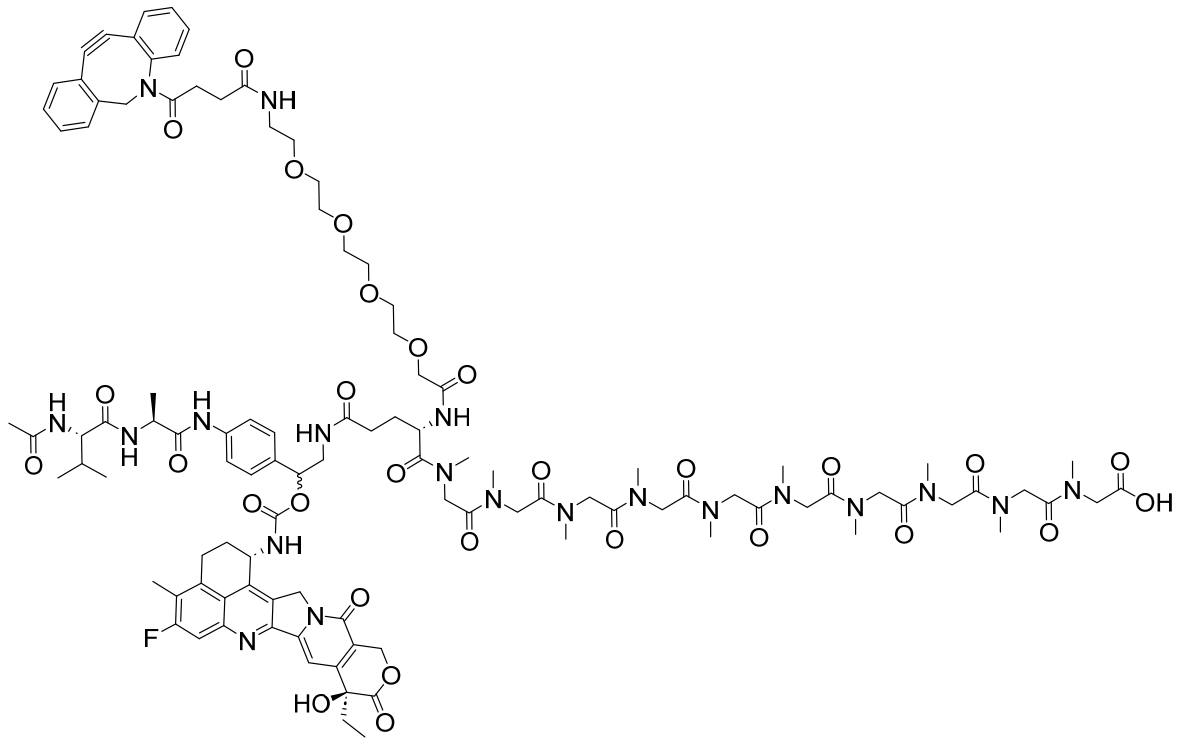
(SEQ ID NO: 26),



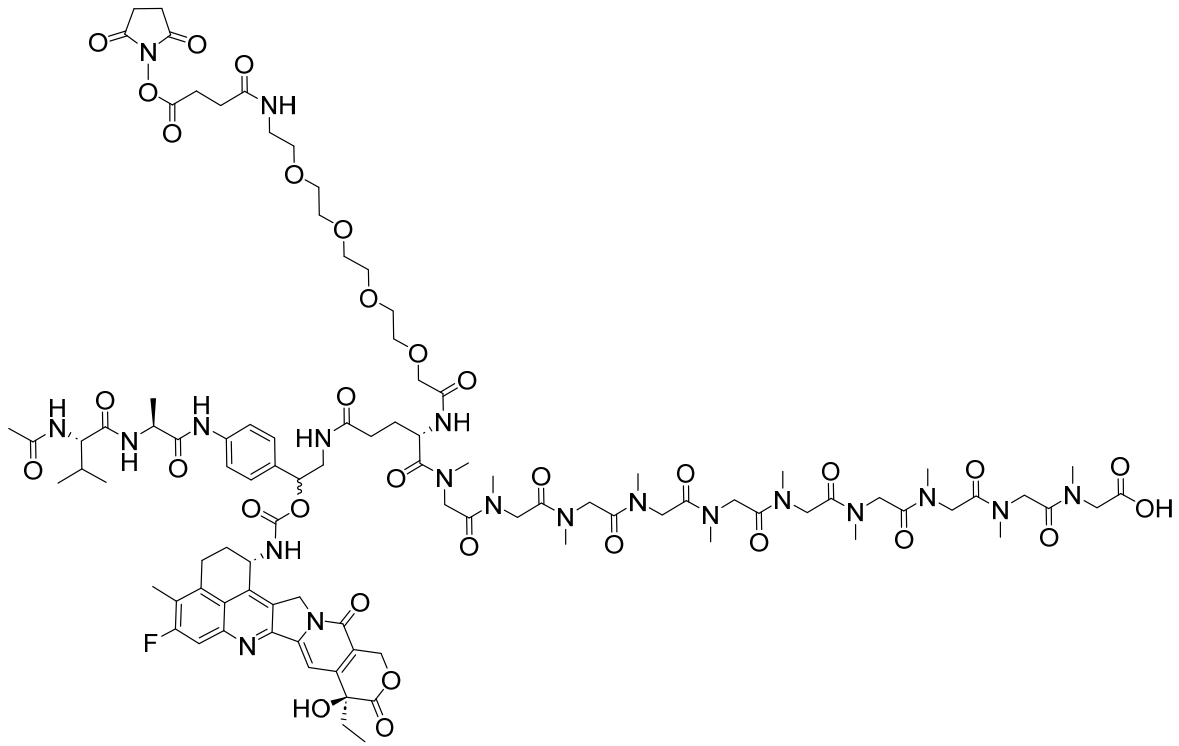
(SEQ ID NO: 26),



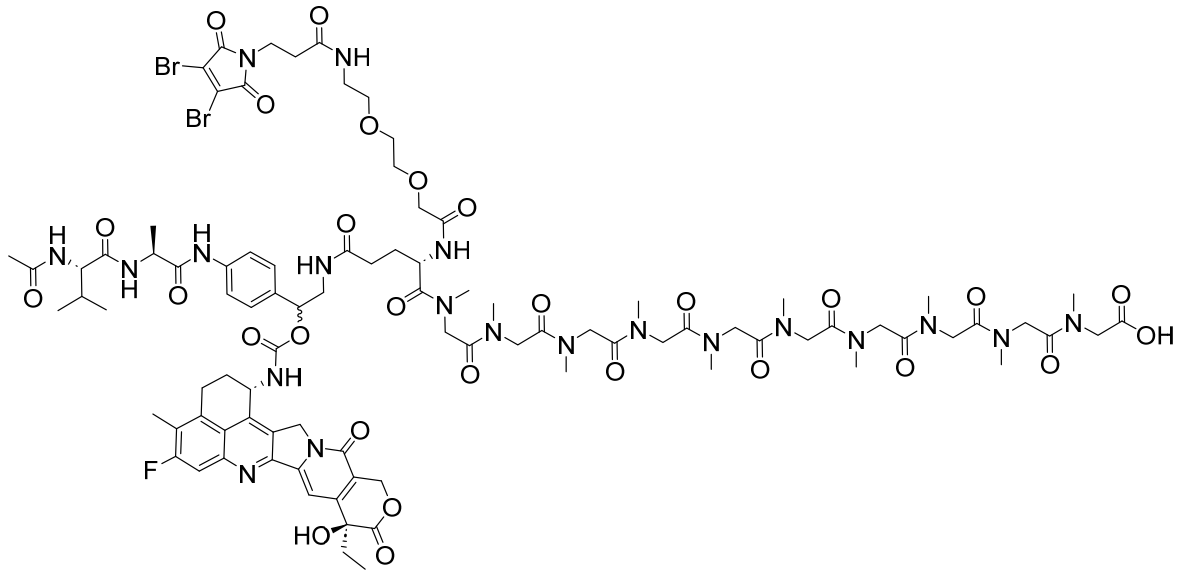
(SEQ ID NOS 39 and 25, respectively, in order of appearance),



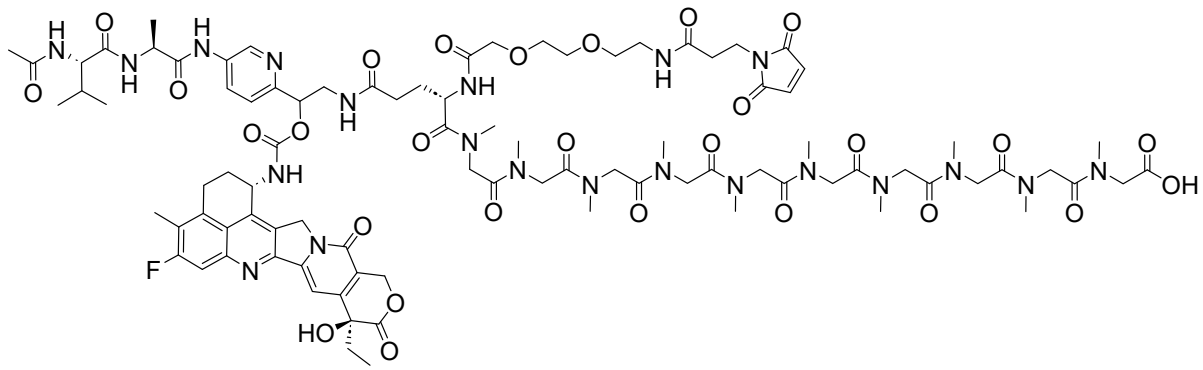
(SEQ ID NO: 25),



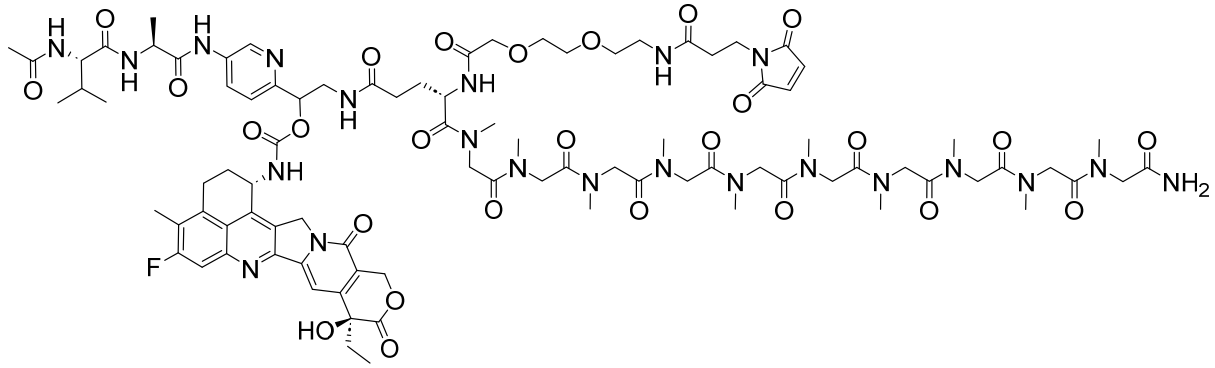
(SEQ ID NO: 25),



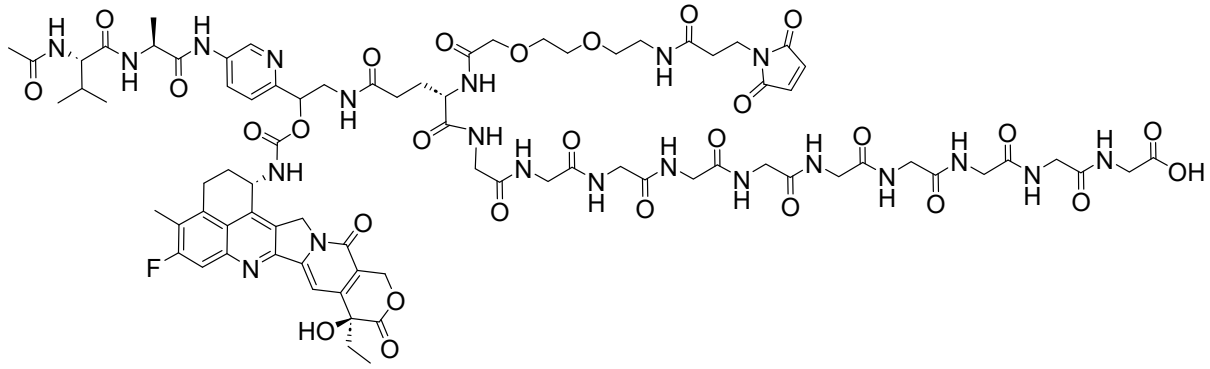
(SEQ ID NO: 25),



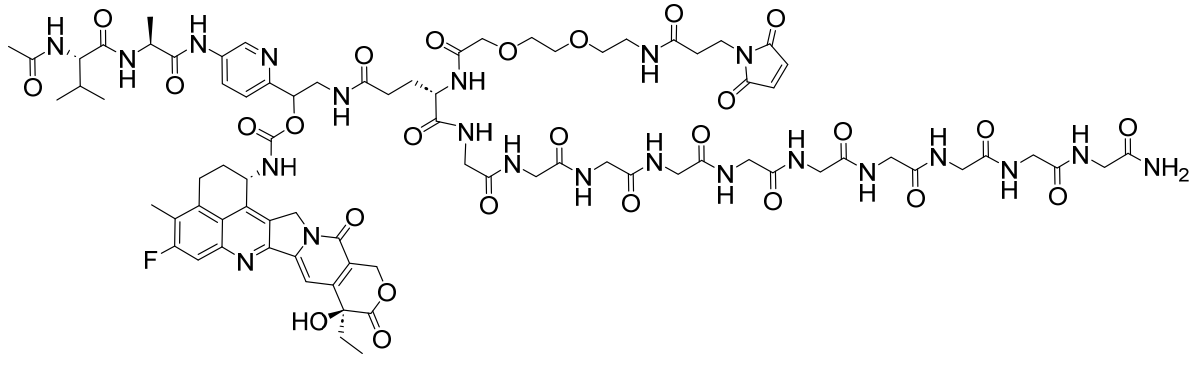
(SEQ ID NO: 25),



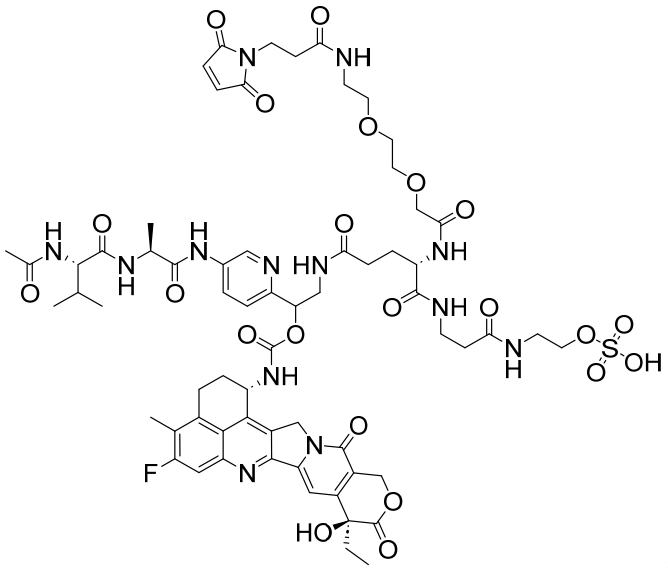
(SEQ ID NO: 25),



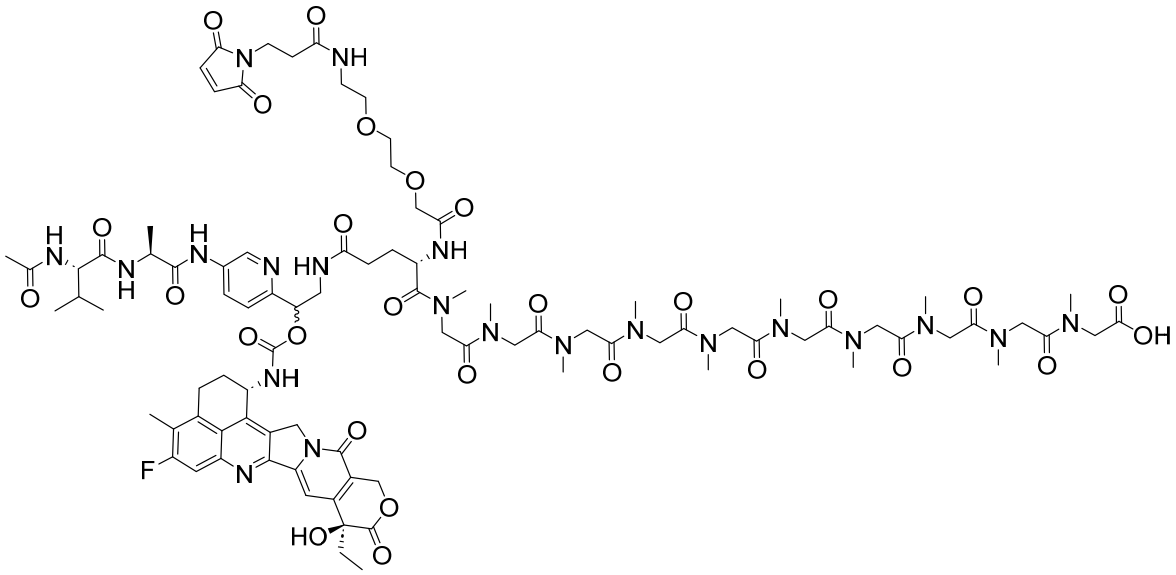
(SEQ ID NO: 24),



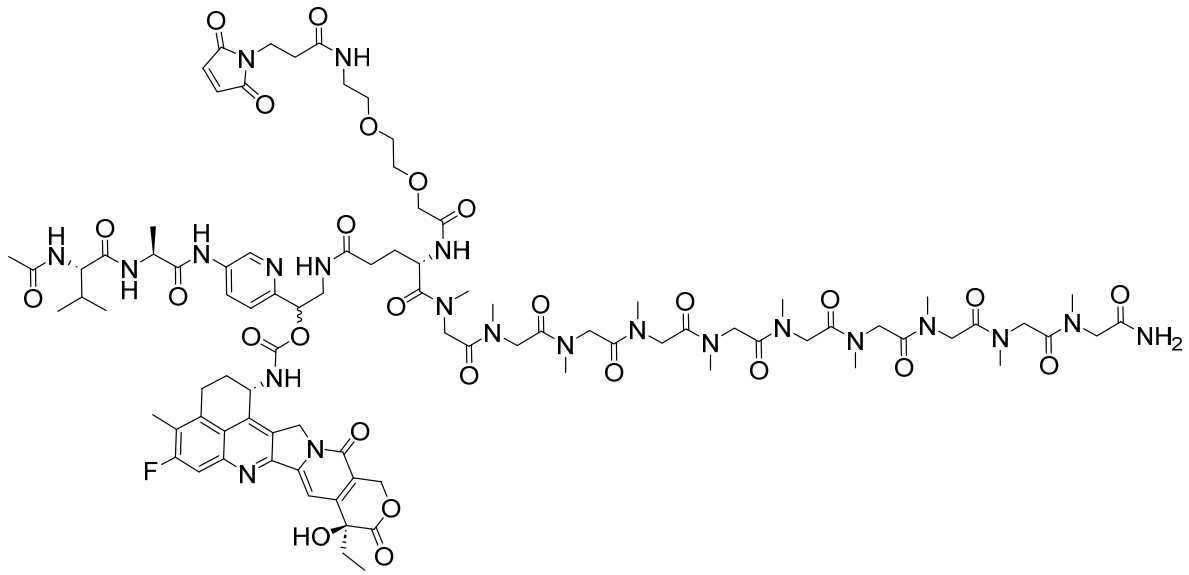
(SEQ ID NO: 24),



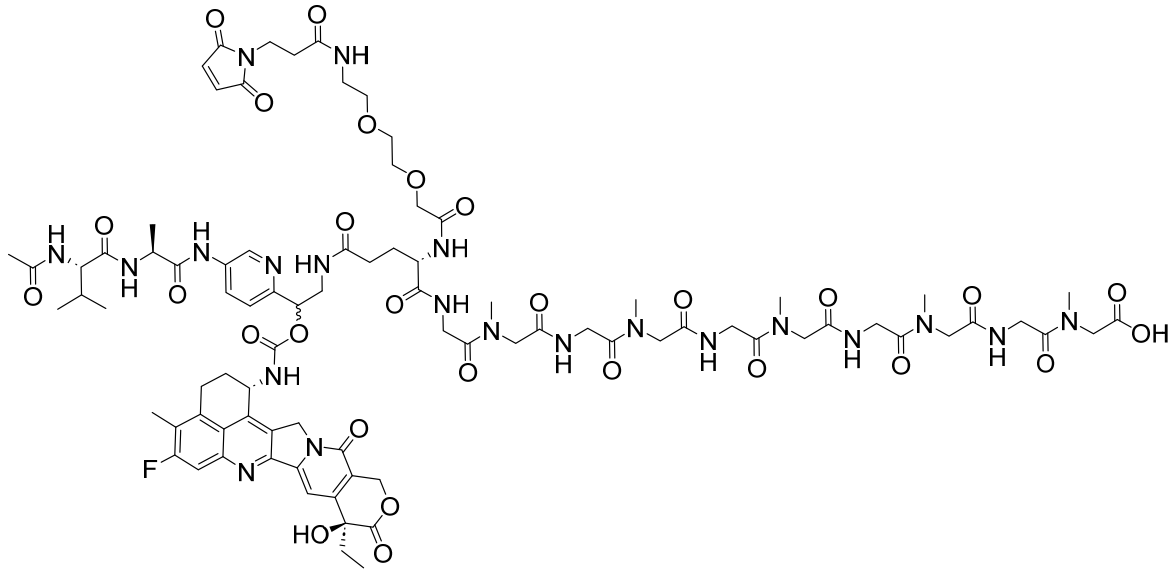
,



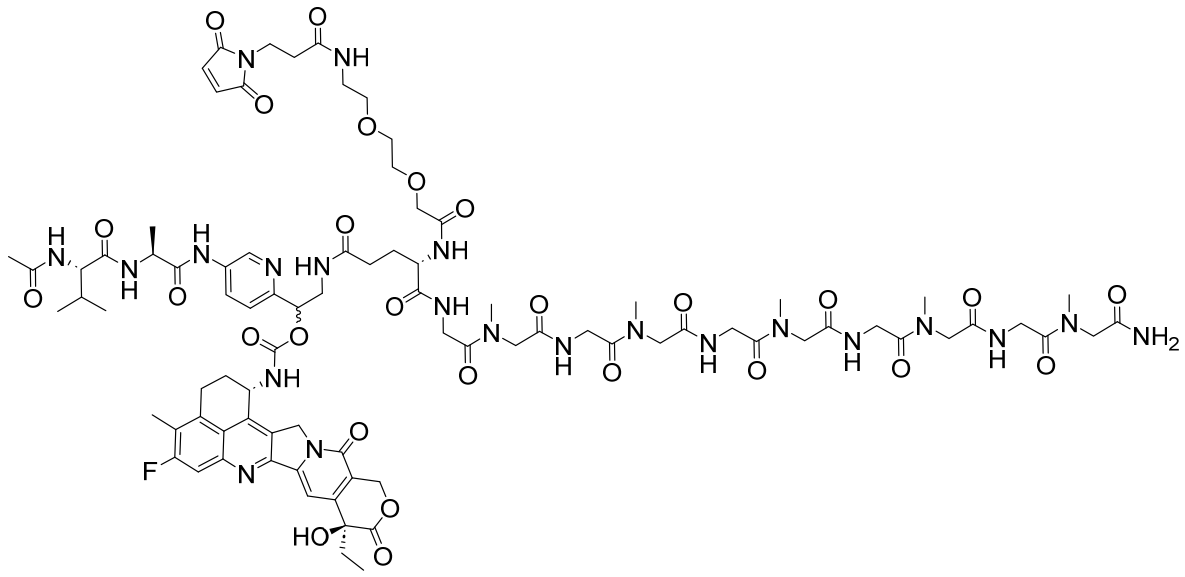
(SEQ ID NO: 25),



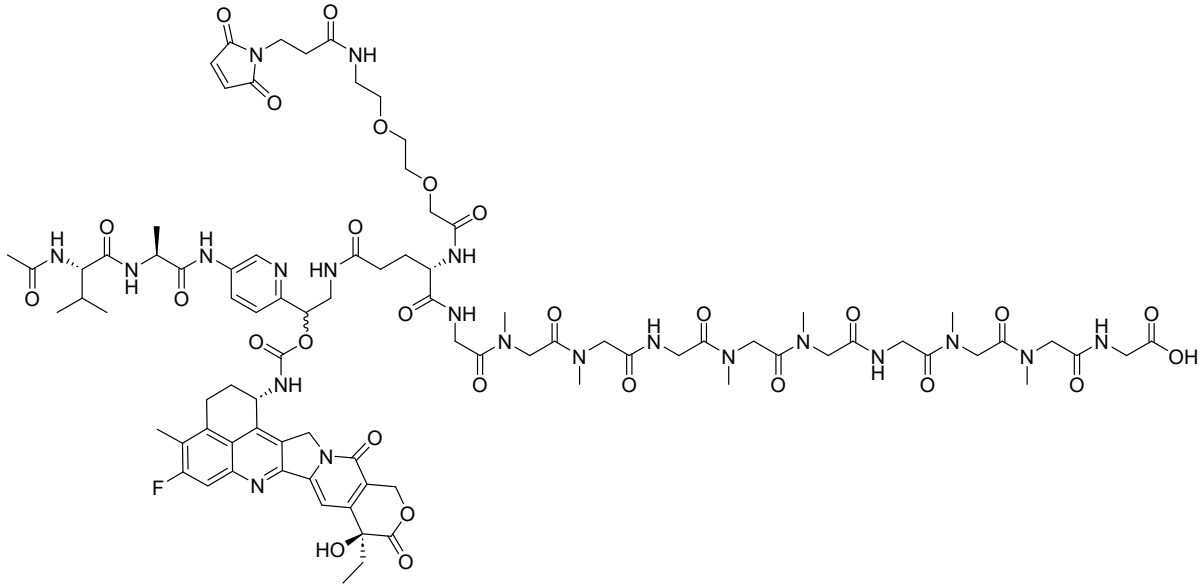
(SEQ ID NO: 25),



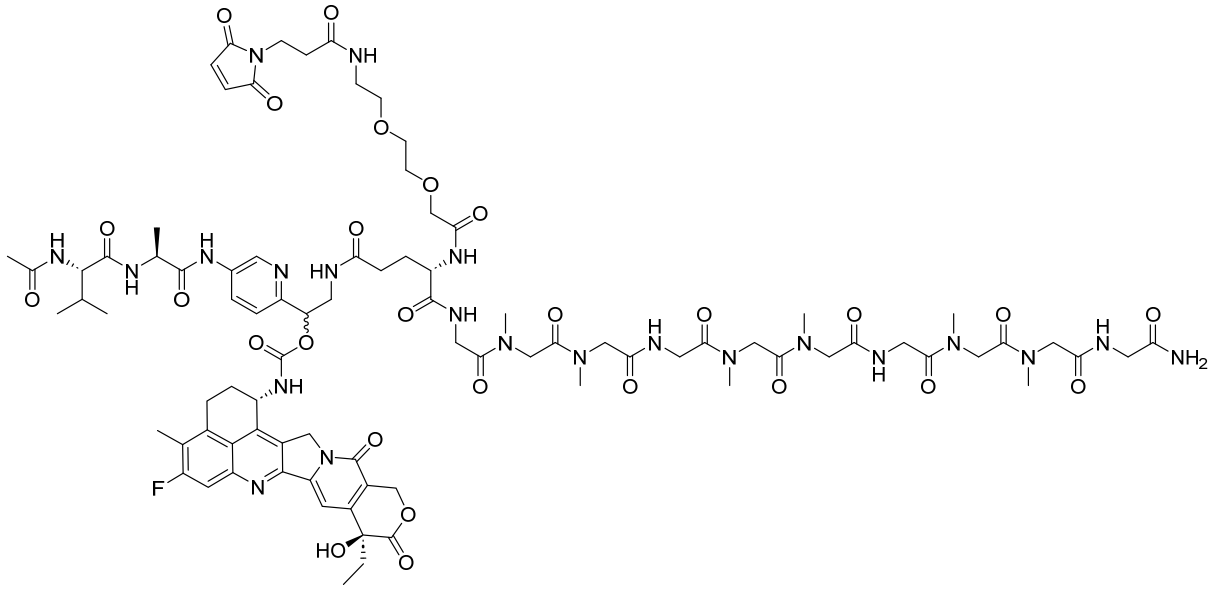
(SEQ ID NO: 26),



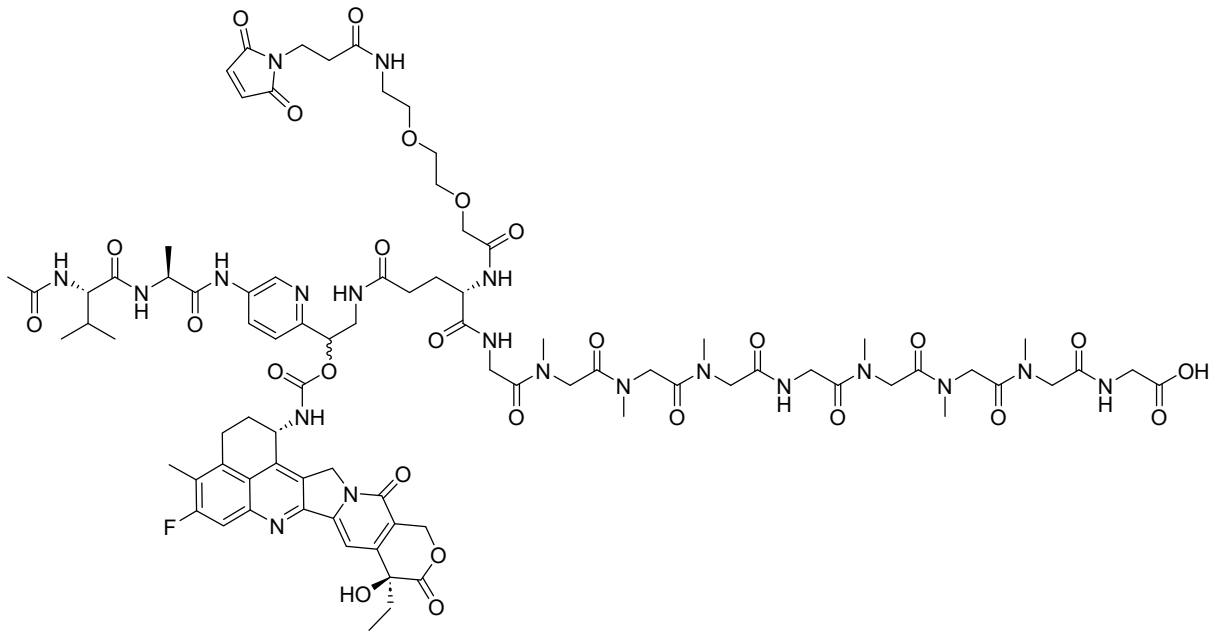
(SEQ ID NO: 26),



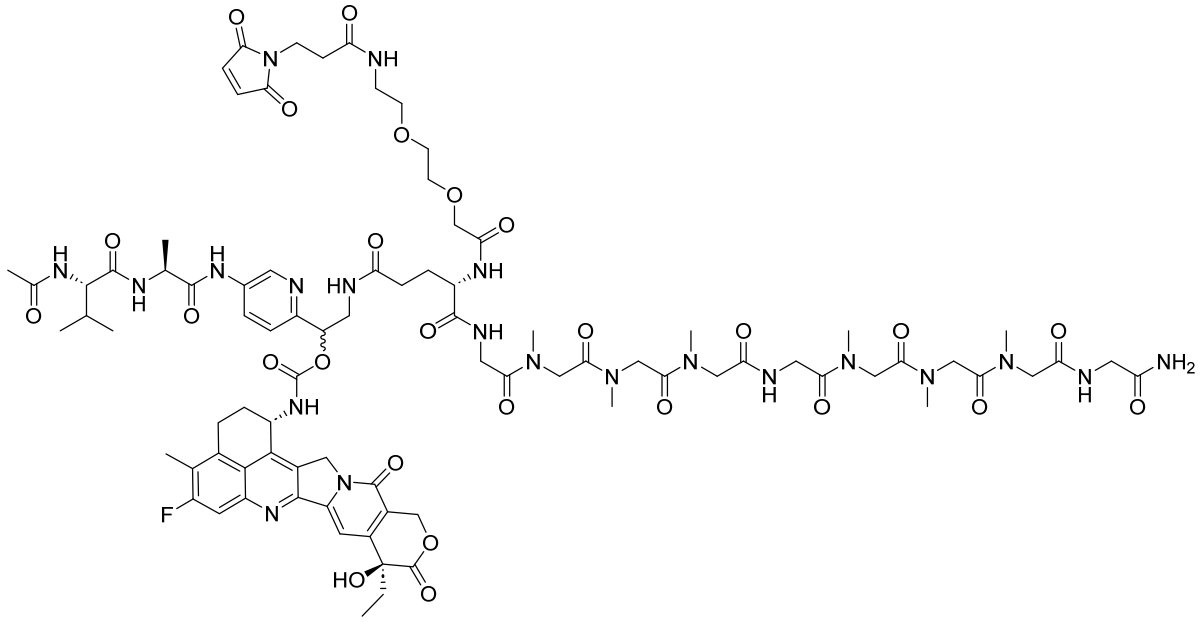
(SEQ ID NO: 31),



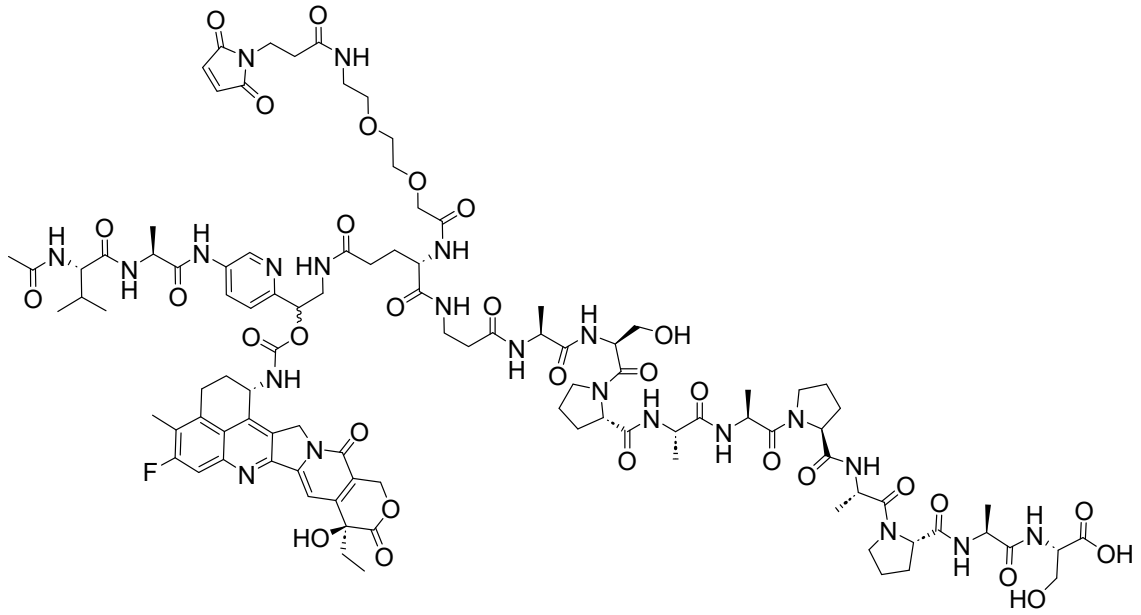
(SEQ ID NO: 31),



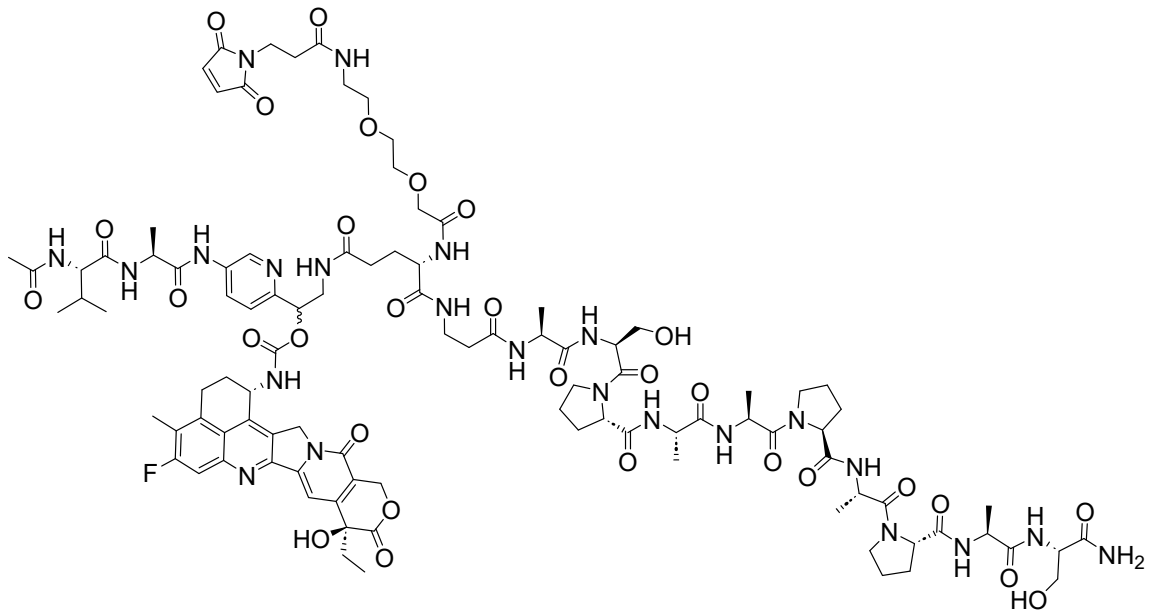
(SEQ ID NO: 32),



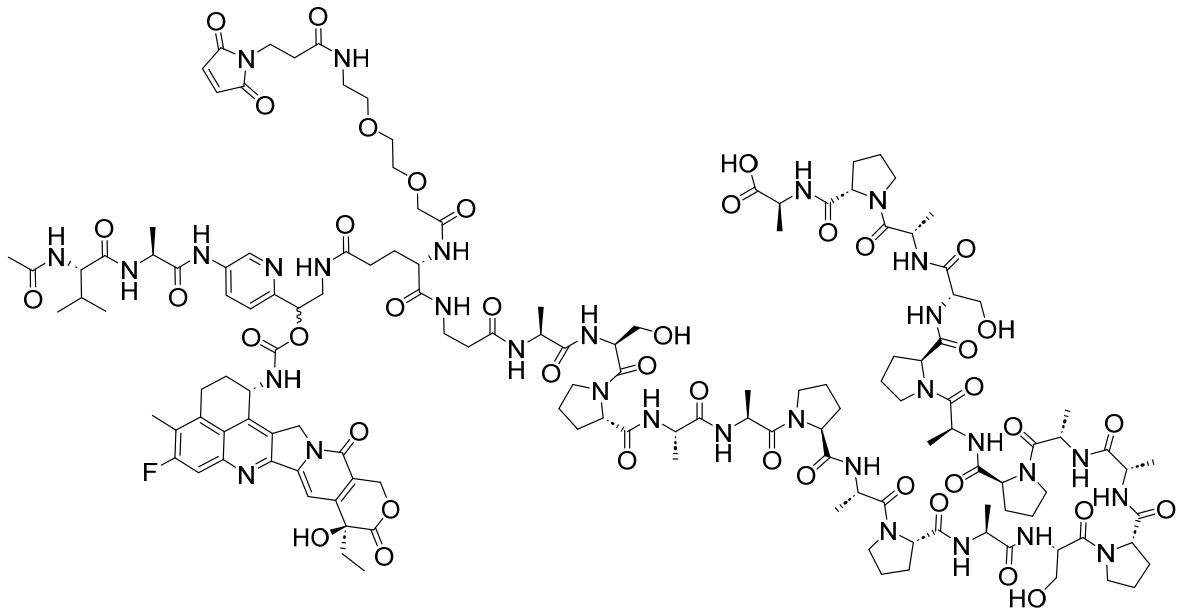
(SEQ ID NO: 32),



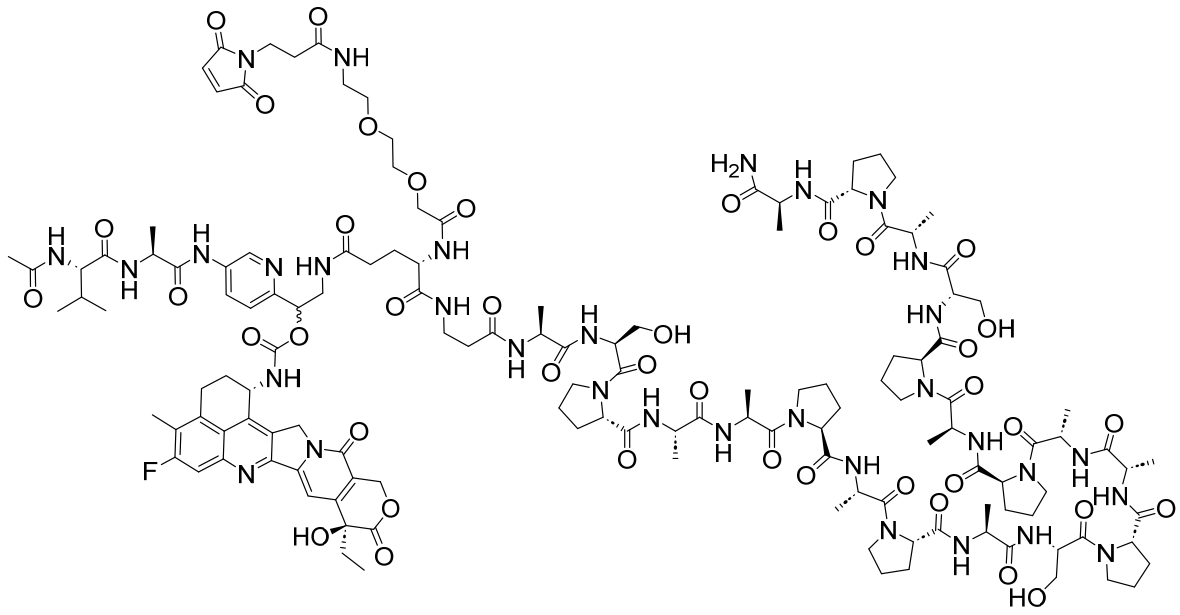
(SEQ ID NO: 27),



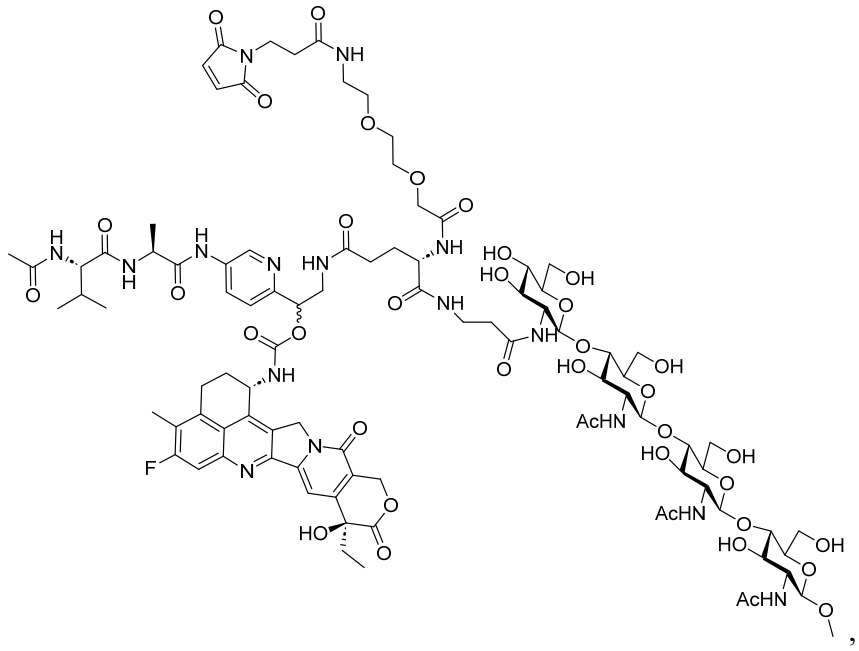
(SEQ ID NO: 27),



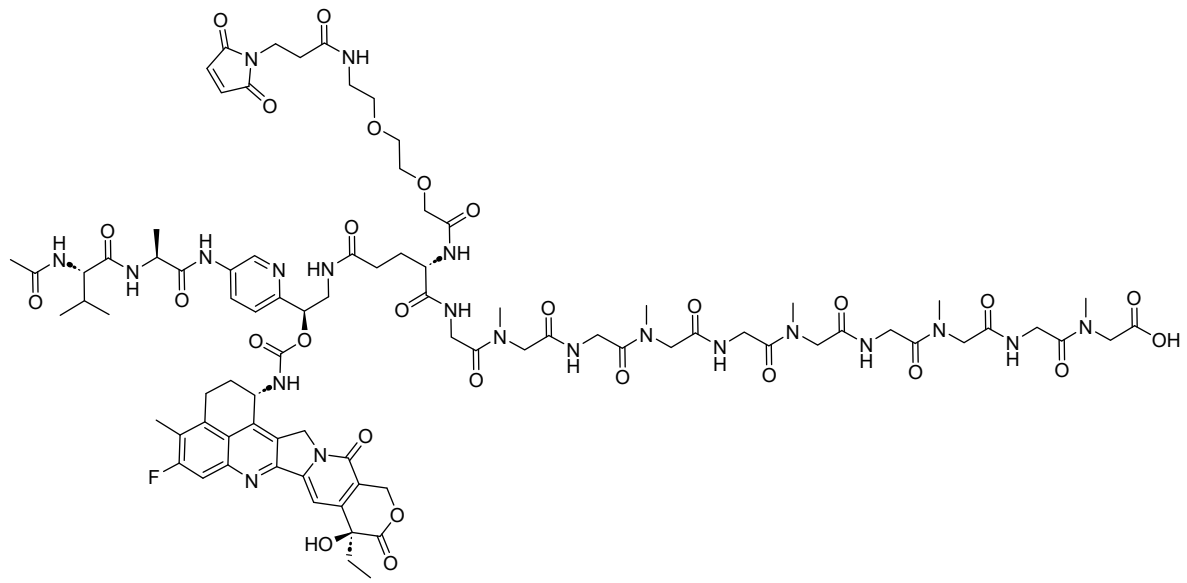
(SEQ ID NO: 28),



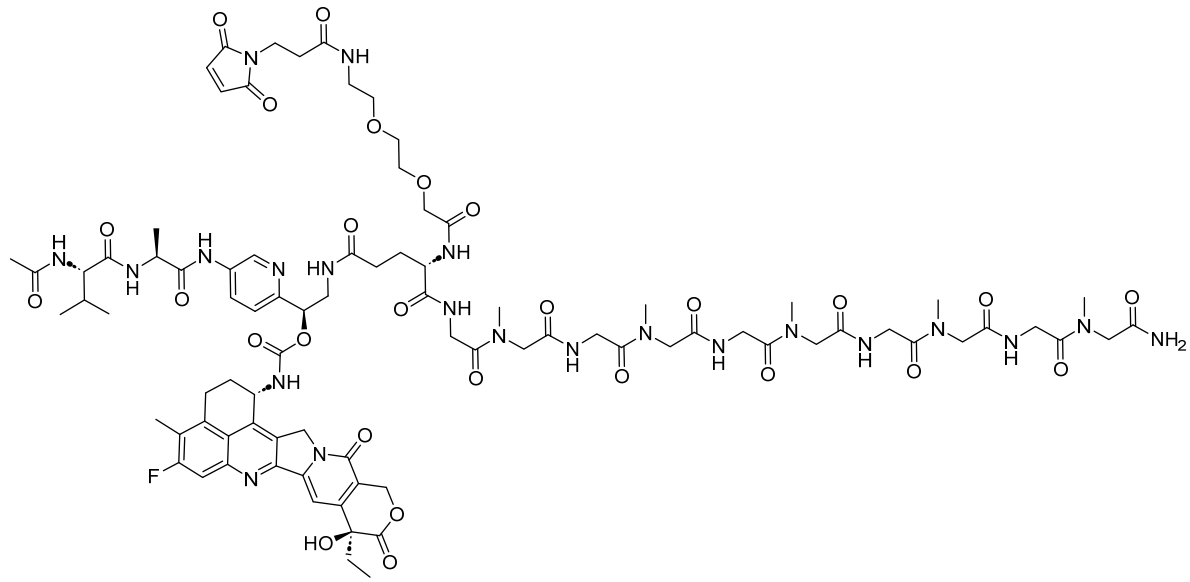
(SEQ ID NO: 28),



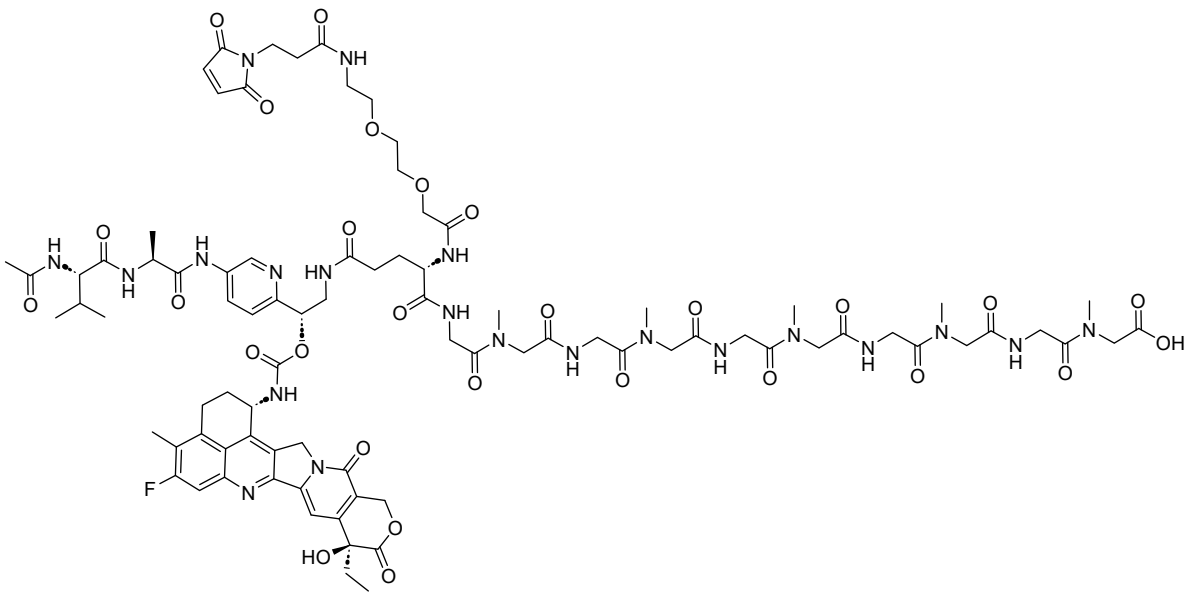
,



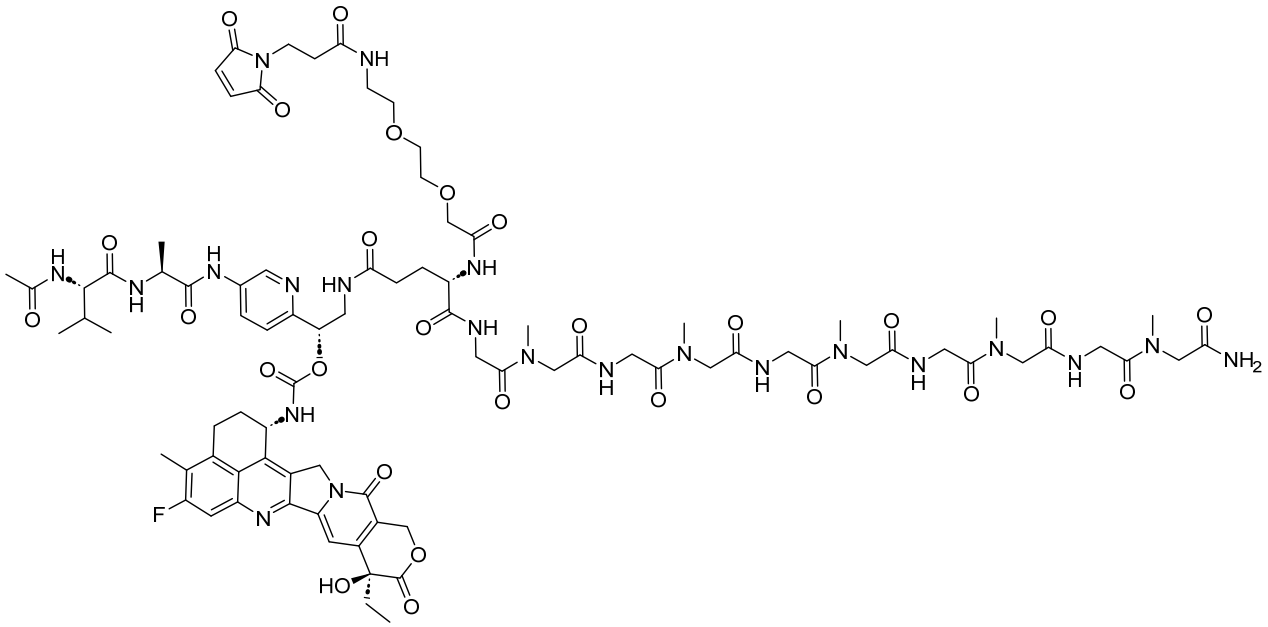
(SEQ ID NO: 26),



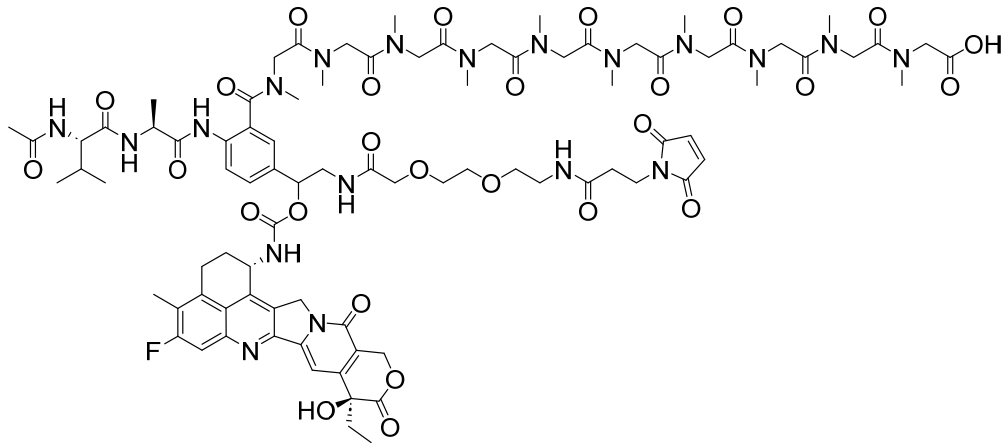
(SEQ ID NO: 26),



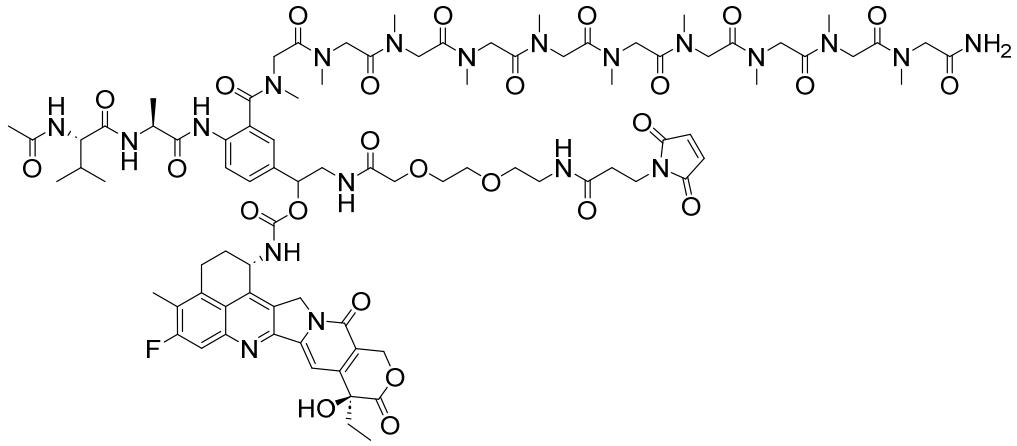
(SEQ ID NO: 26),



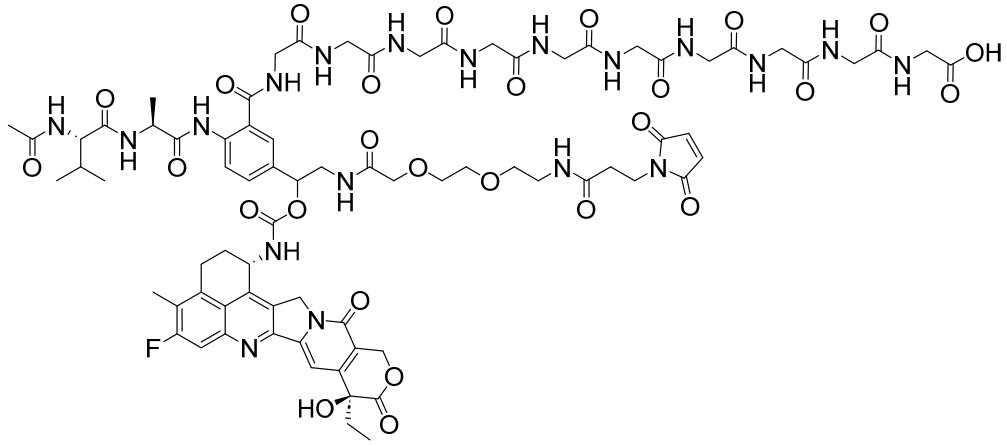
(SEQ ID NO: 26),



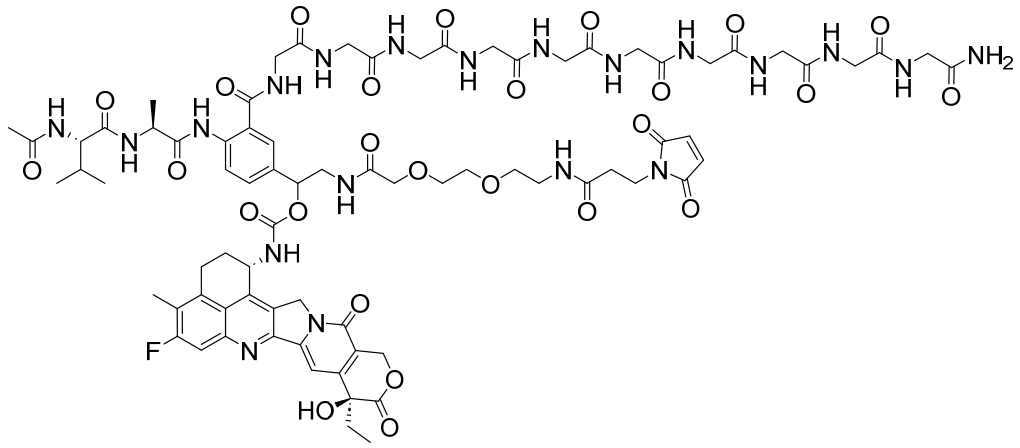
(SEQ ID NO: 29),



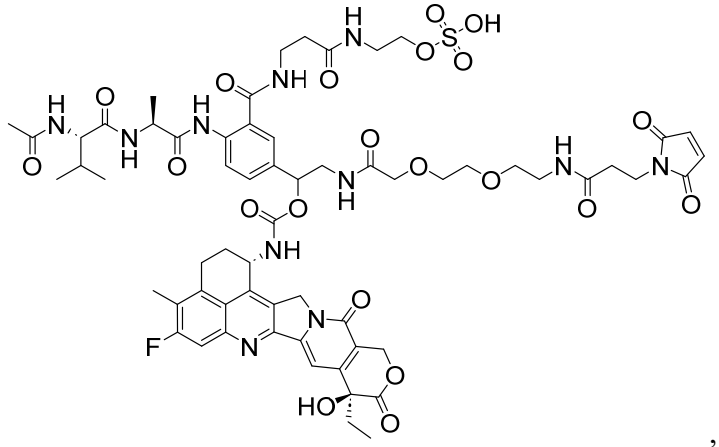
(SEQ ID NO: 29),



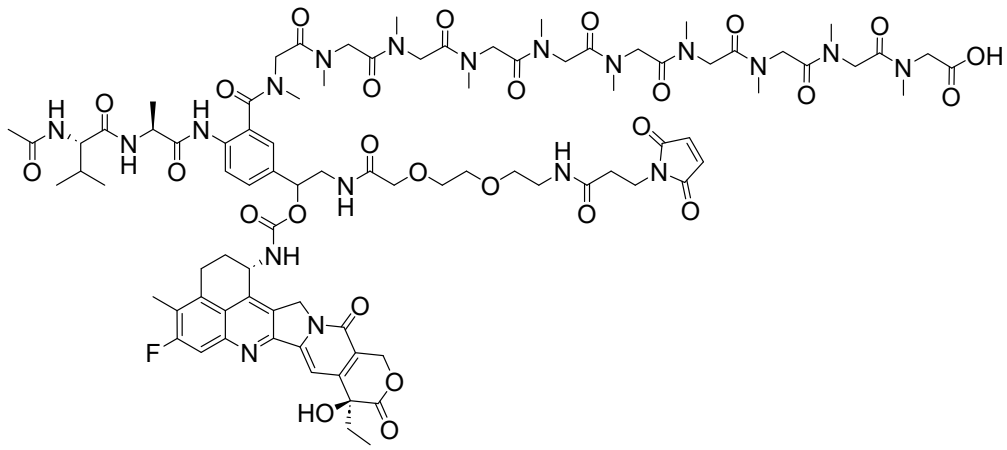
(SEQ ID NO: 38),



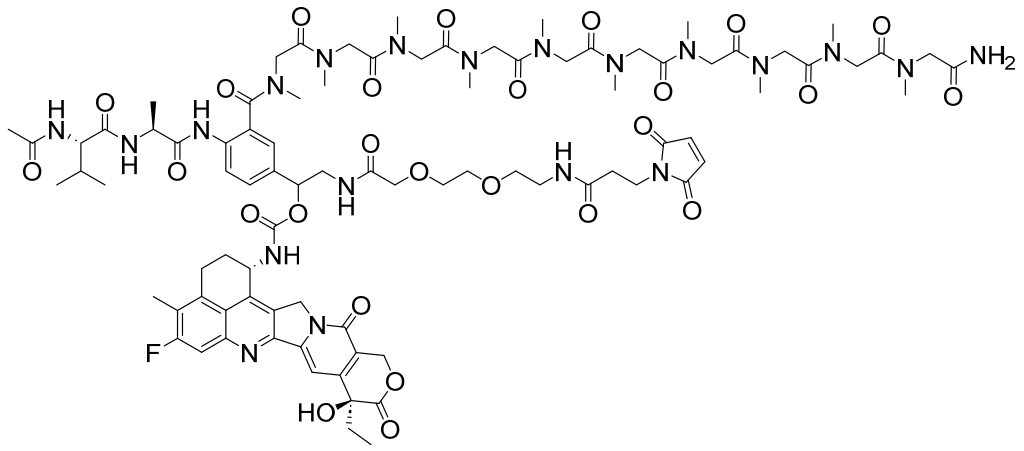
(SEQ ID NO: 38),



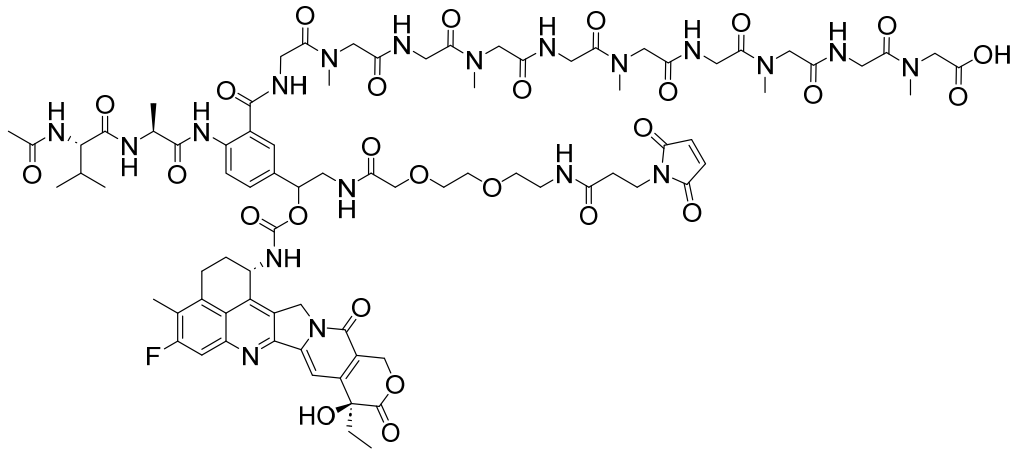
,



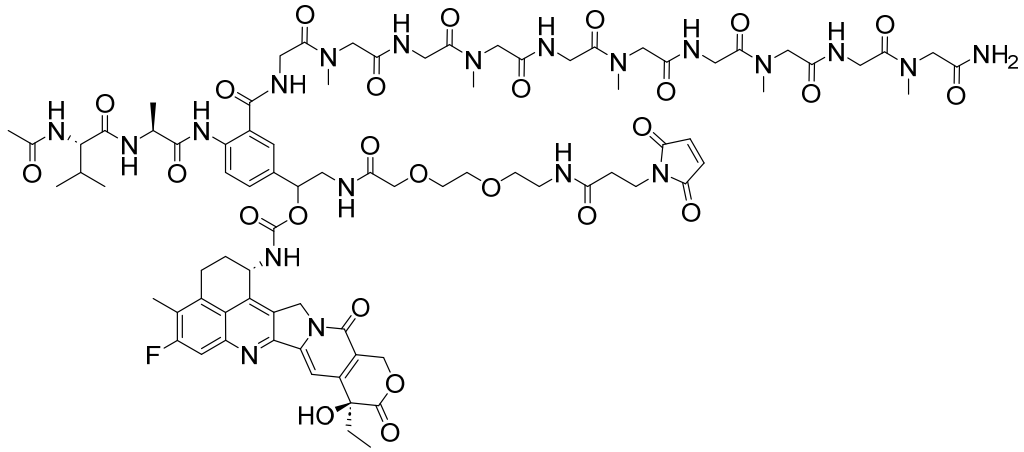
(SEQ ID NO: 29),



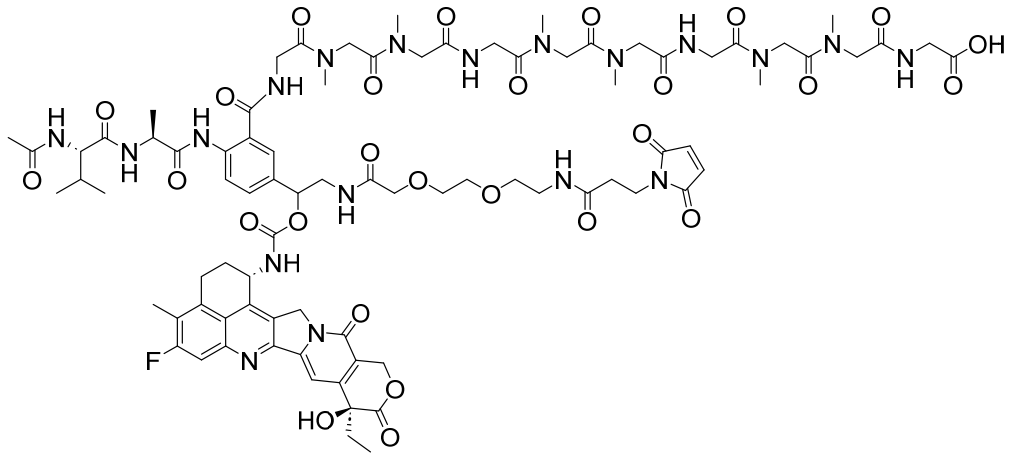
(SEQ ID NO: 29),



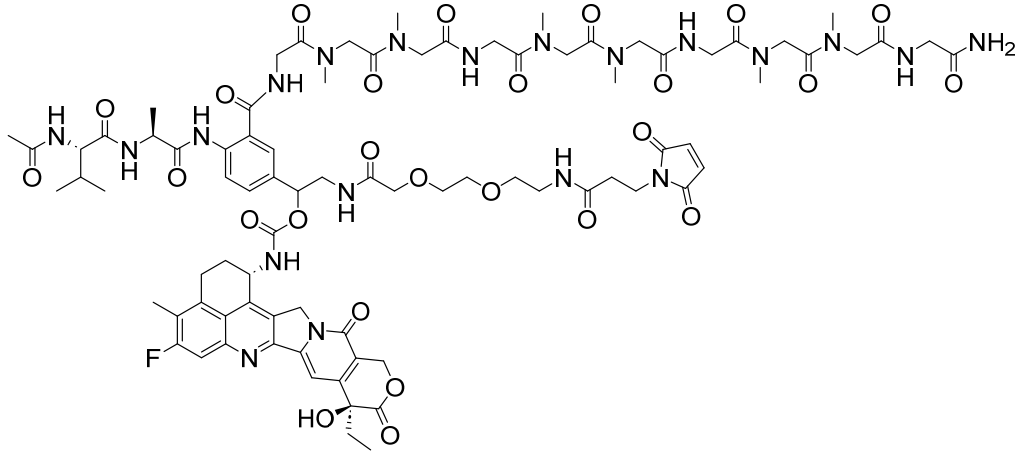
(SEQ ID NO: 30),



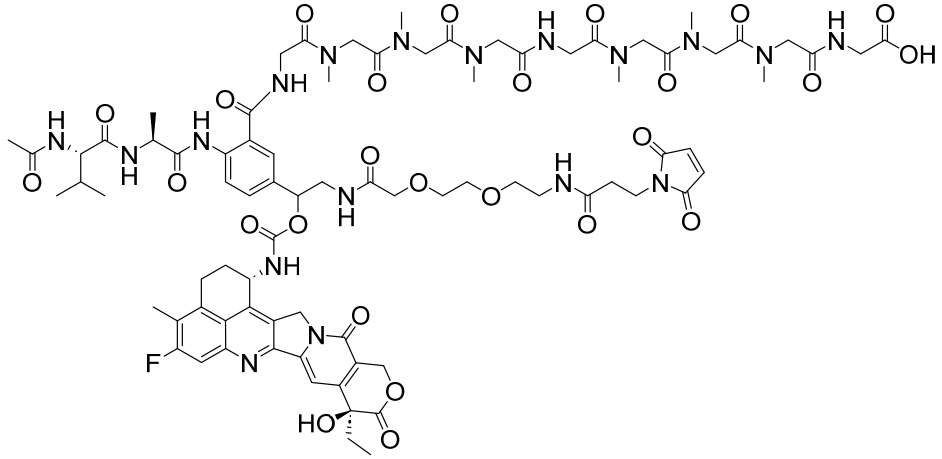
(SEQ ID NO: 30),



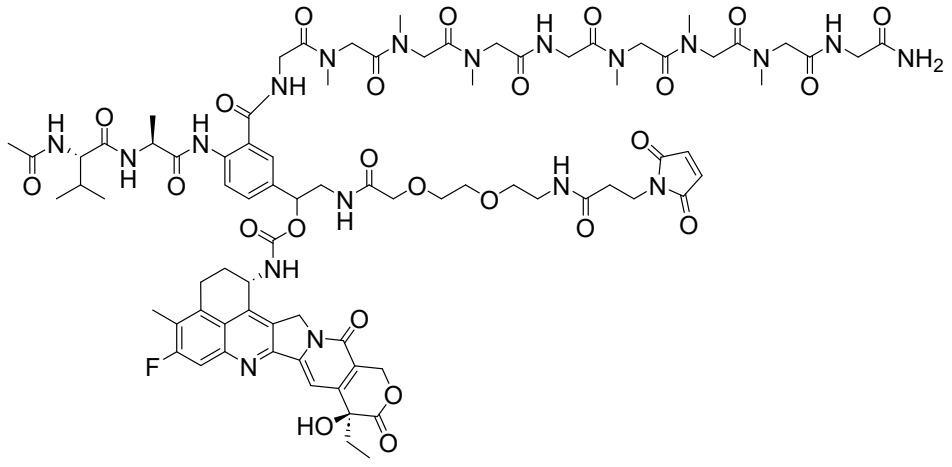
(SEQ ID NO: 33),



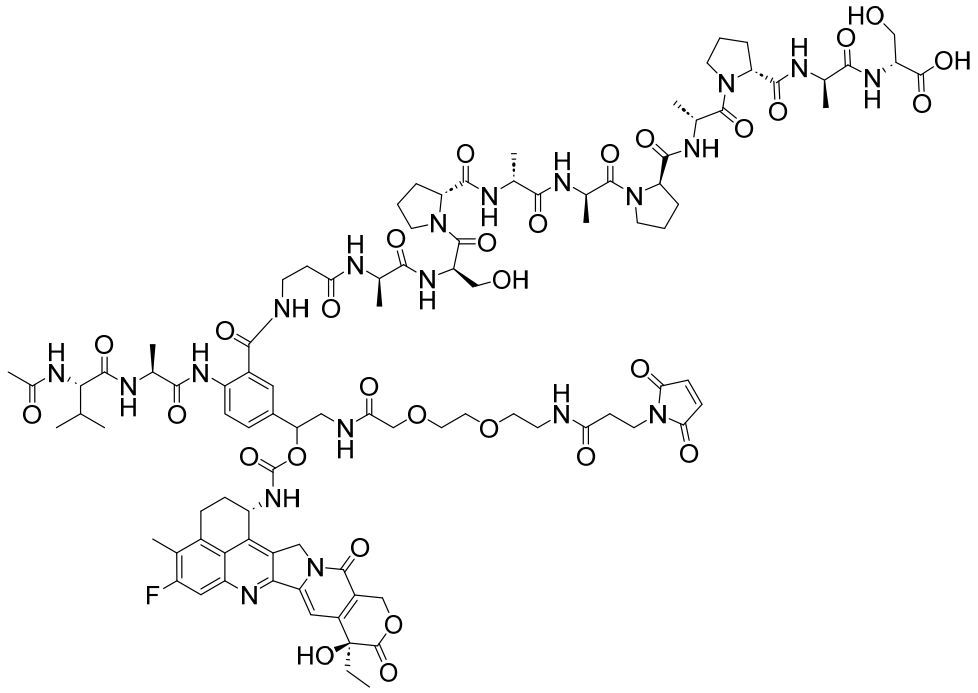
(SEQ ID NO: 33),



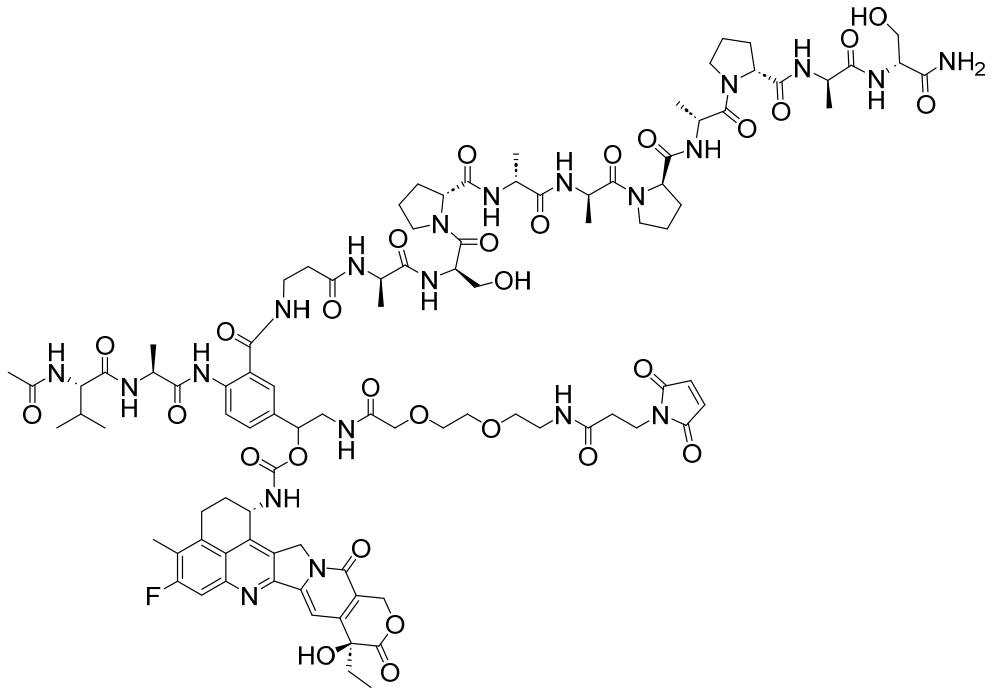
(SEQ ID NO: 34),



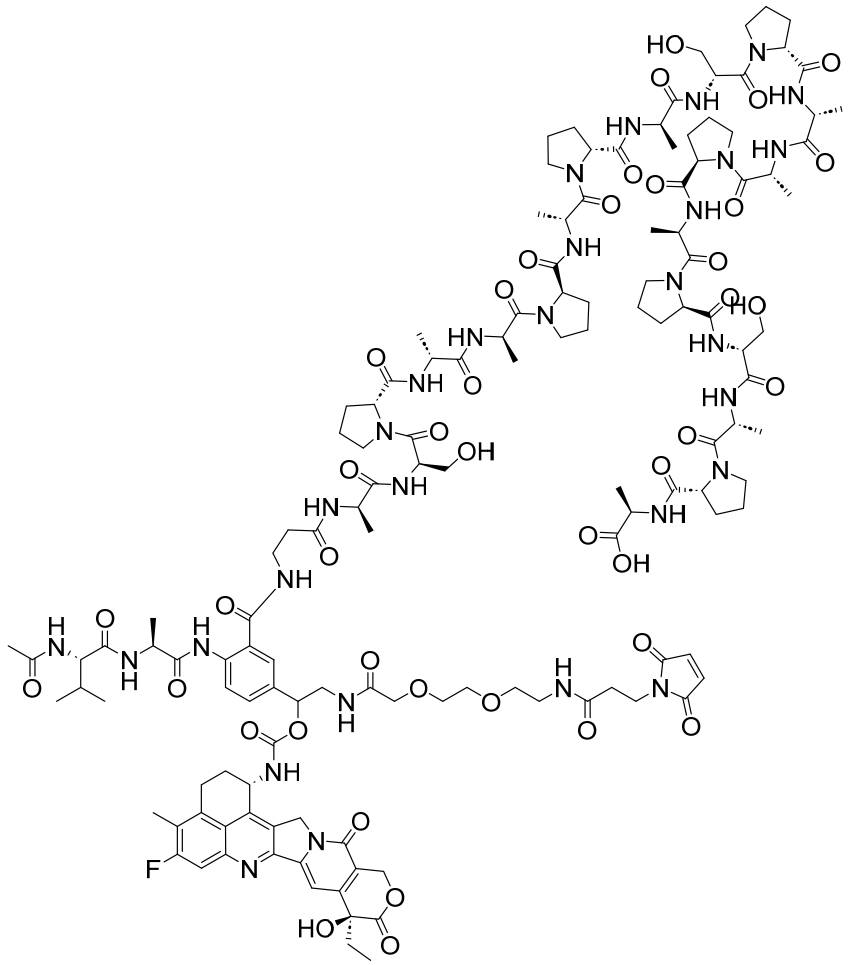
(SEQ ID NO: 34),



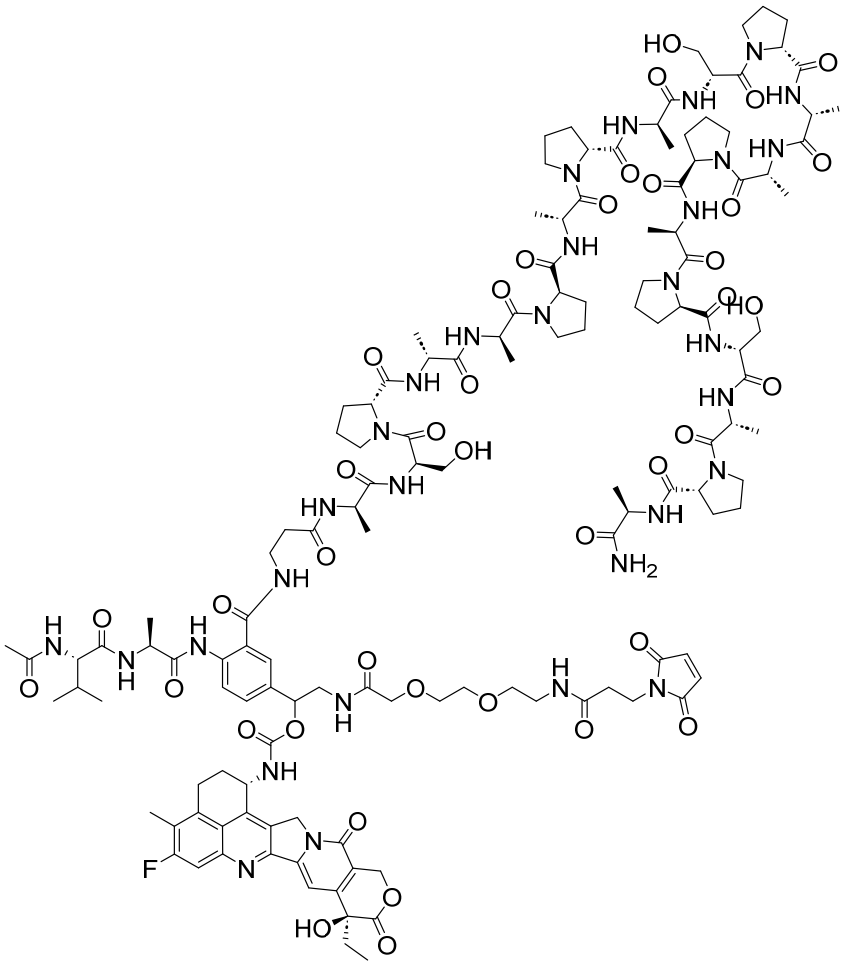
(SEQ ID NO: 35),



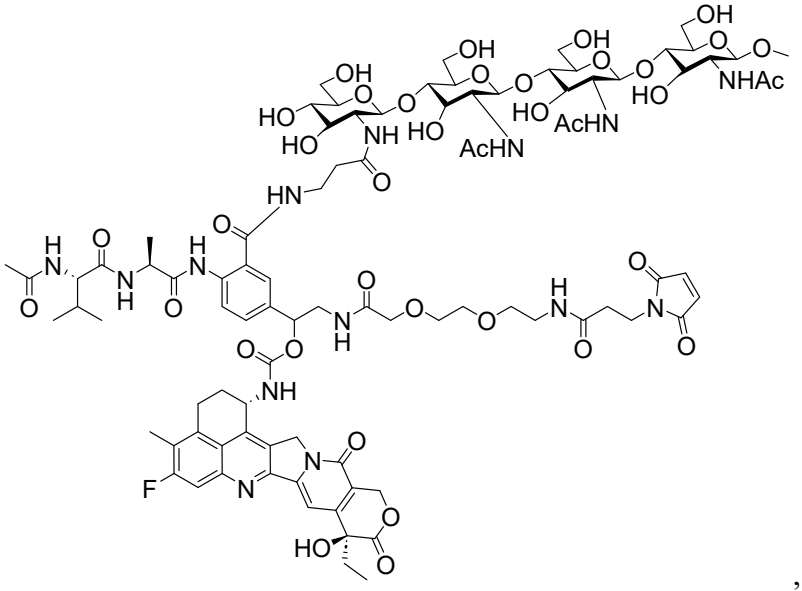
(SEQ ID NO: 35),



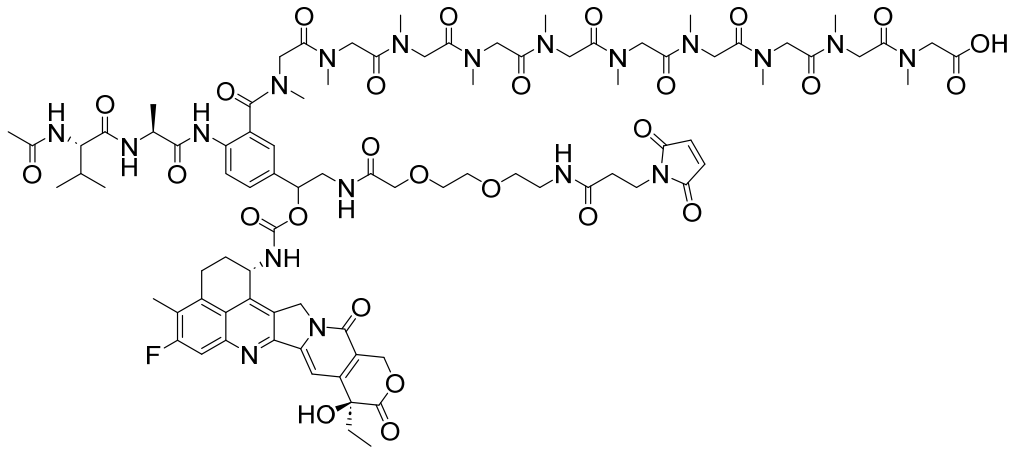
(SEQ ID NO: 36),



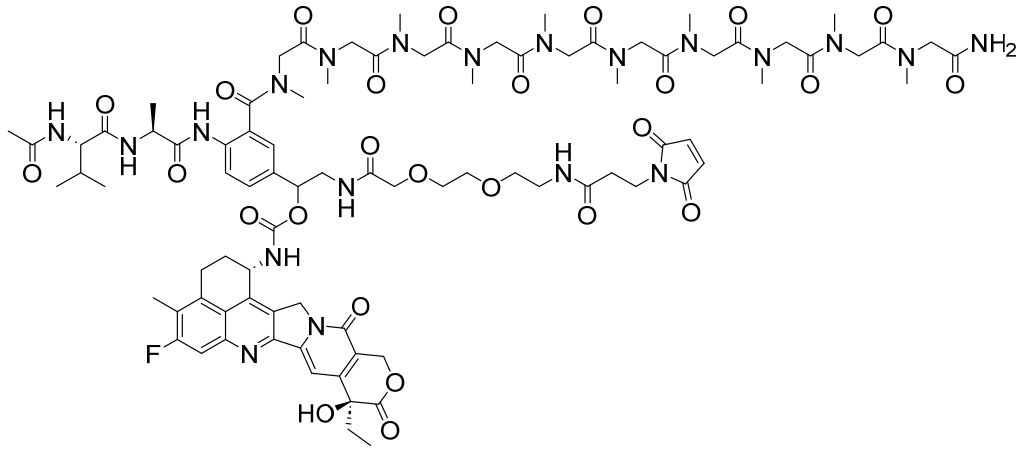
(SEQ ID NO: 36),



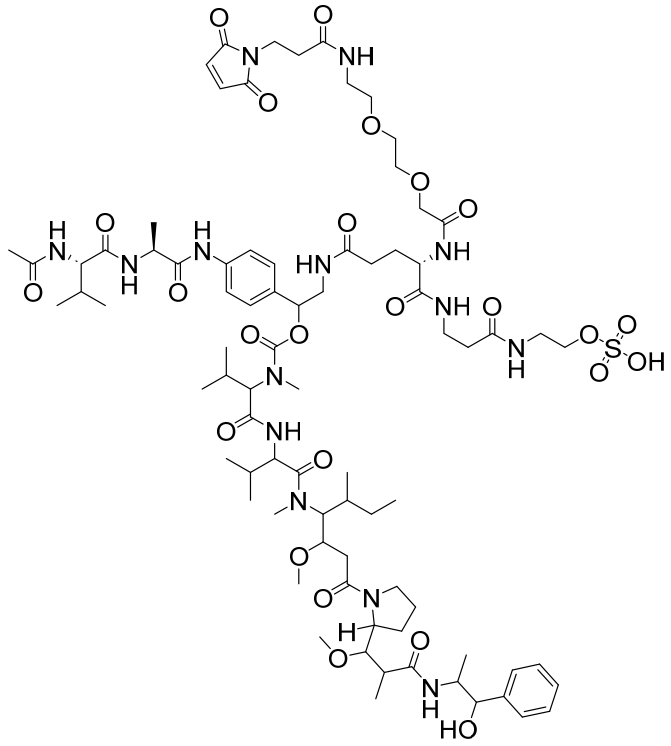
,



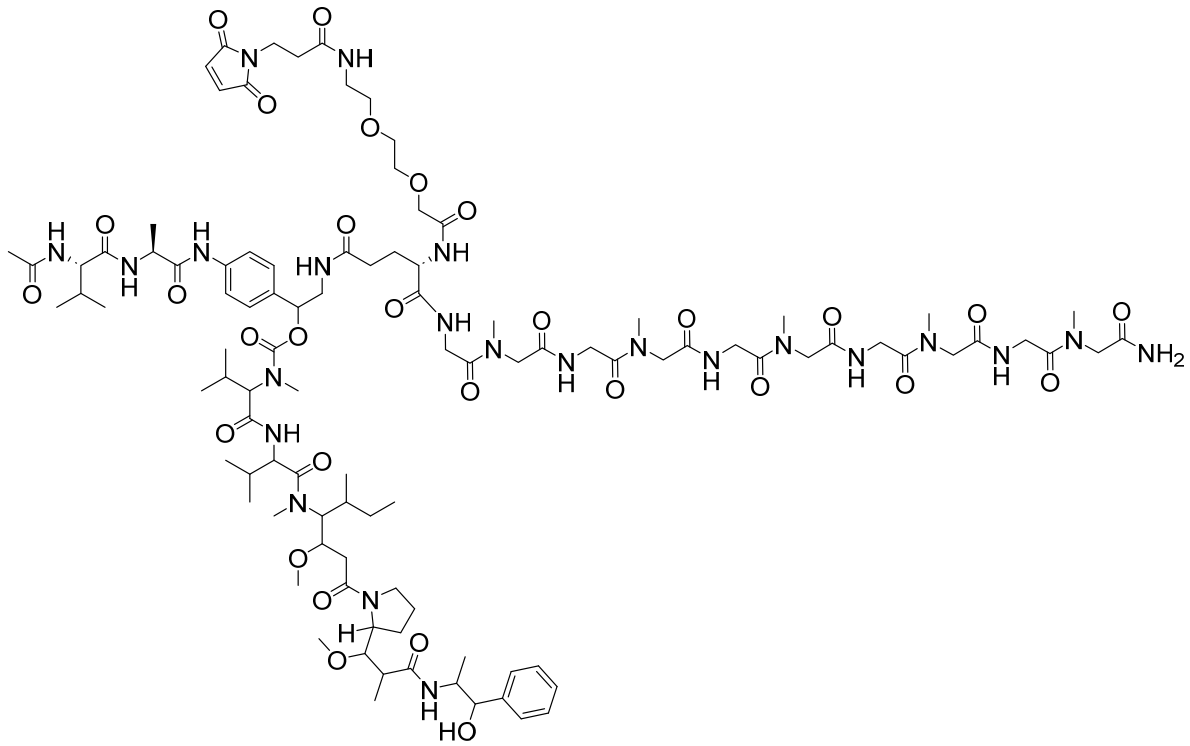
(SEQ ID NO: 29),



(SEQ ID NO: 29),

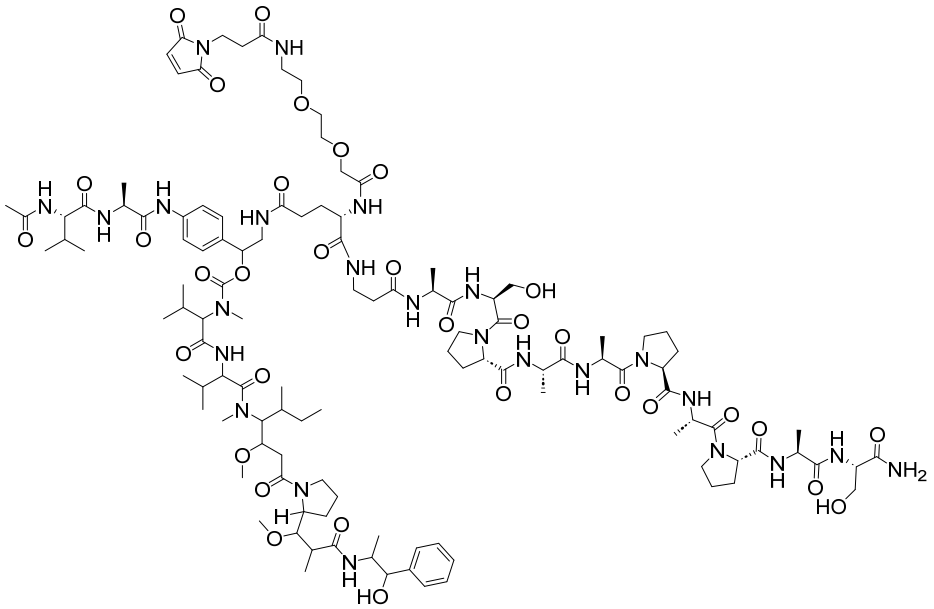


(SEQ ID NO: 22),



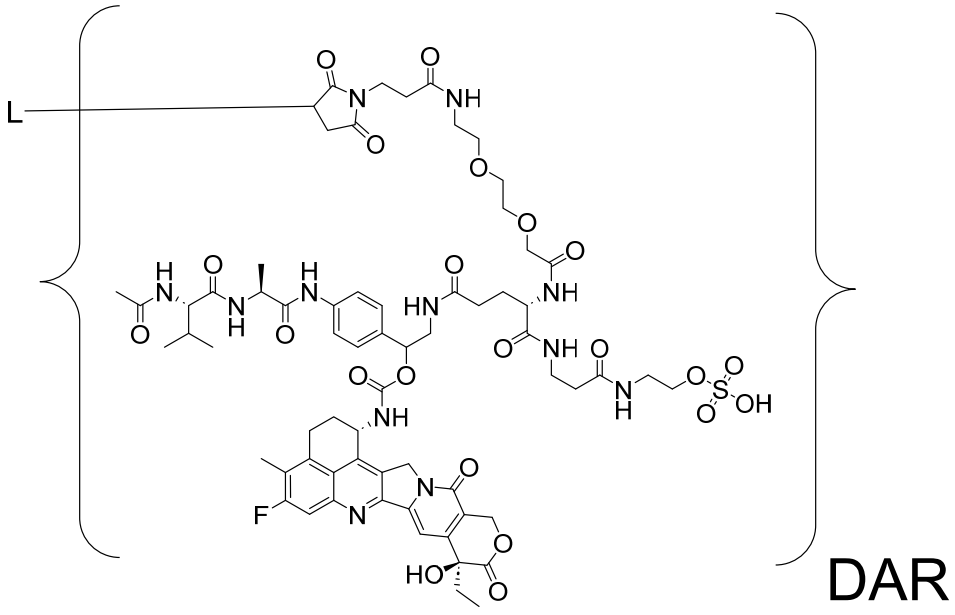
(SEQ ID NOS 26 and 22, respectively, in order of appearance)

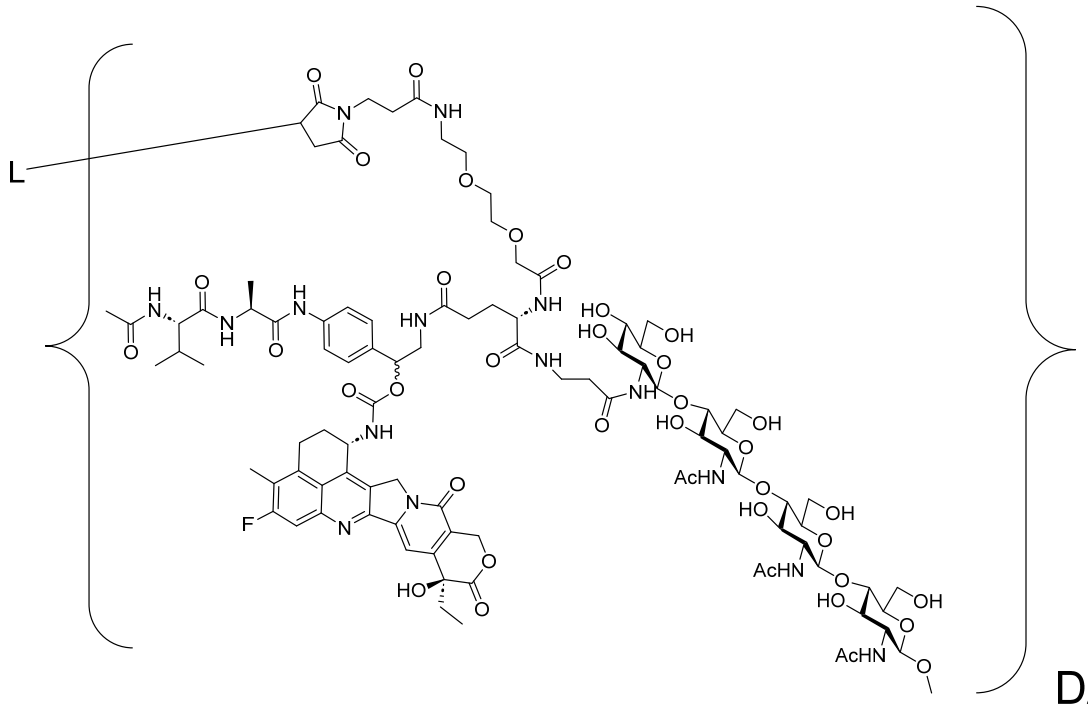
, and

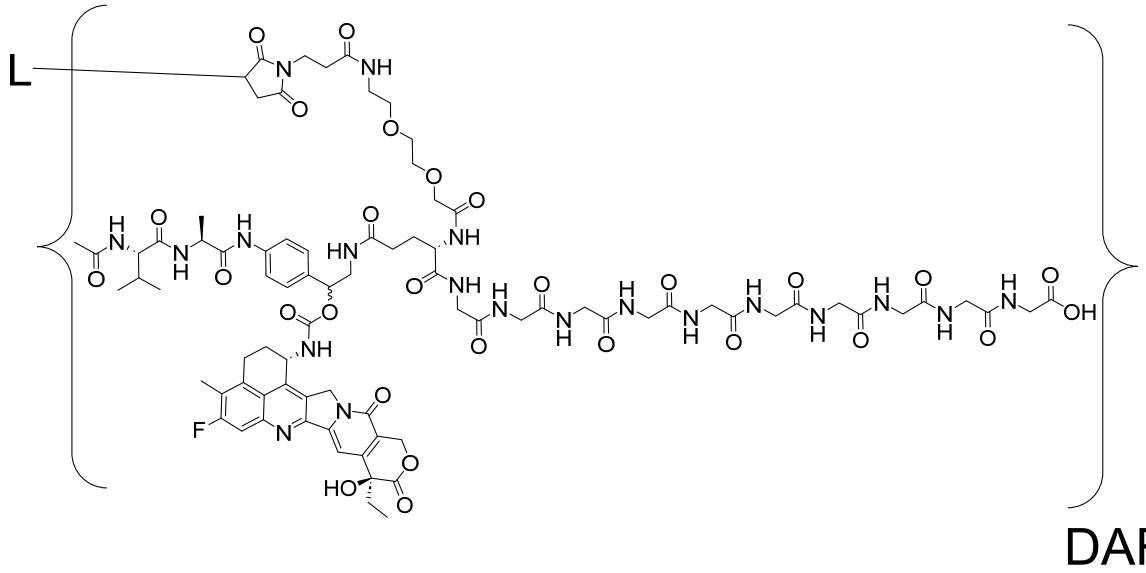


(SEQ ID NOS 27 and 22, respectively, in order of appearance).

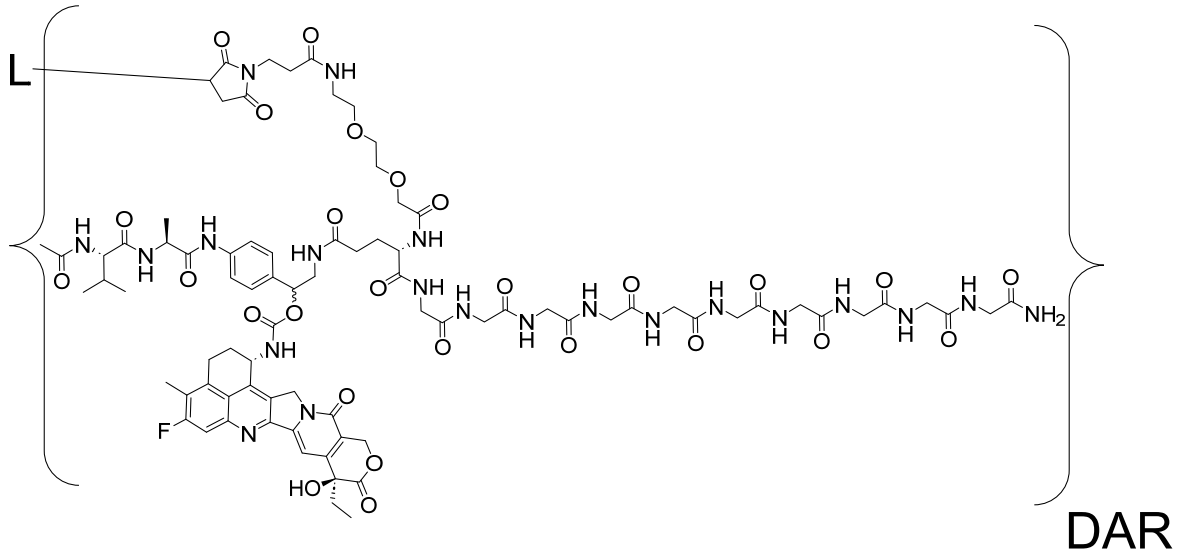
[00198] In some embodiments, a conjugate of Formula (XX) or Formula (A) is represented by:



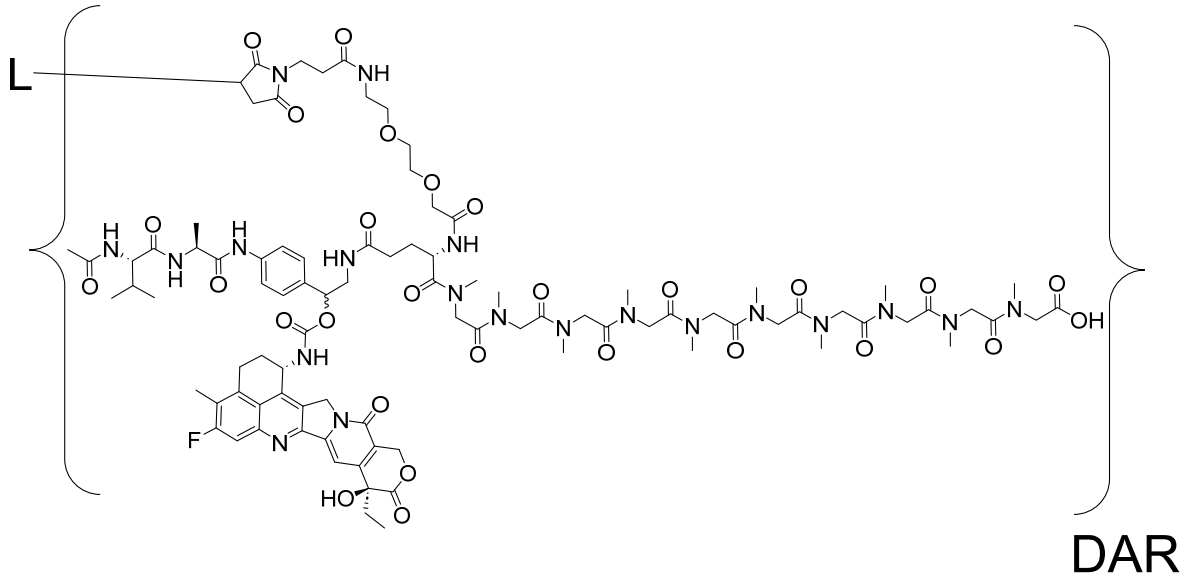




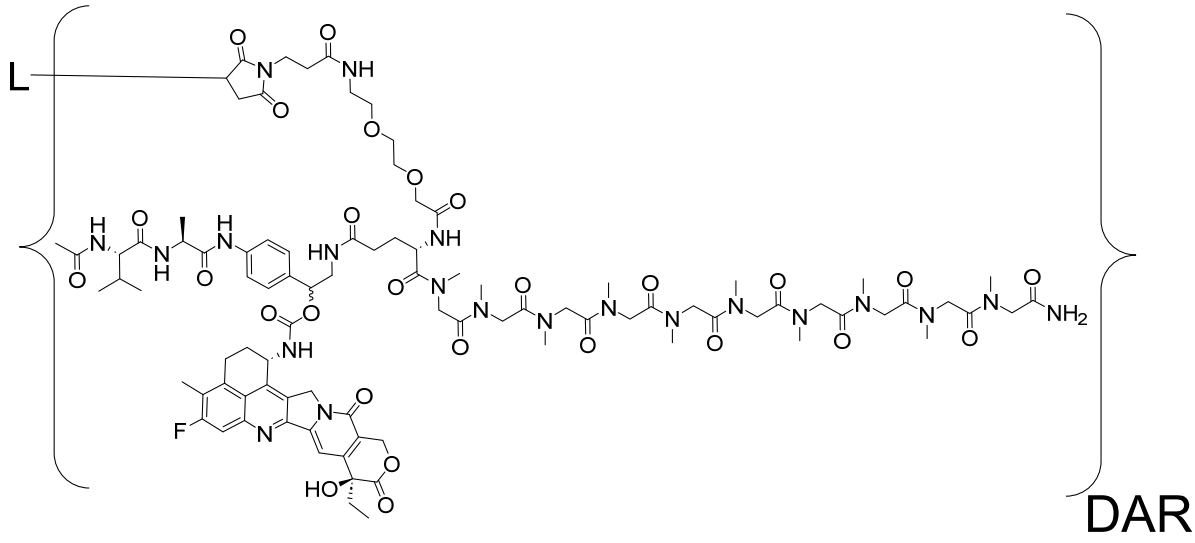
(SEQ ID NO: 24),



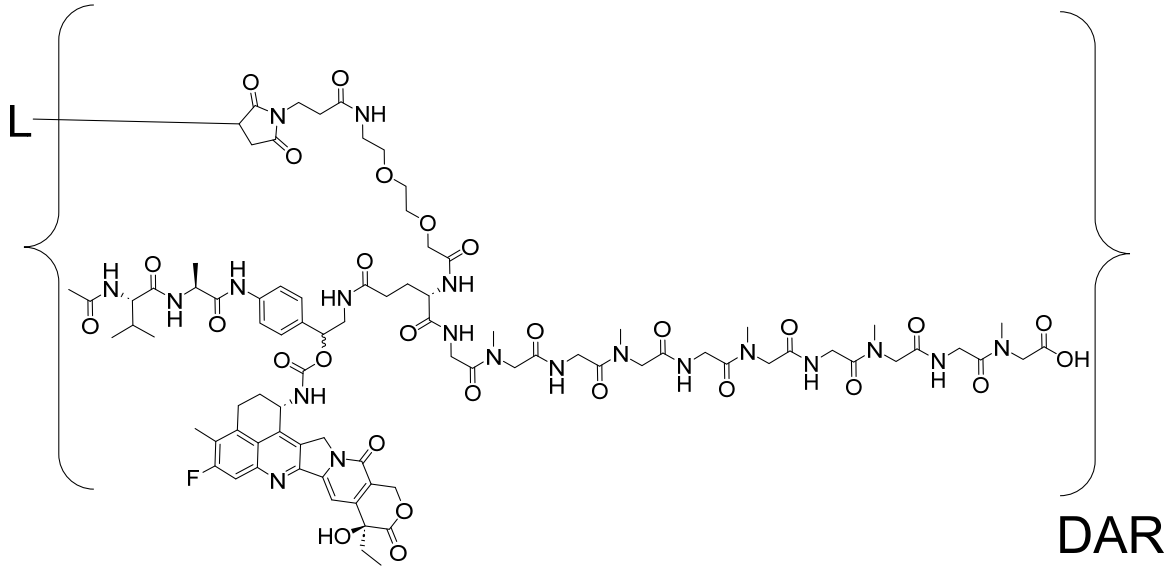
(SEQ ID NO: 24),



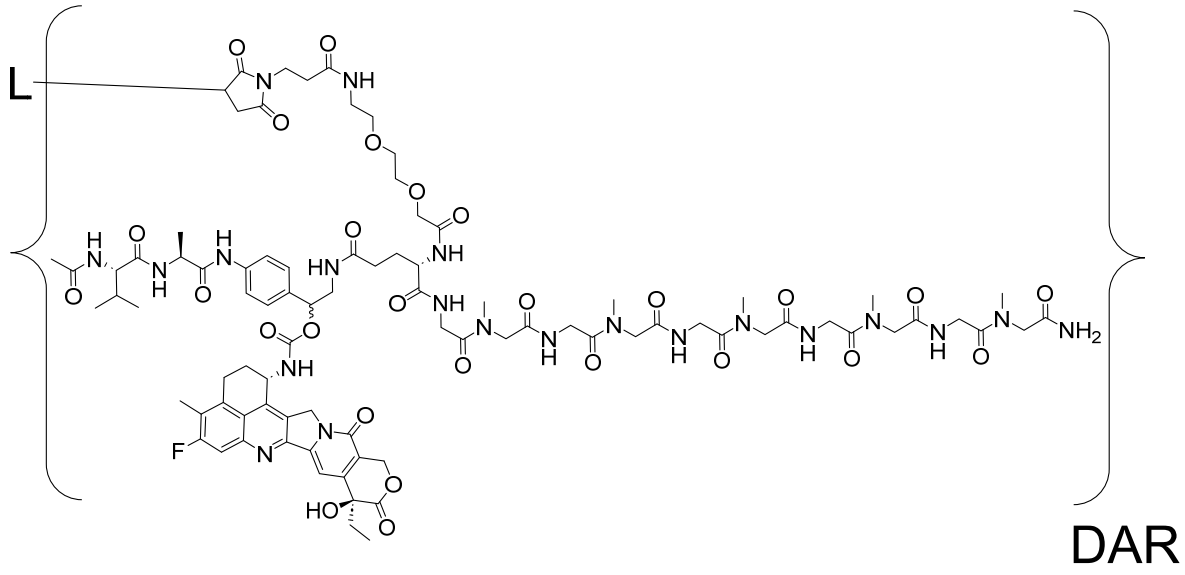
(SEQ ID NO: 25),



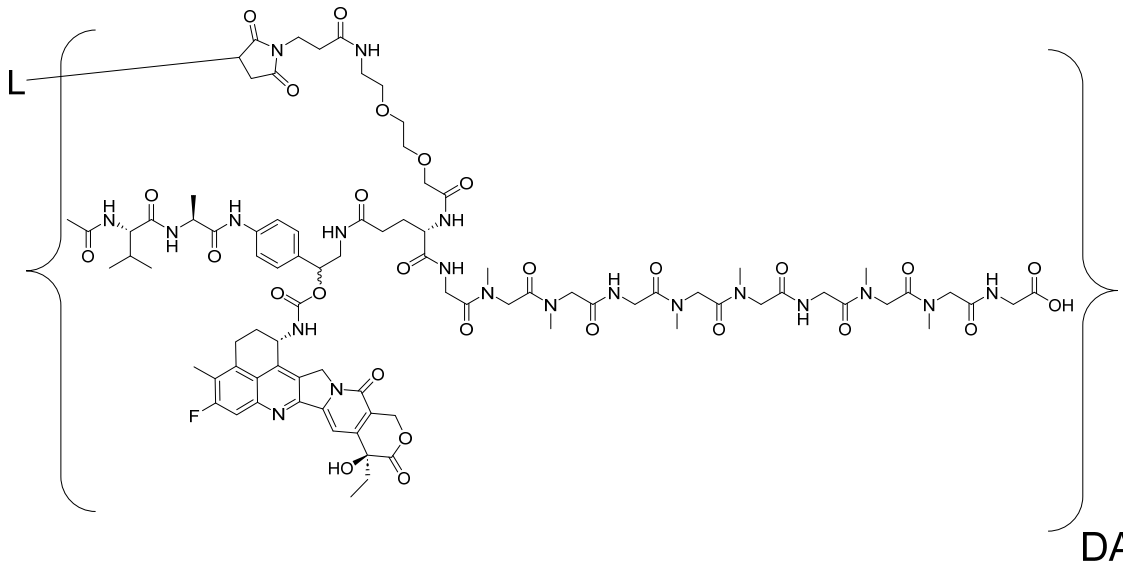
(SEQ ID NO: 25),



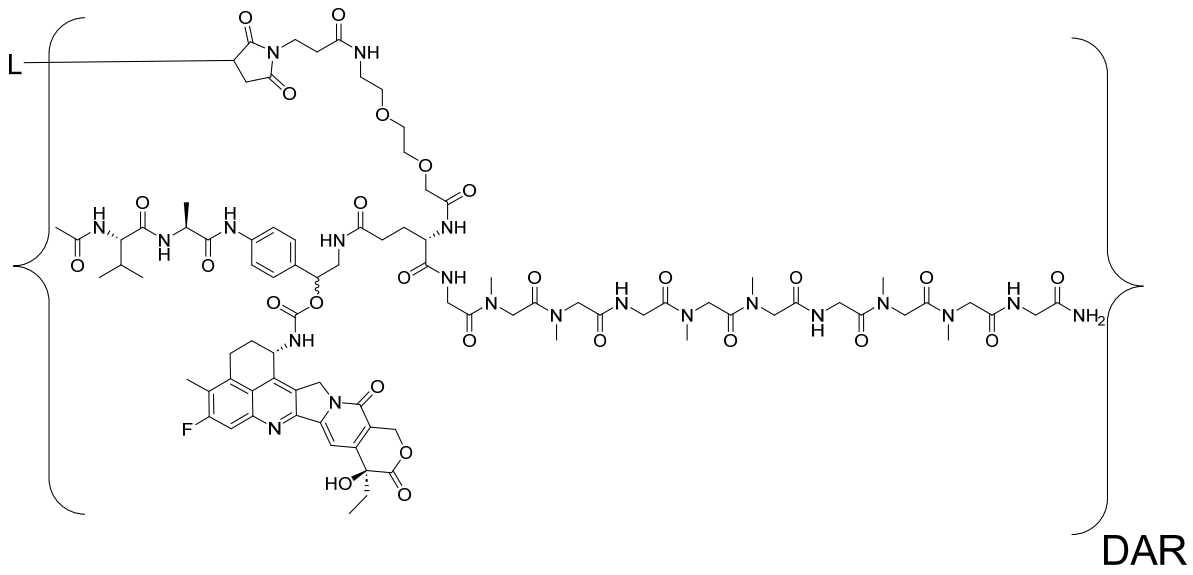
(SEQ ID NO: 26),



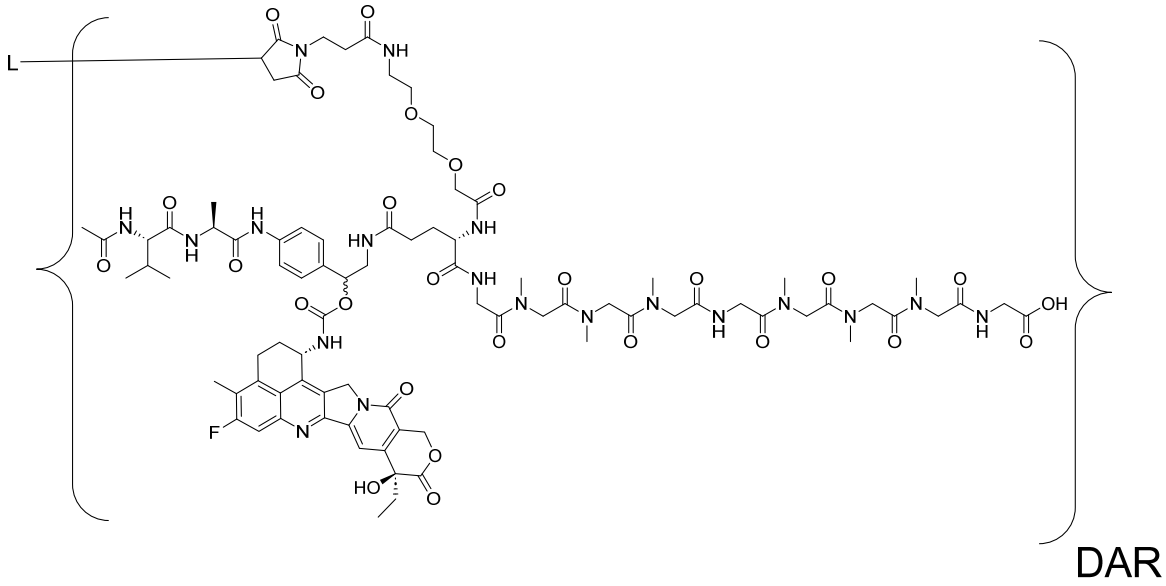
(SEQ ID NO: 26),



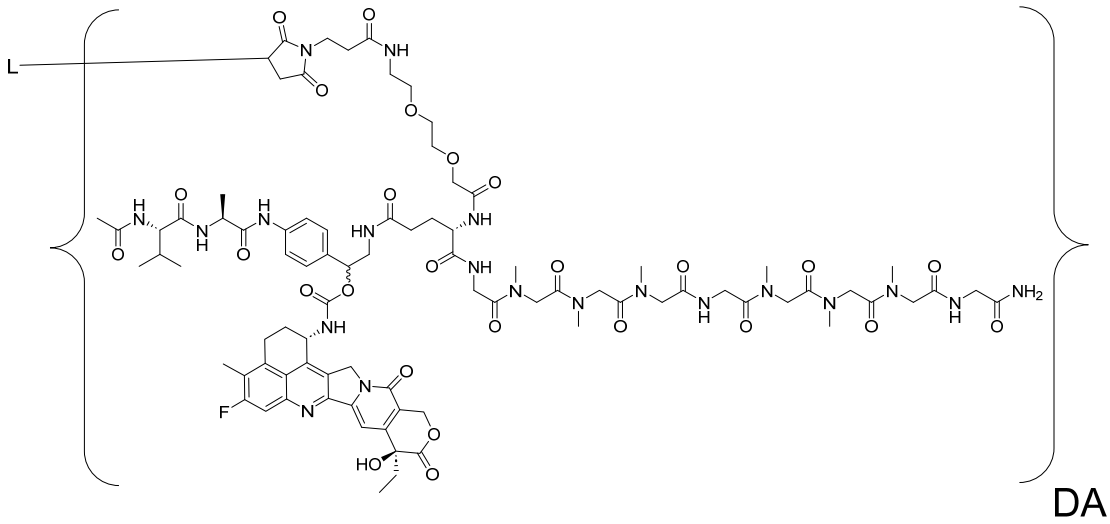
(SEQ ID NO: 31),



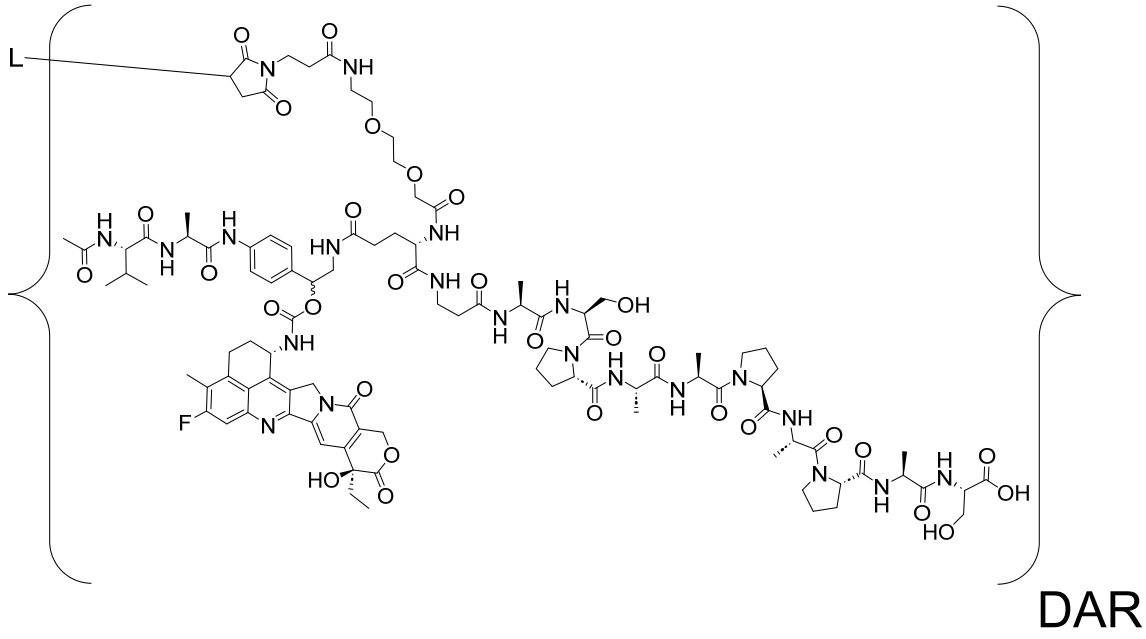
(SEQ ID NO: 31),



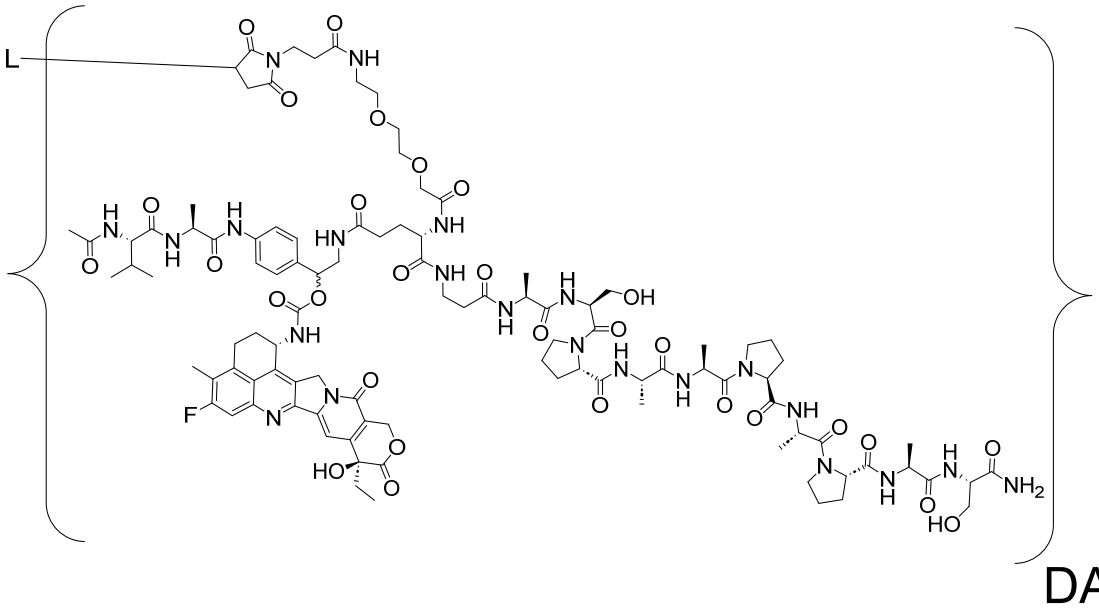
(SEQ ID NO: 32),



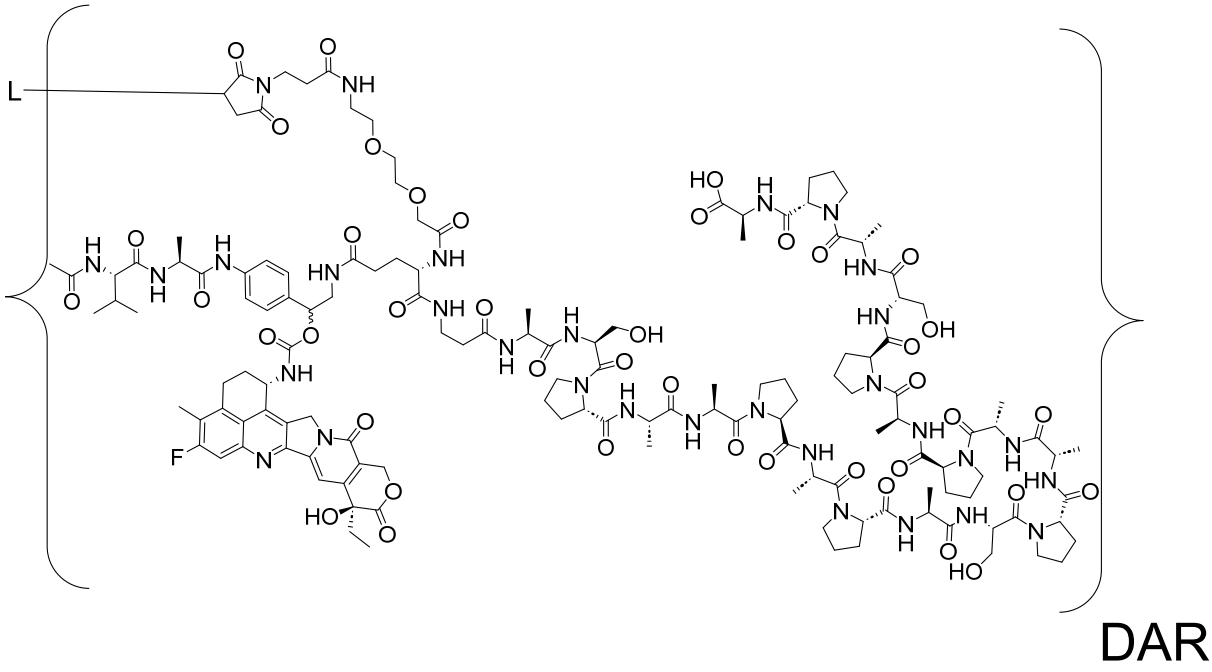
(SEQ ID NO: 32),



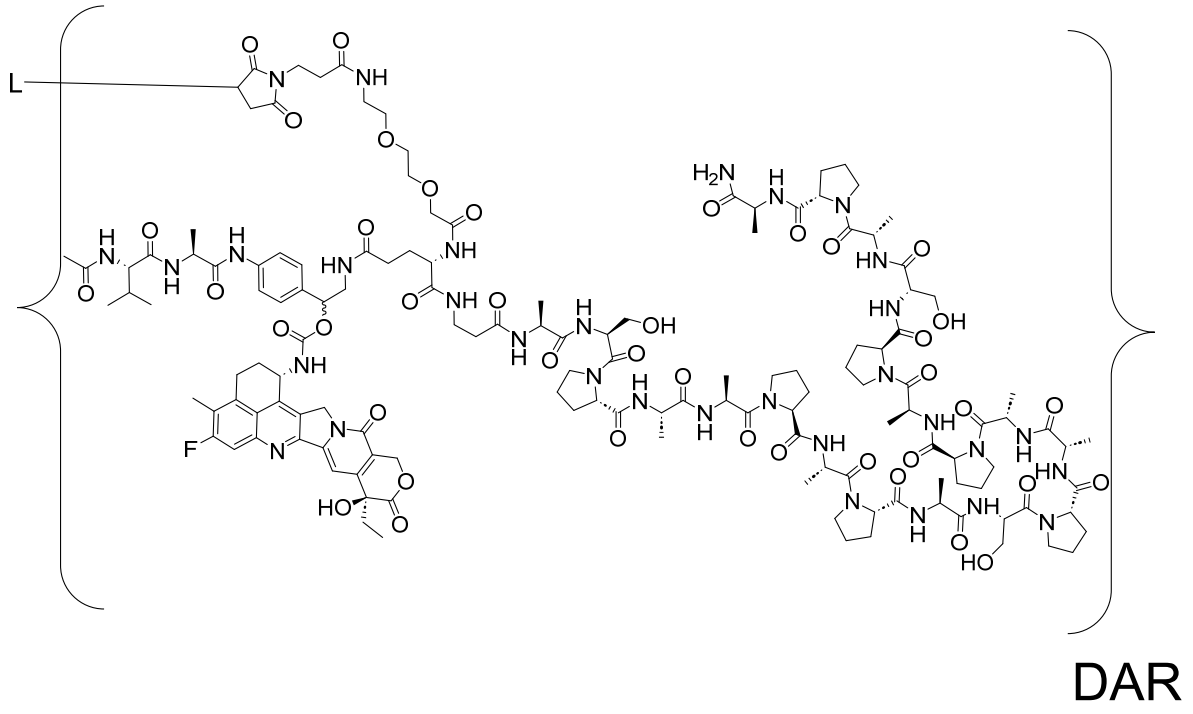
(SEQ ID NO: 27),



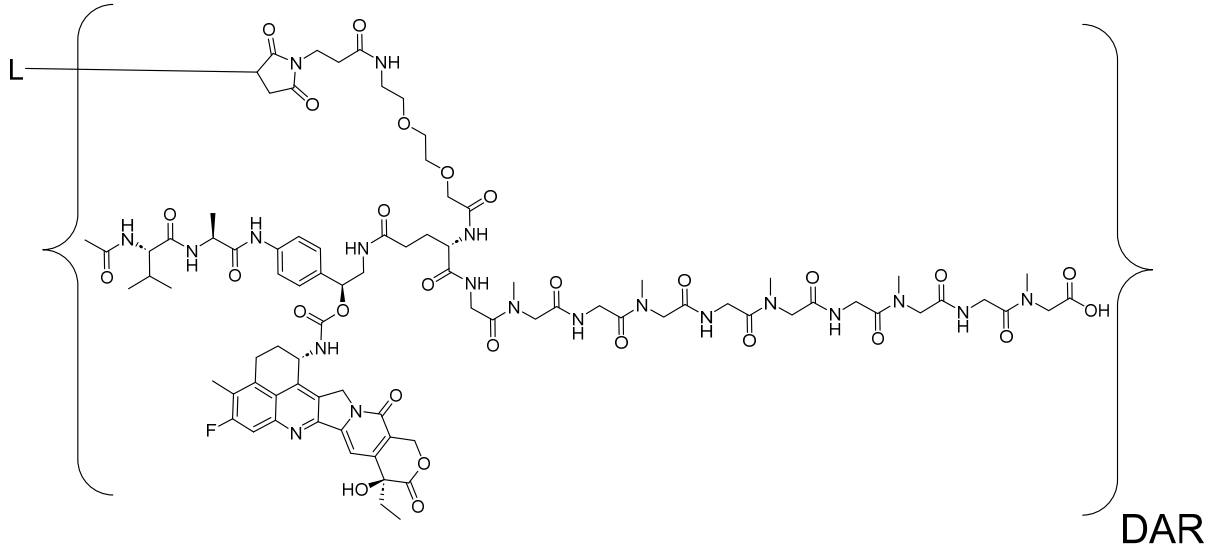
(SEQ ID NO: 27),



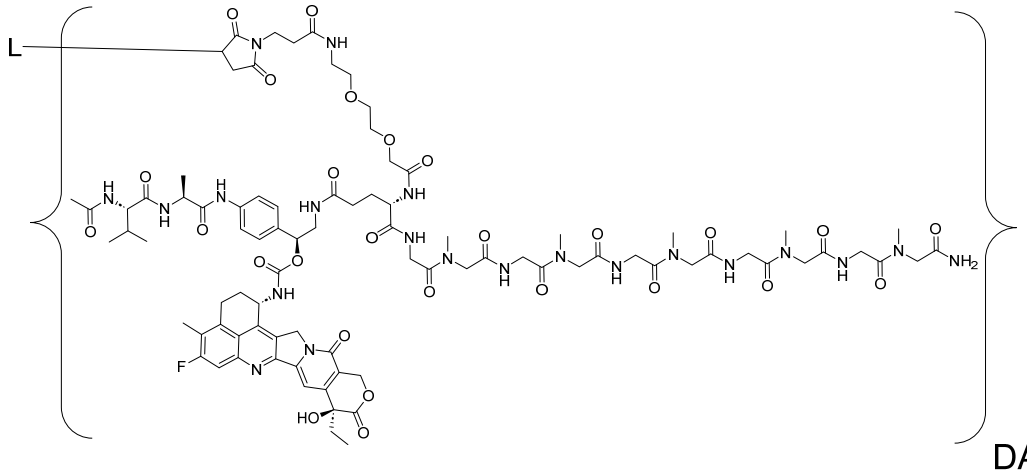
(SEQ ID NO: 28),



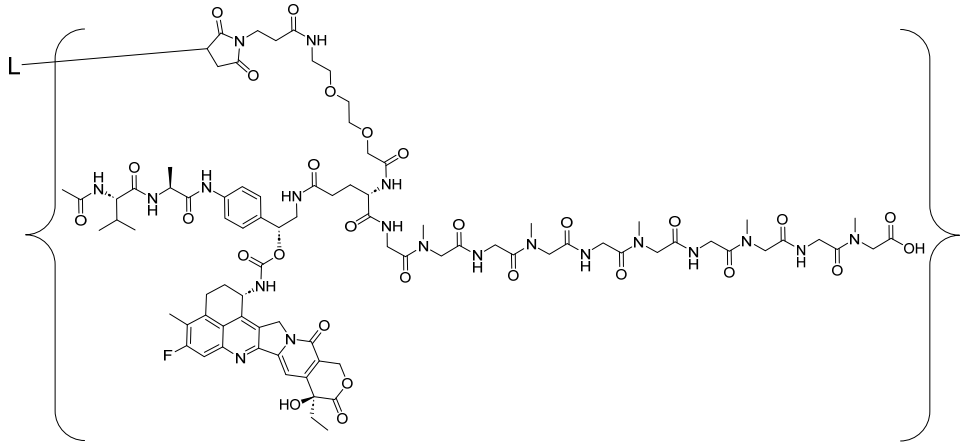
(SEQ ID NO: 28),



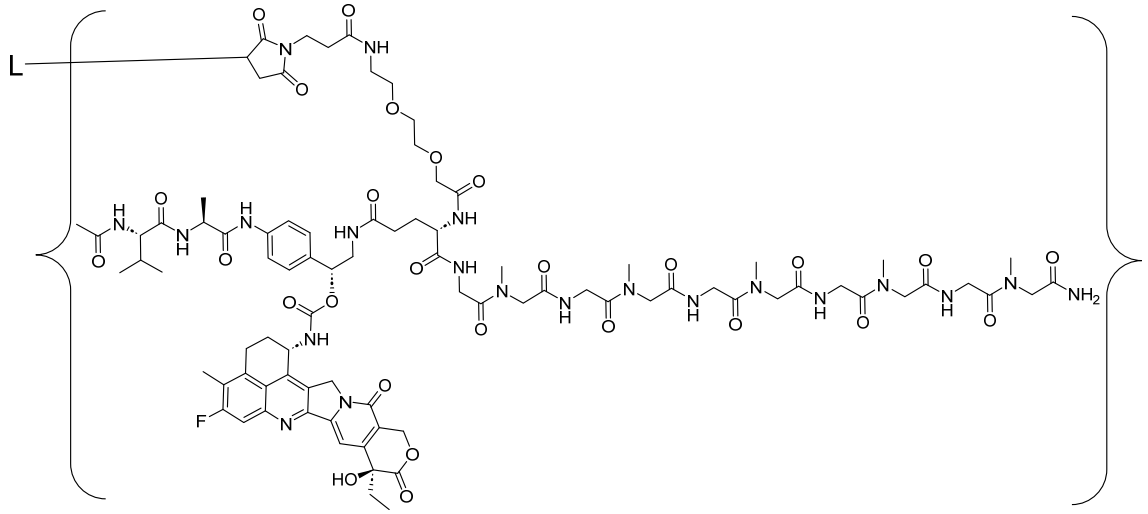
(SEQ ID NO: 26),



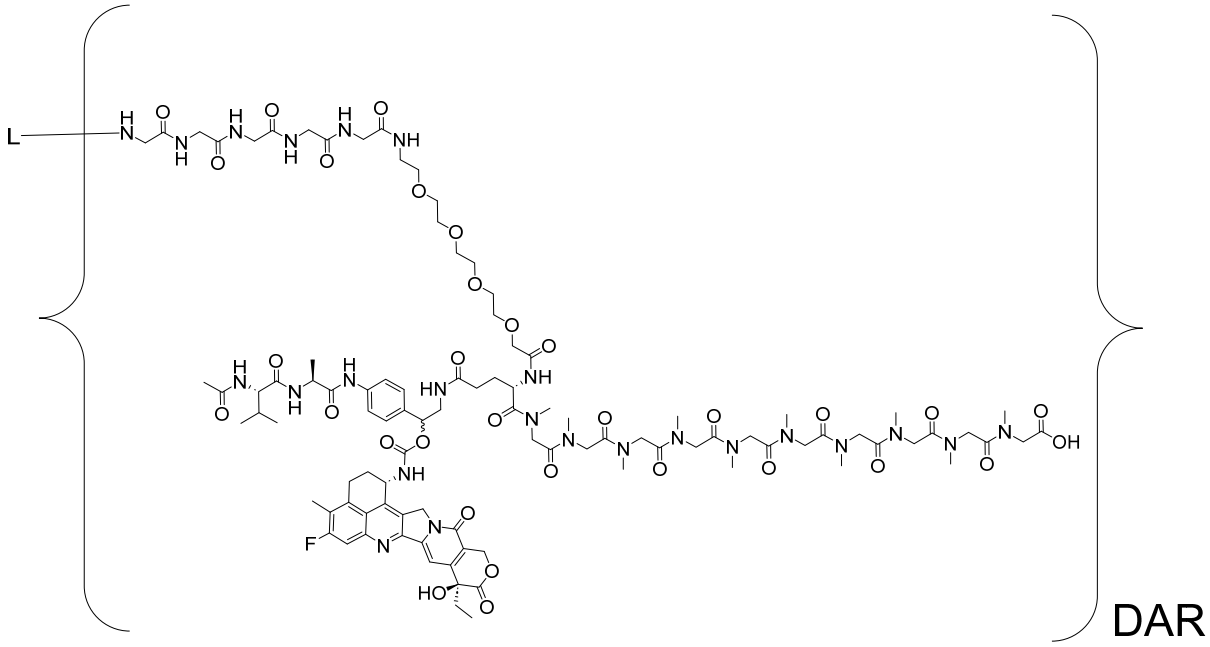
DAR (SEQ ID NO: 26),



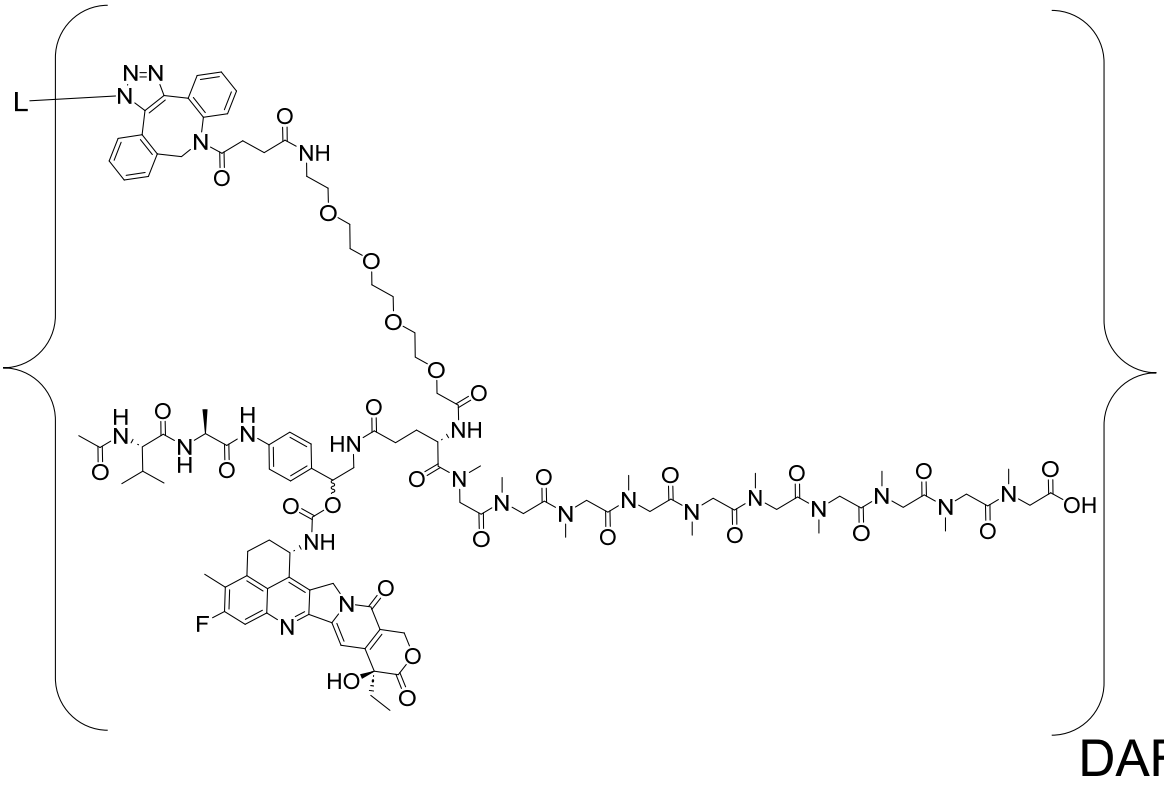
DAR (SEQ ID NO: 26),



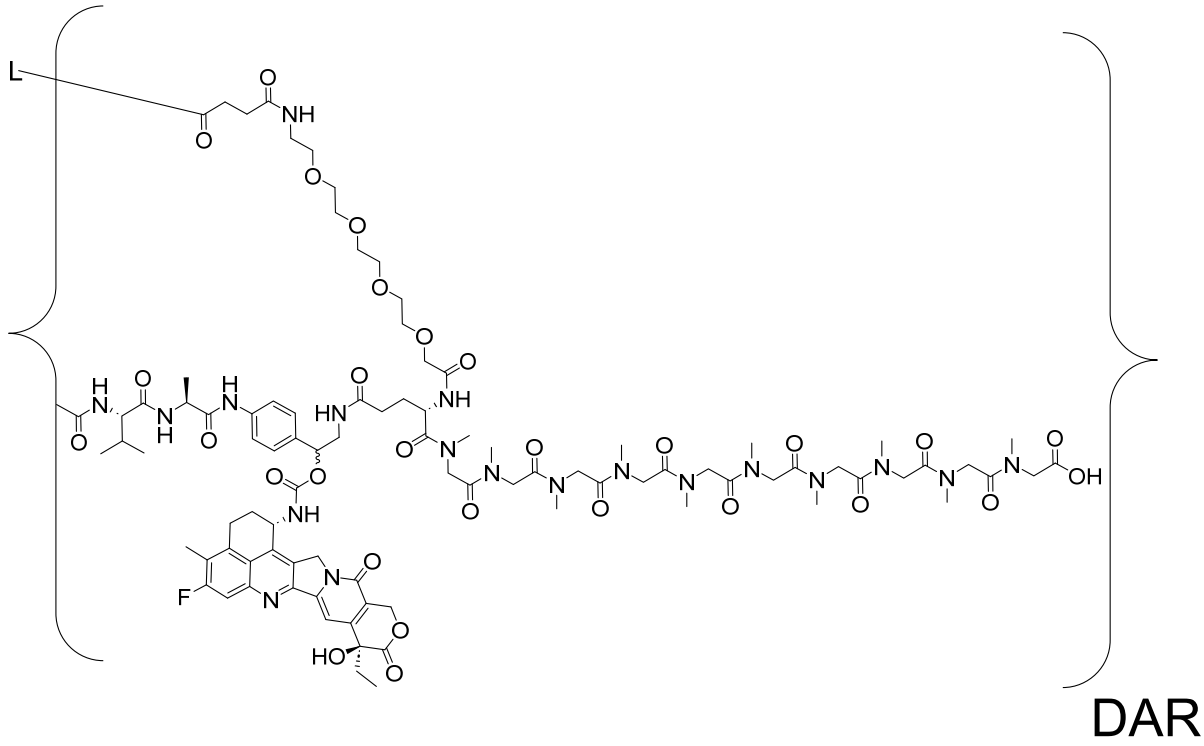
DAR (SEQ ID NO: 26),



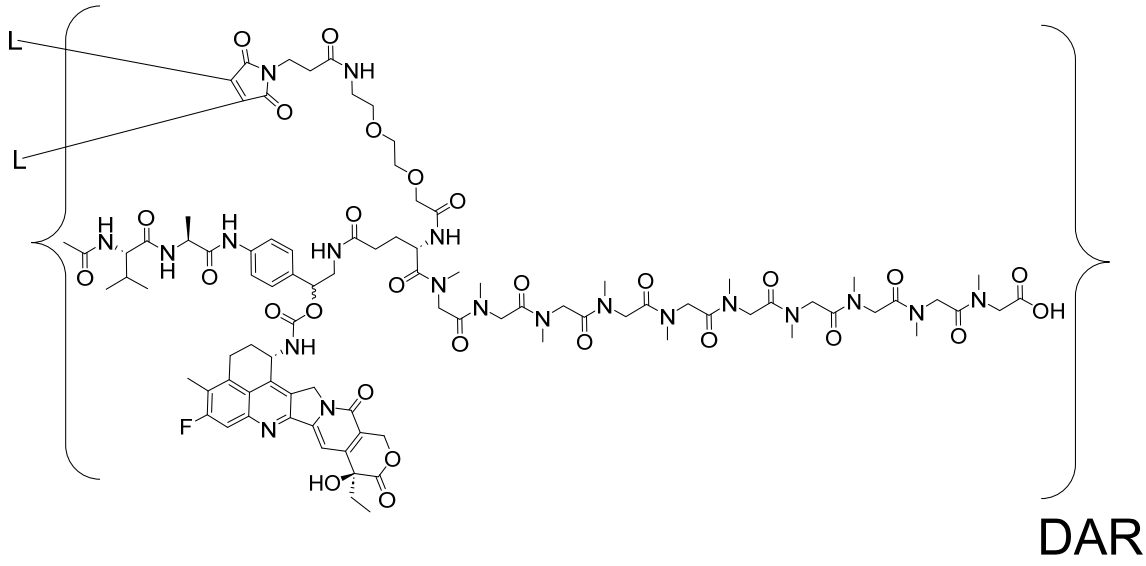
(SEQ ID NOS 39 and 25, respectively, in order of appearance),



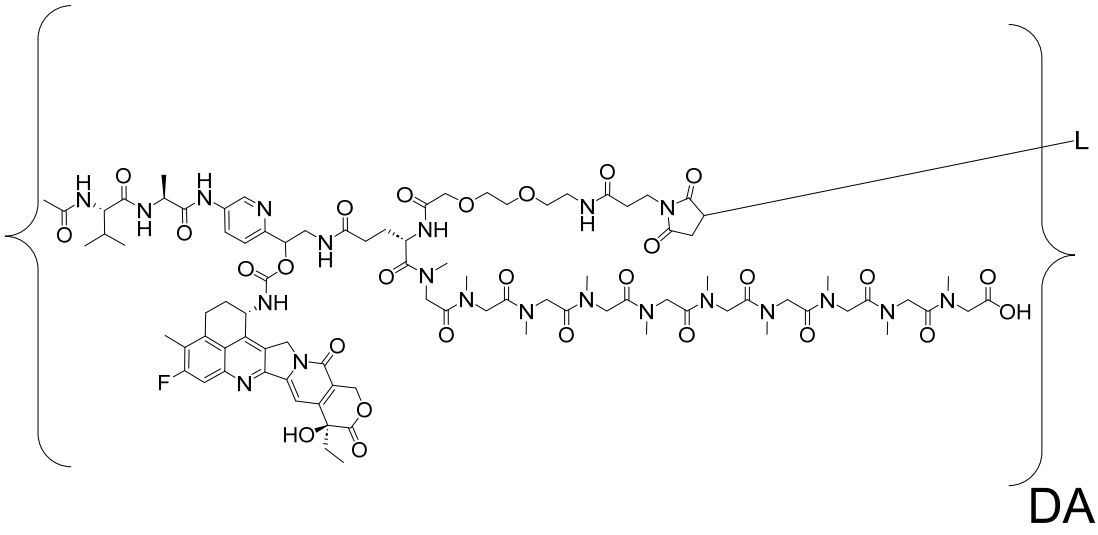
(SEQ ID NO: 25),



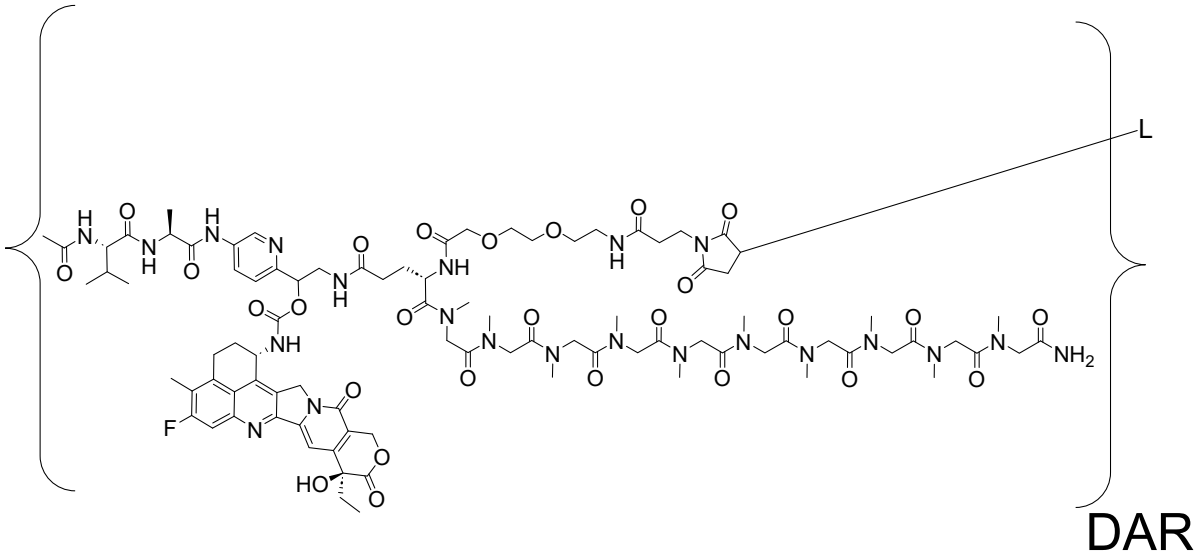
(SEQ ID NO: 25),



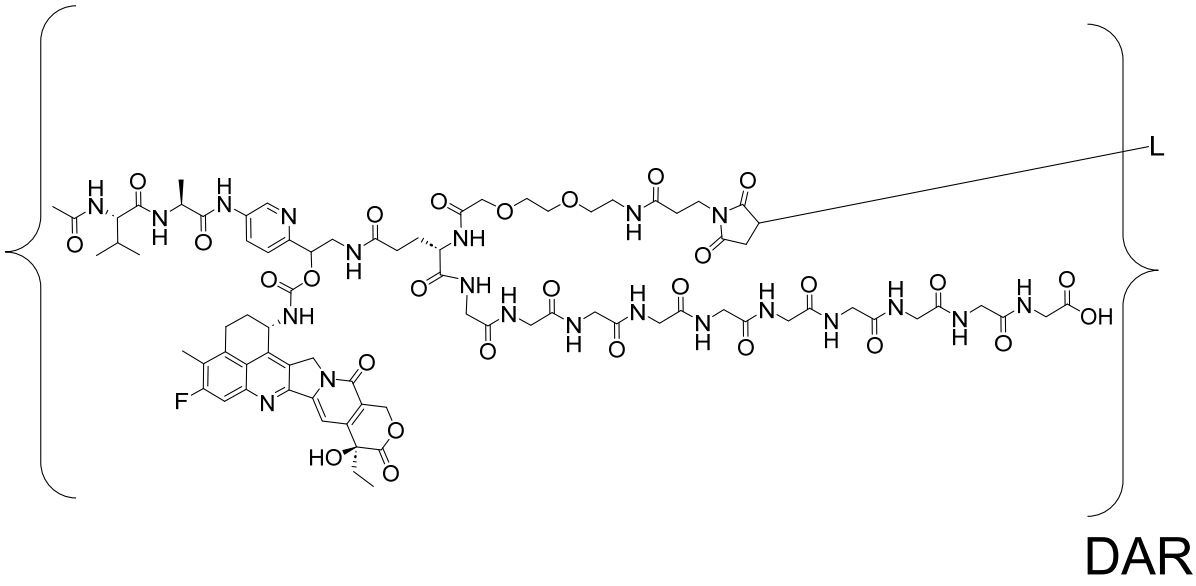
(SEQ ID NO: 25),



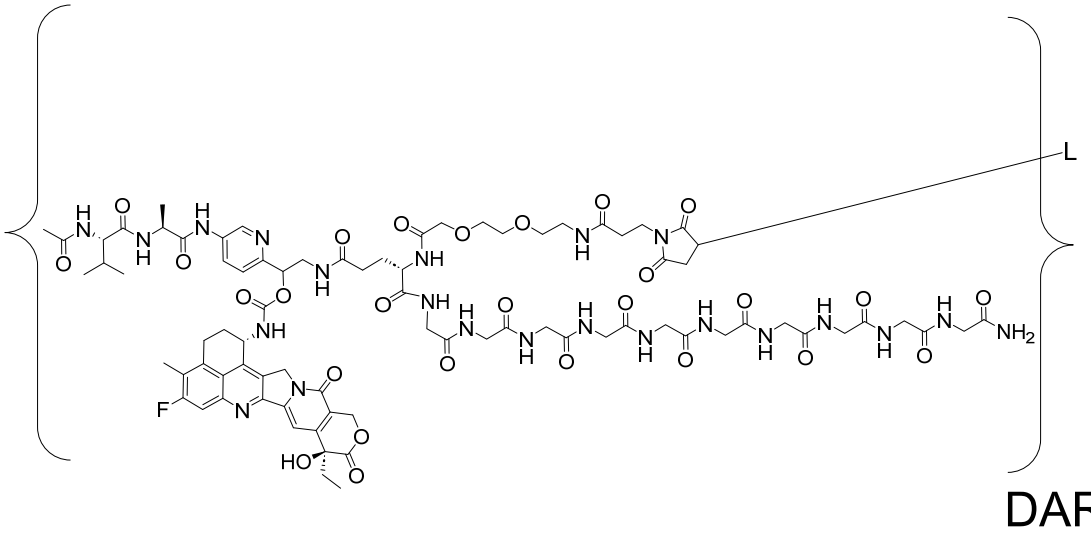
(SEQ ID NO: 25),



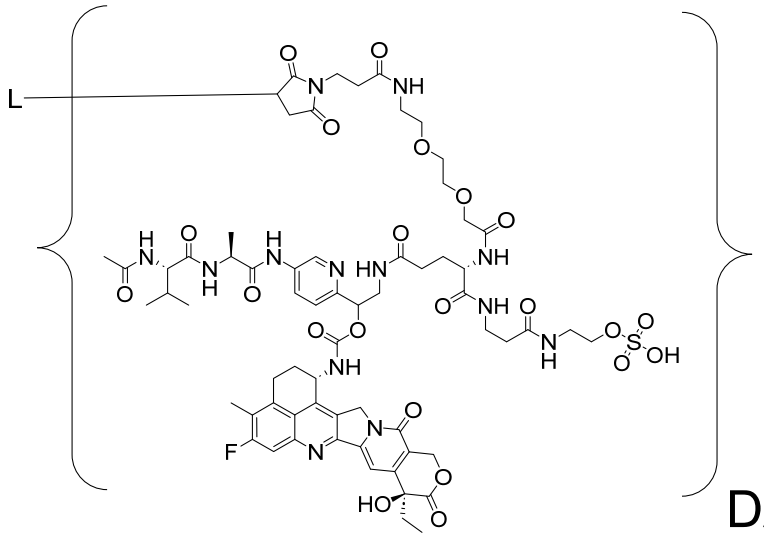
(SEQ ID NO: 25),



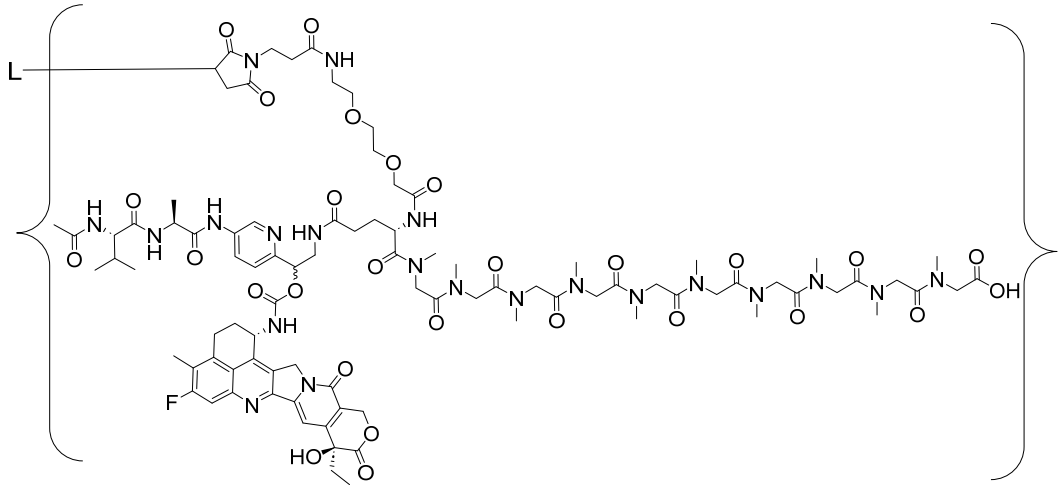
(SEQ ID NO: 24),



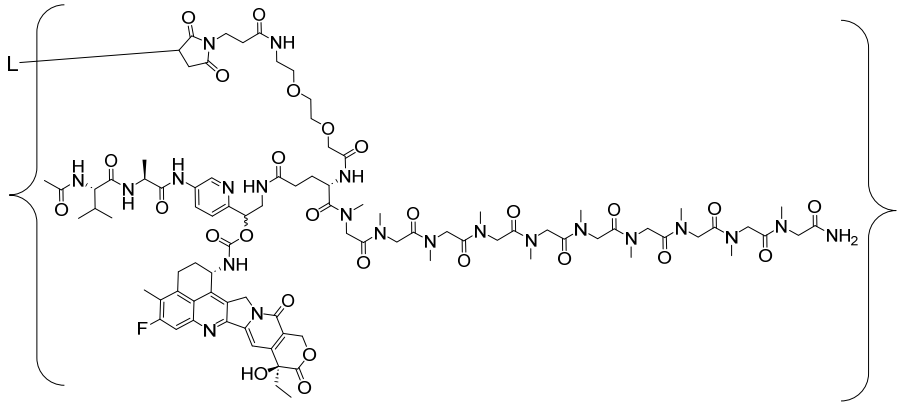
(SEQ ID NO: 24),



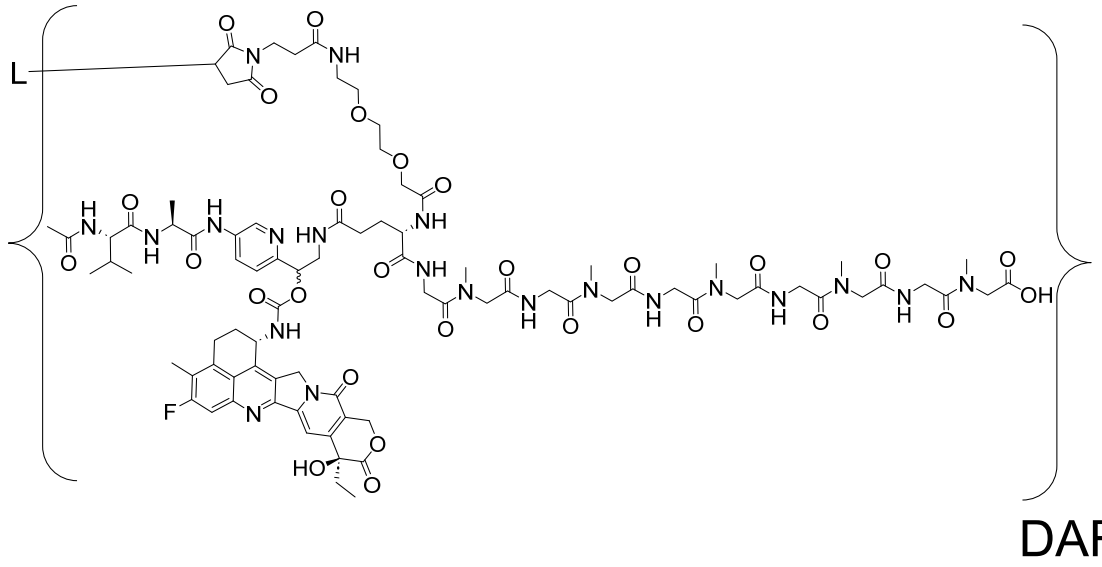
DAR,



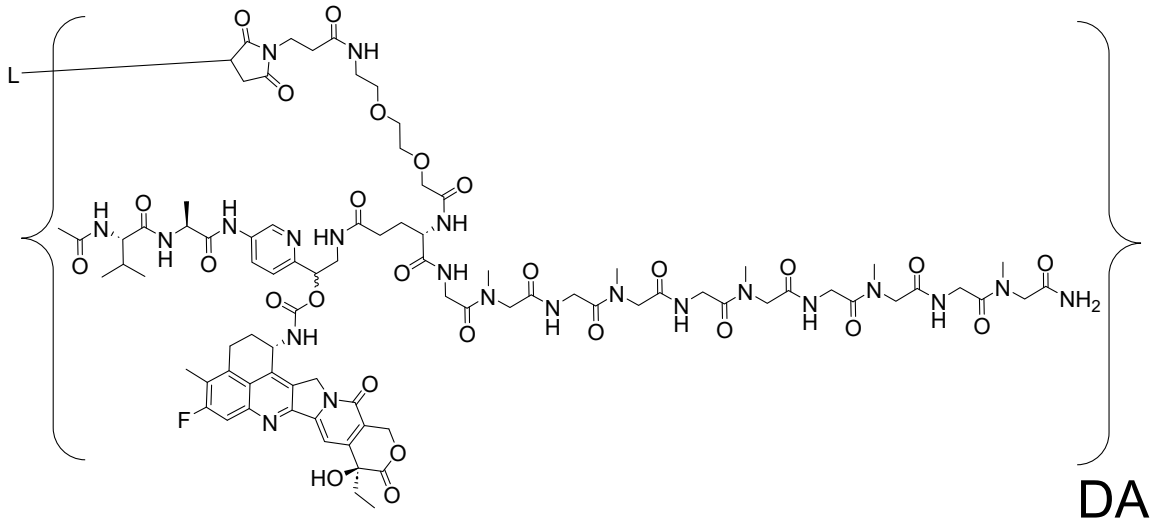
DAR (SEQ ID NO: 25),



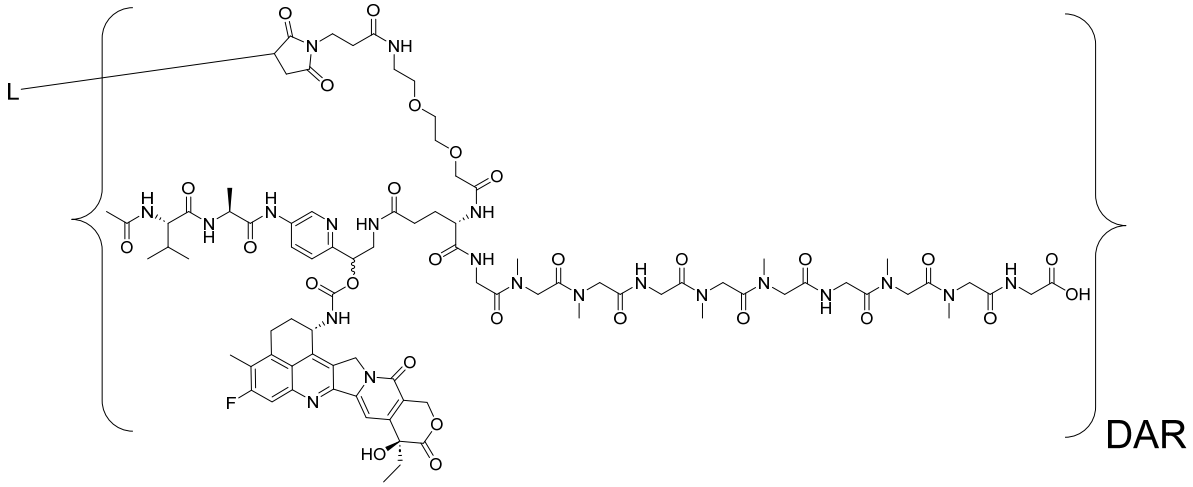
DAR (SEQ ID NO: 25),



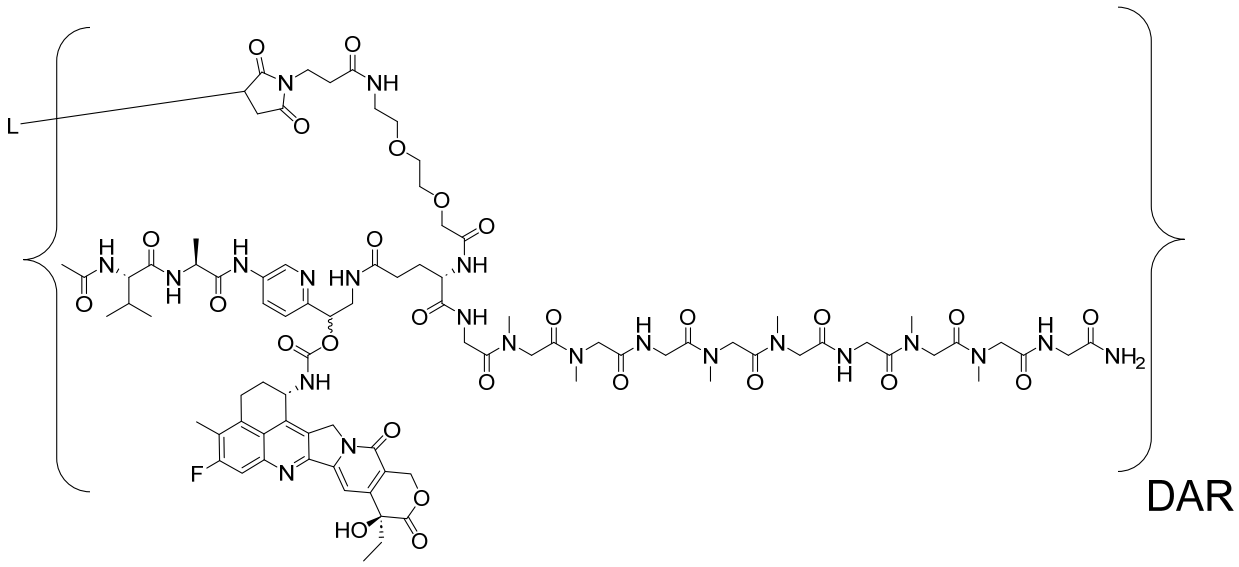
(SEQ ID NO: 26),



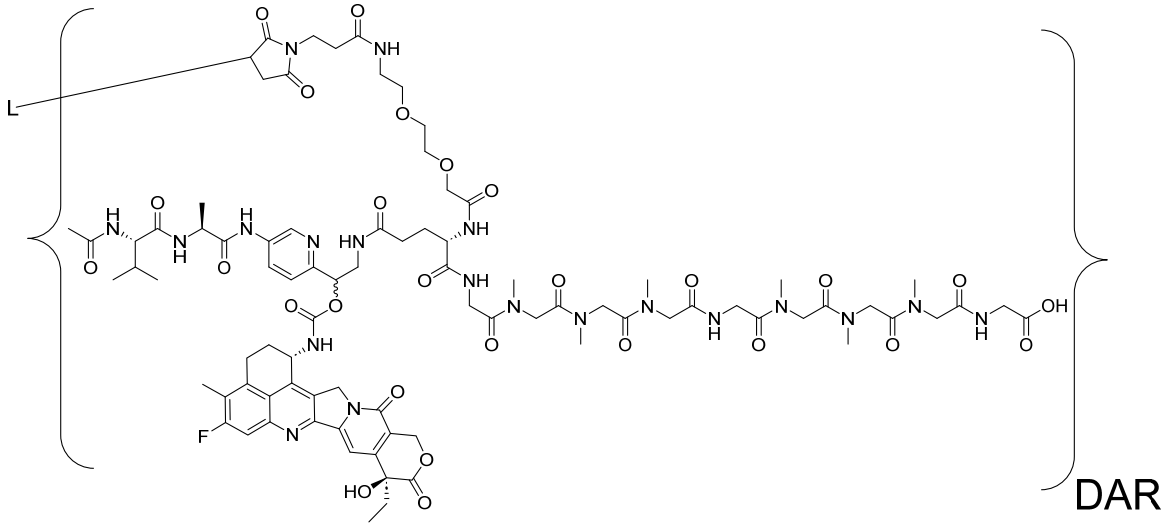
(SEQ ID NO: 26),



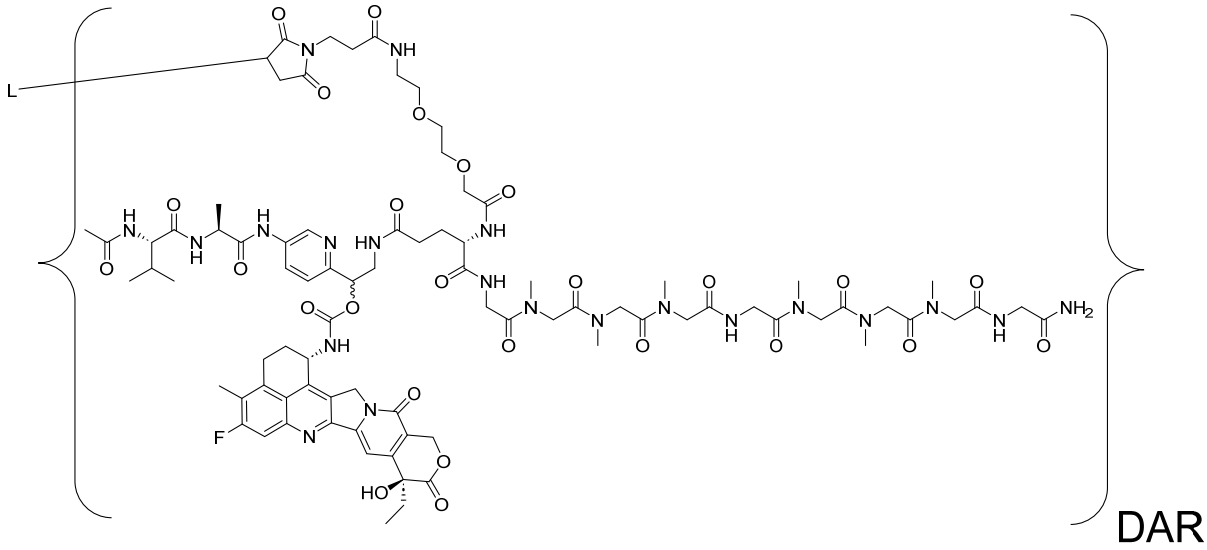
(SEQ ID NO: 31),



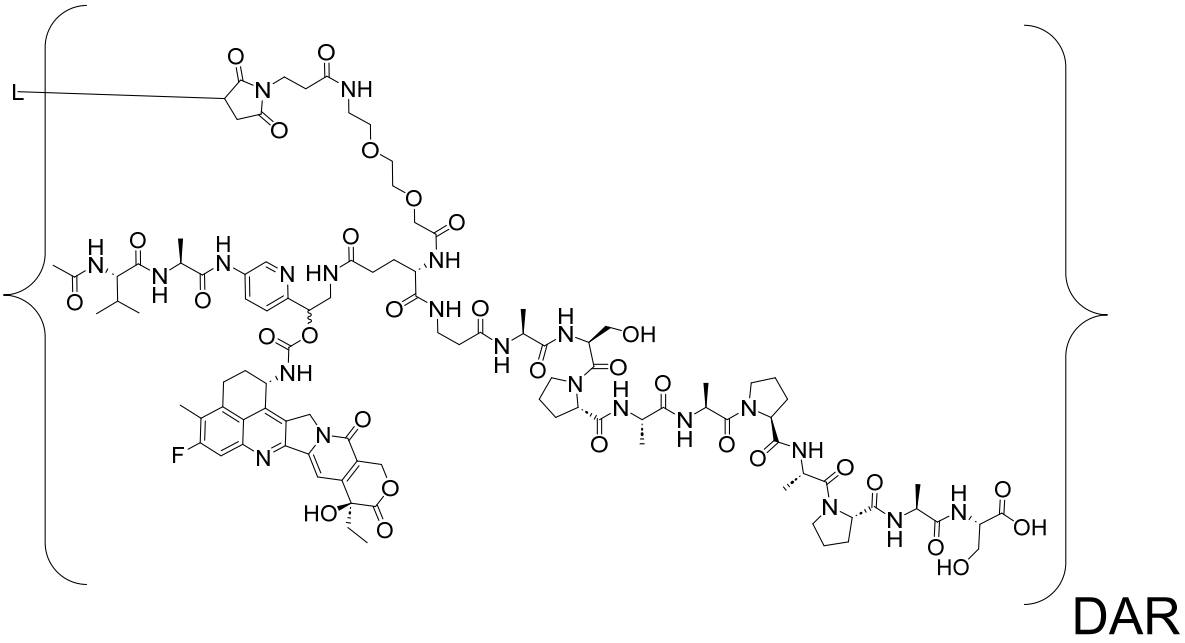
(SEQ ID NO: 31),



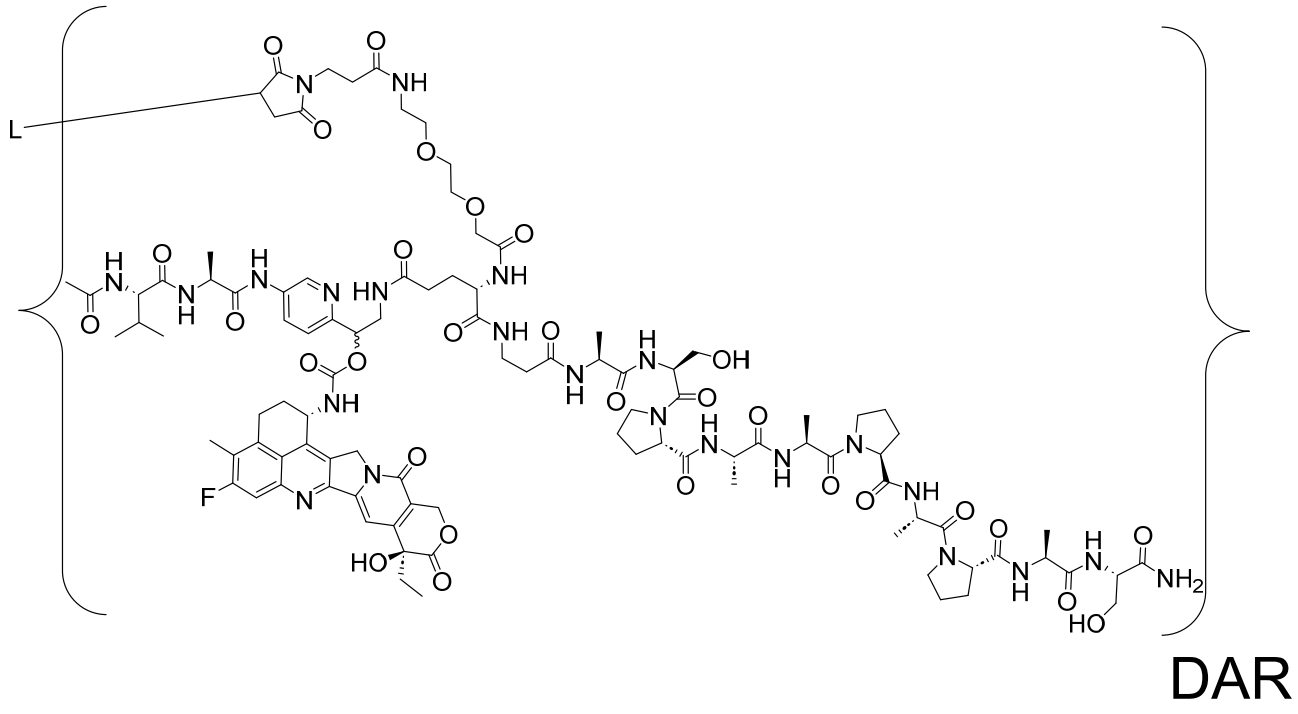
(SEQ ID NO: 32),



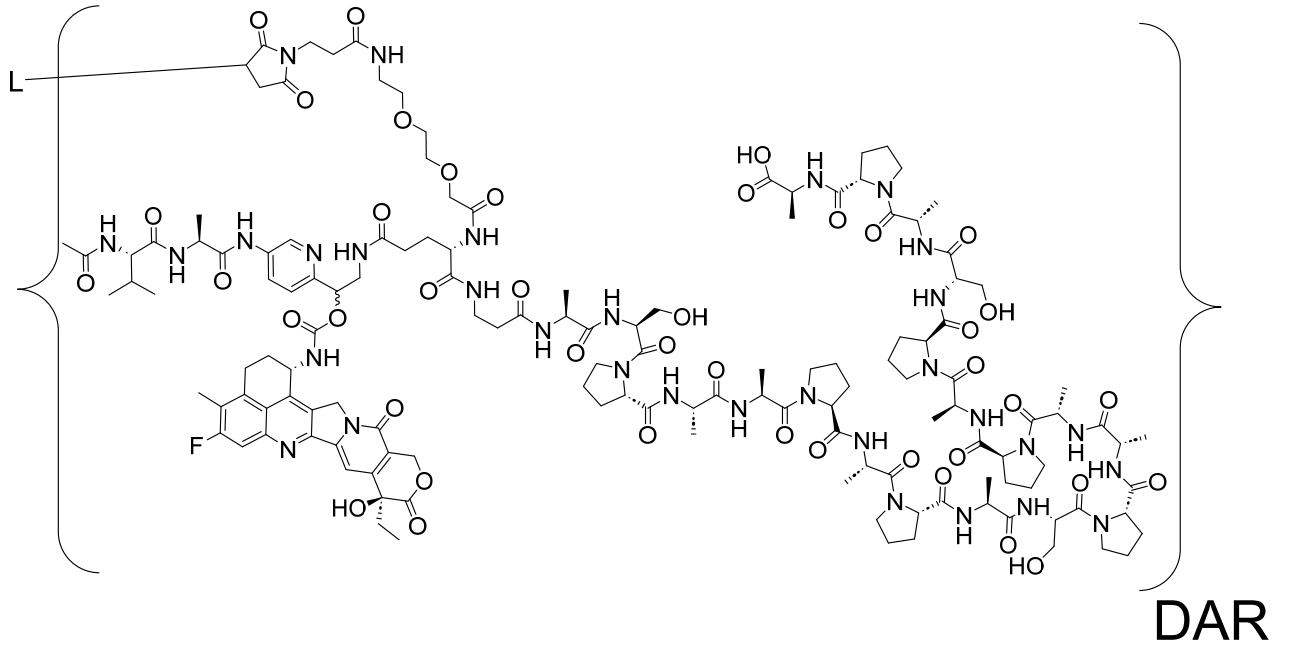
(SEQ ID NO: 32),



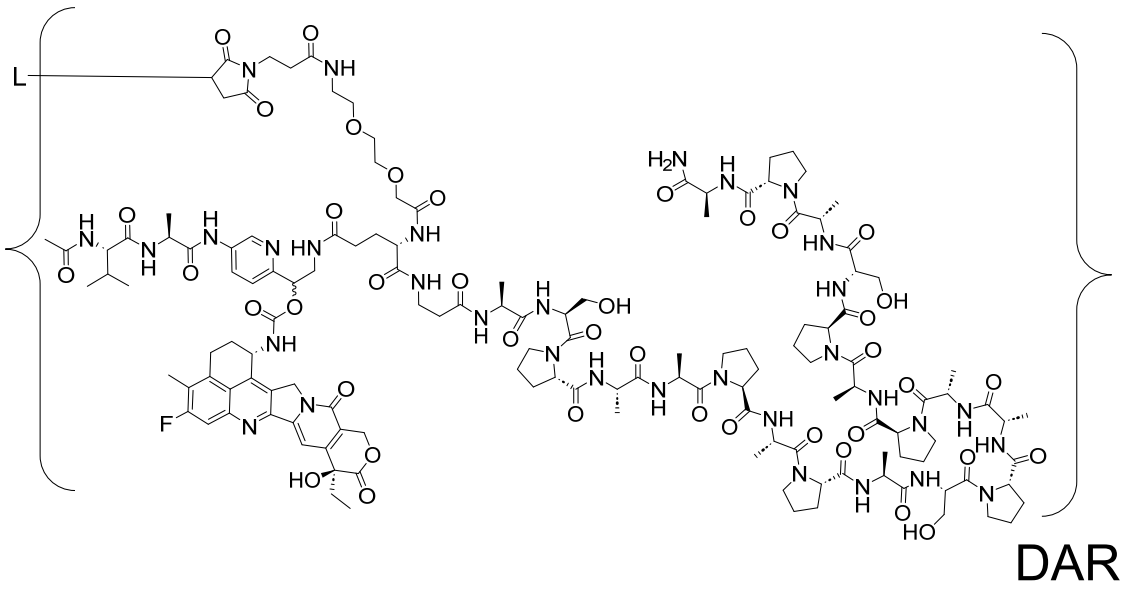
(SEQ ID NO: 27),



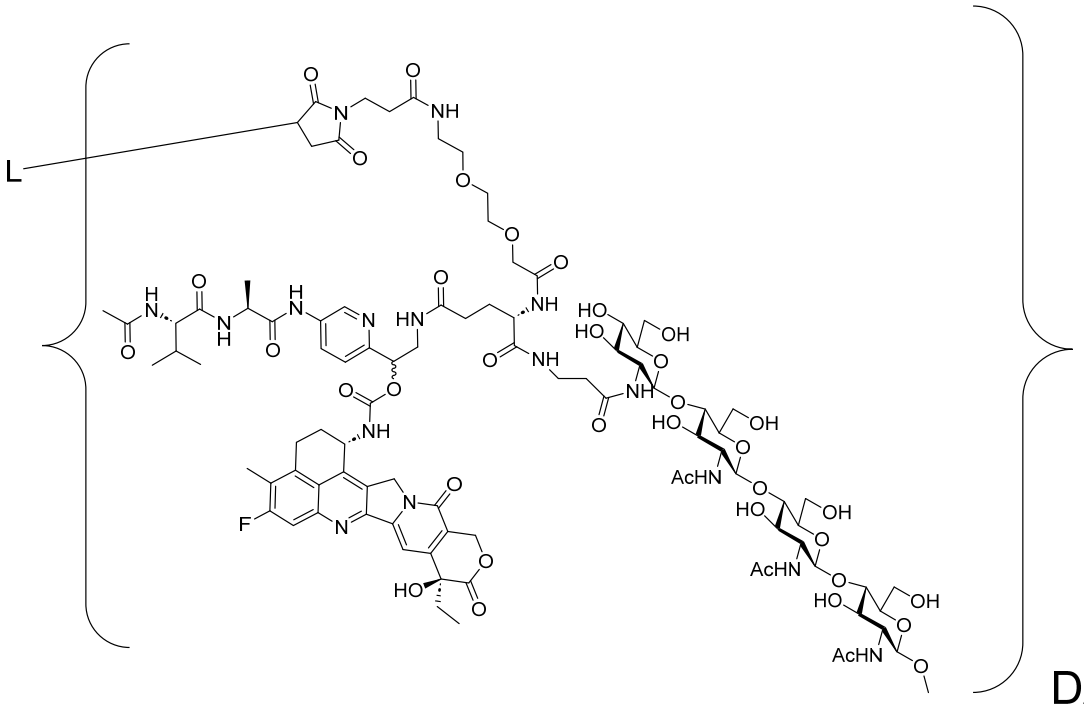
(SEQ ID NO: 27),



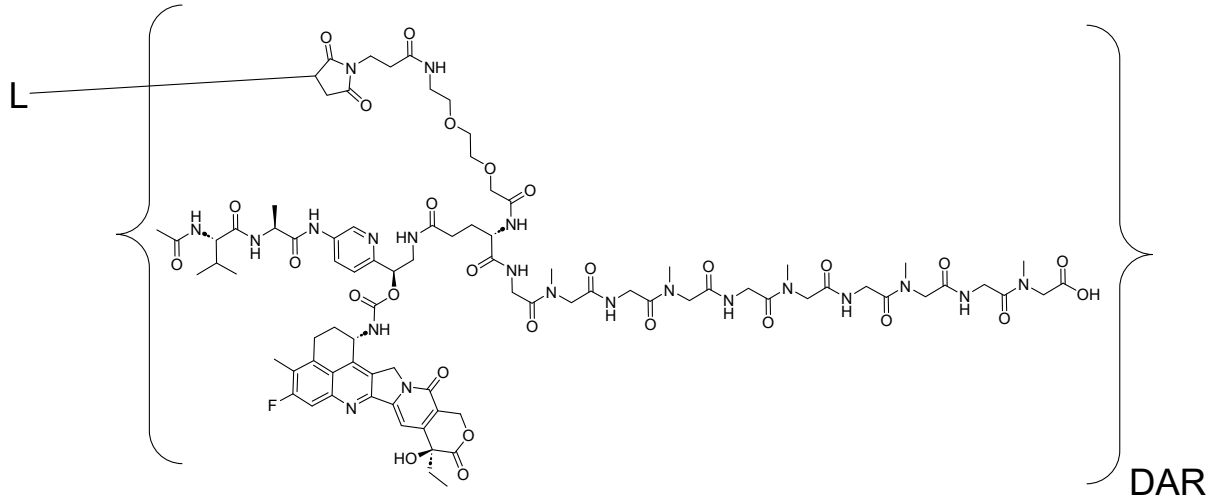
(SEQ ID NO: 28),



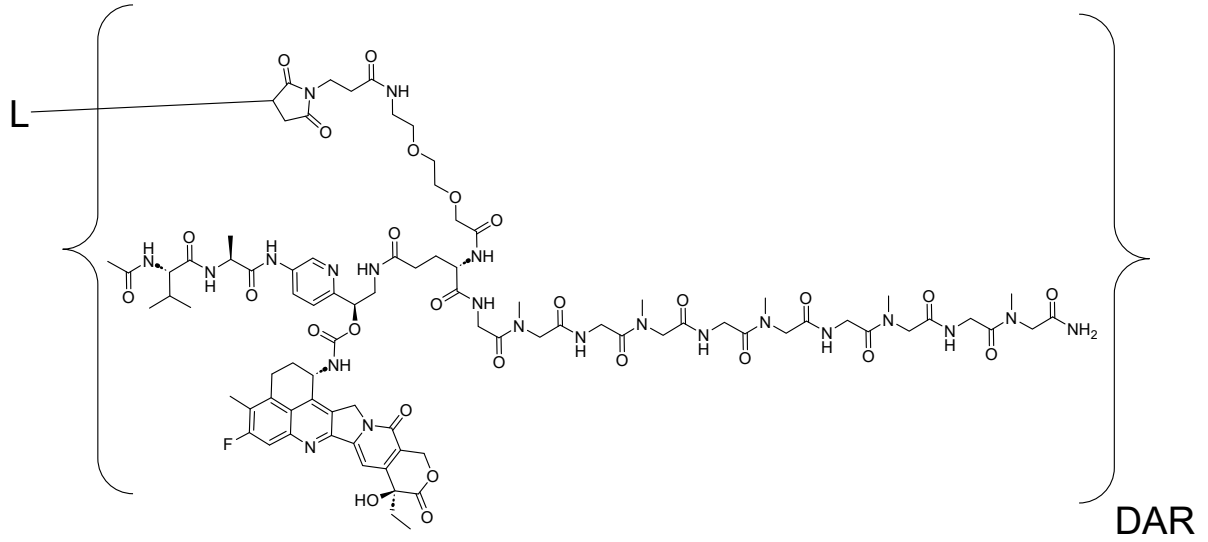
(SEQ ID NO: 28),



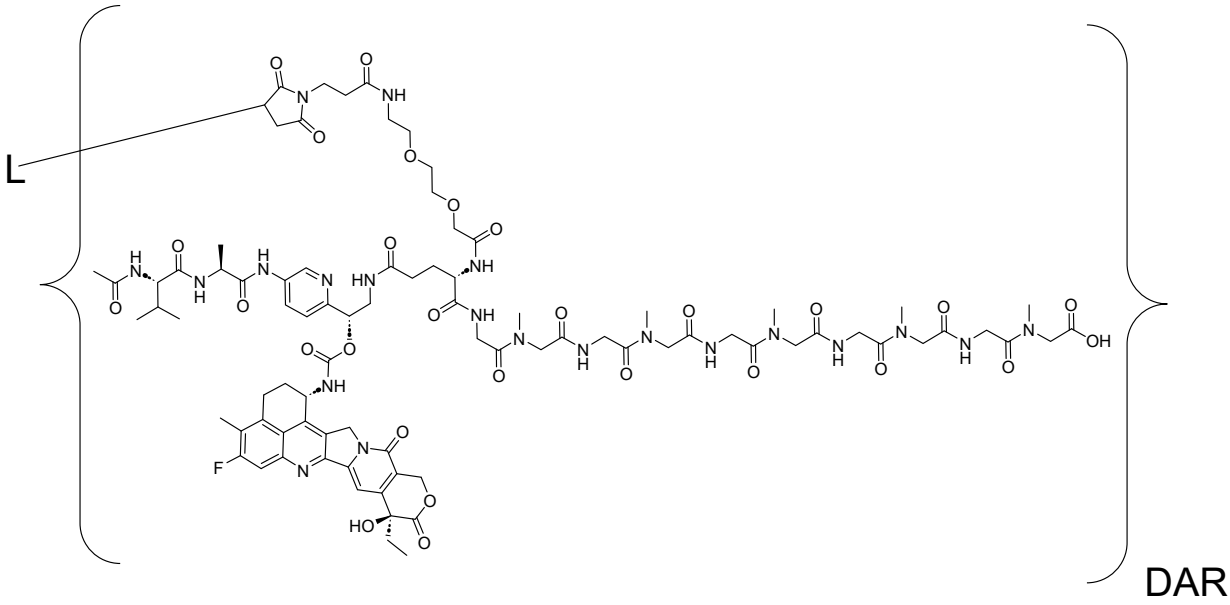
,



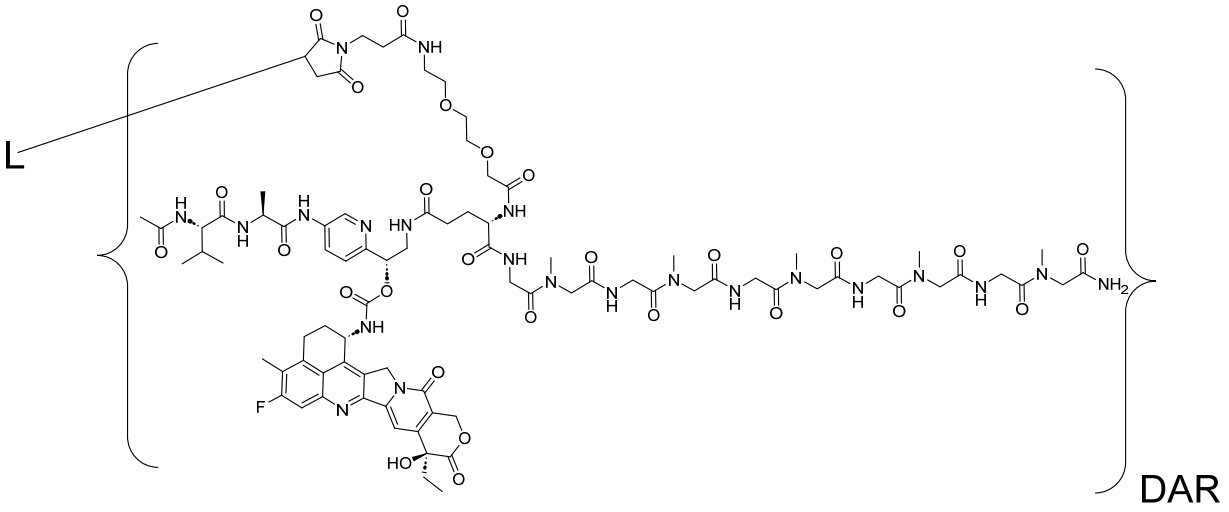
(SEQ ID NO: 26),



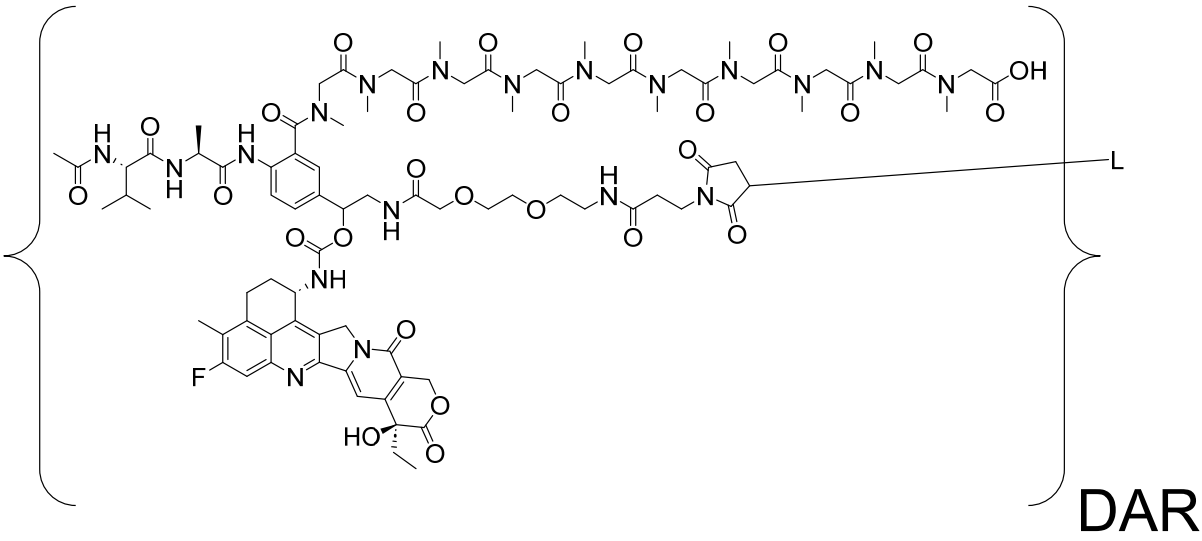
(SEQ ID NO: 26),



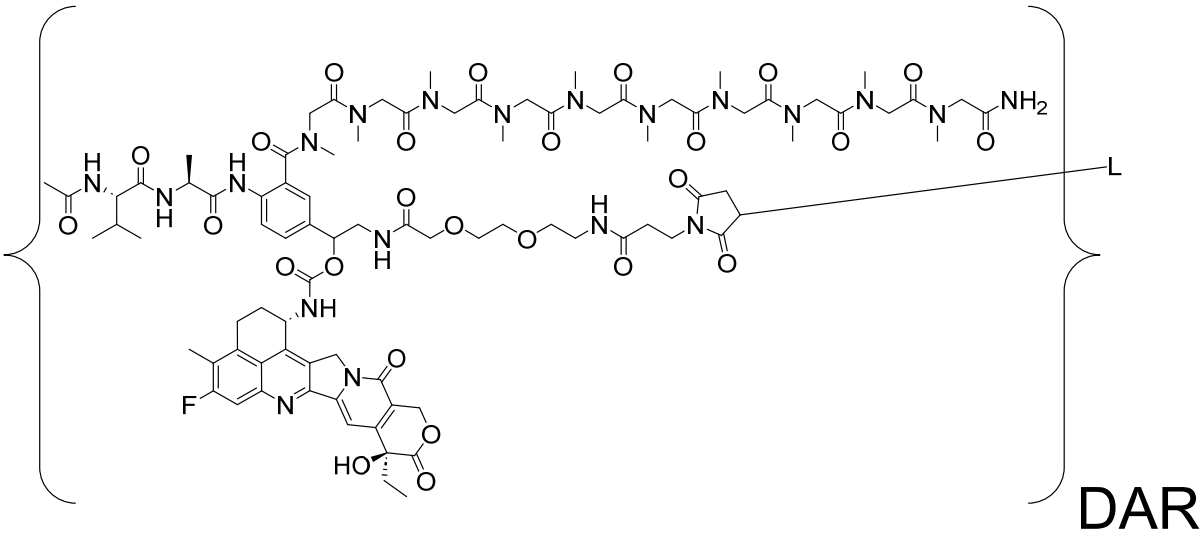
(SEQ ID NO: 26),



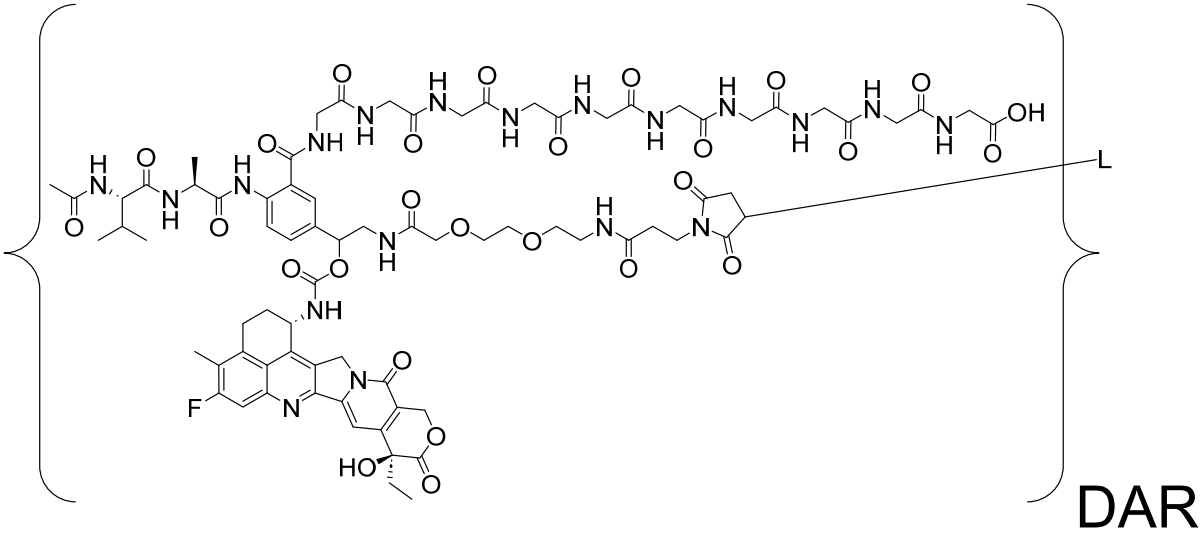
(SEQ ID NO: 26),



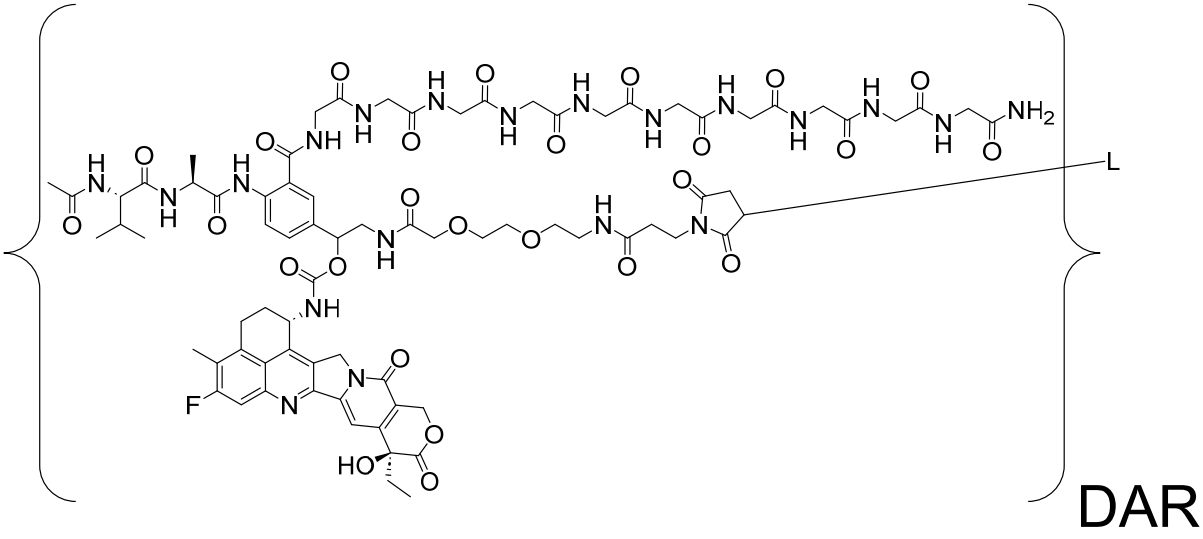
(SEQ ID NO: 29),



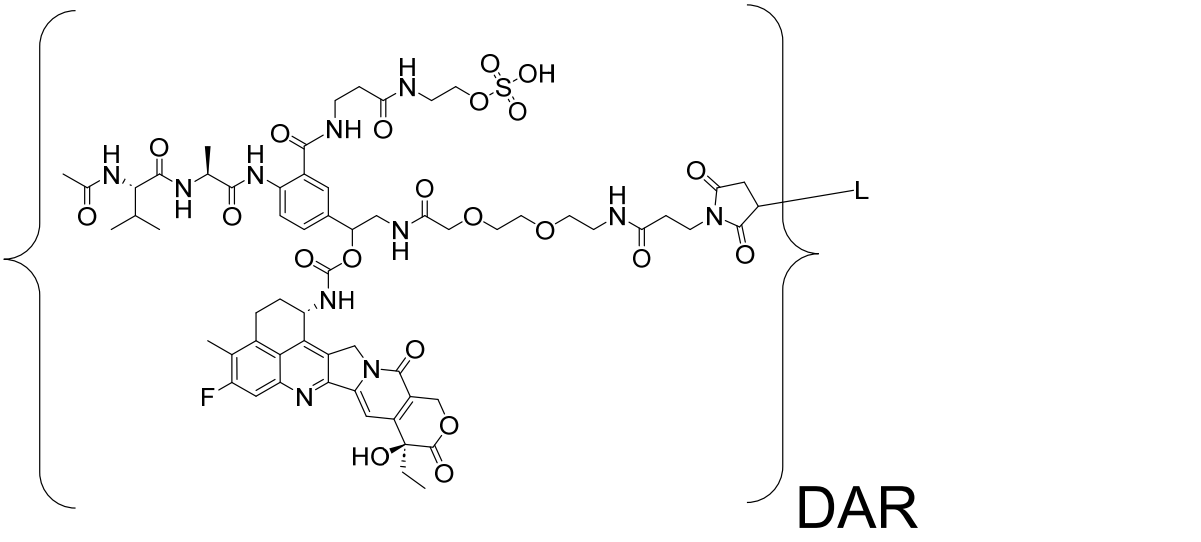
(SEQ ID NO: 29),



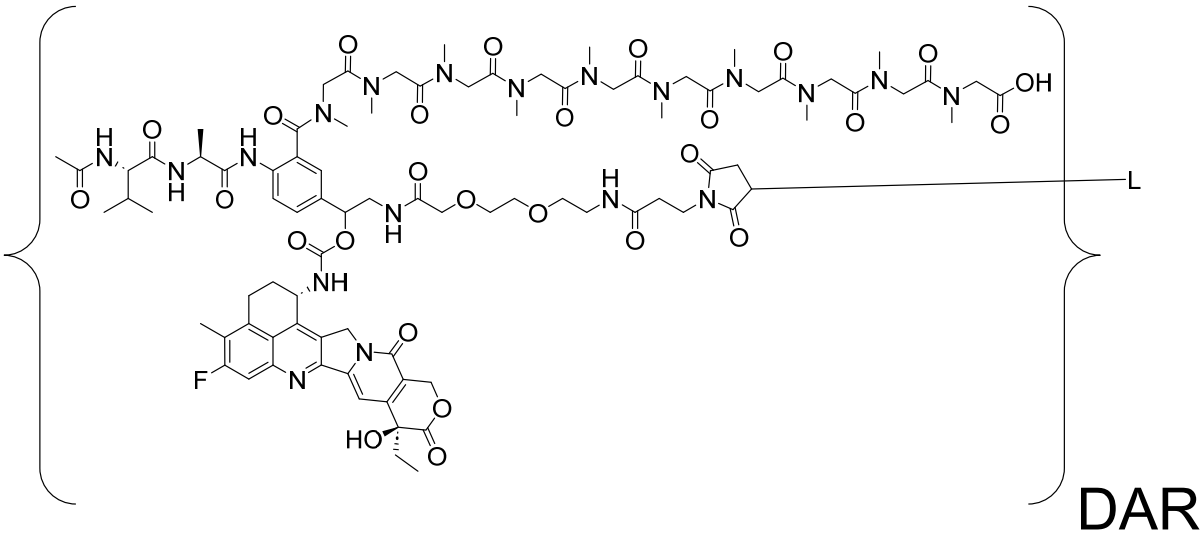
(SEQ ID NO: 38),



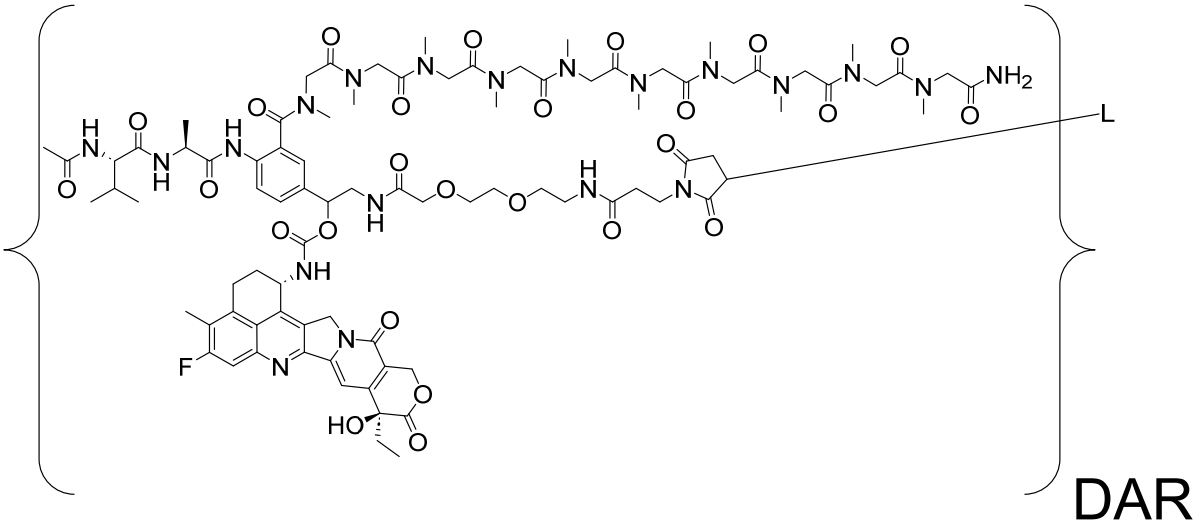
(SEQ ID NO: 38),



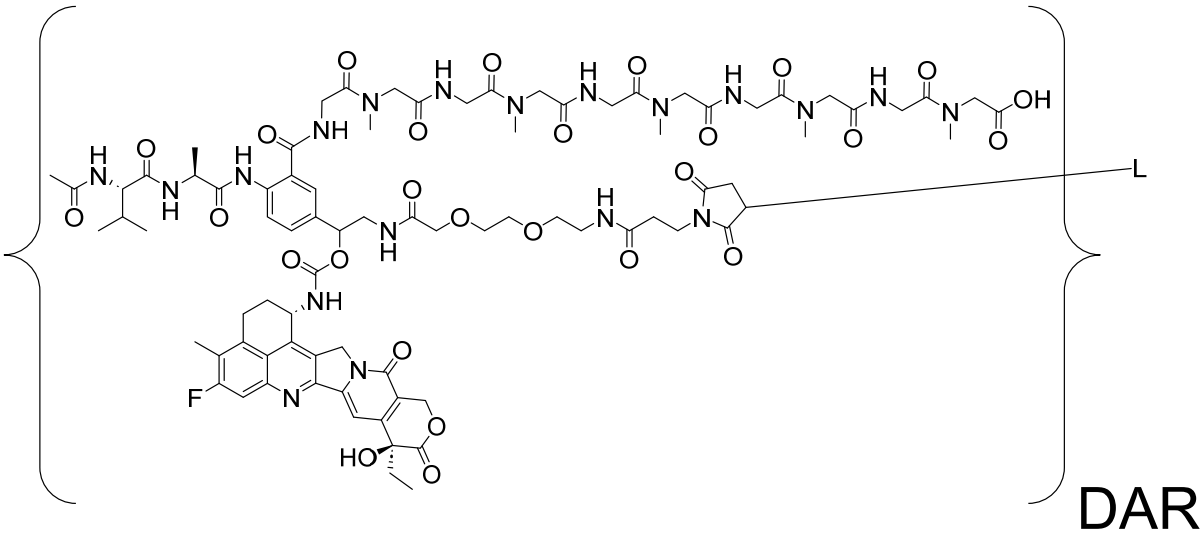
,



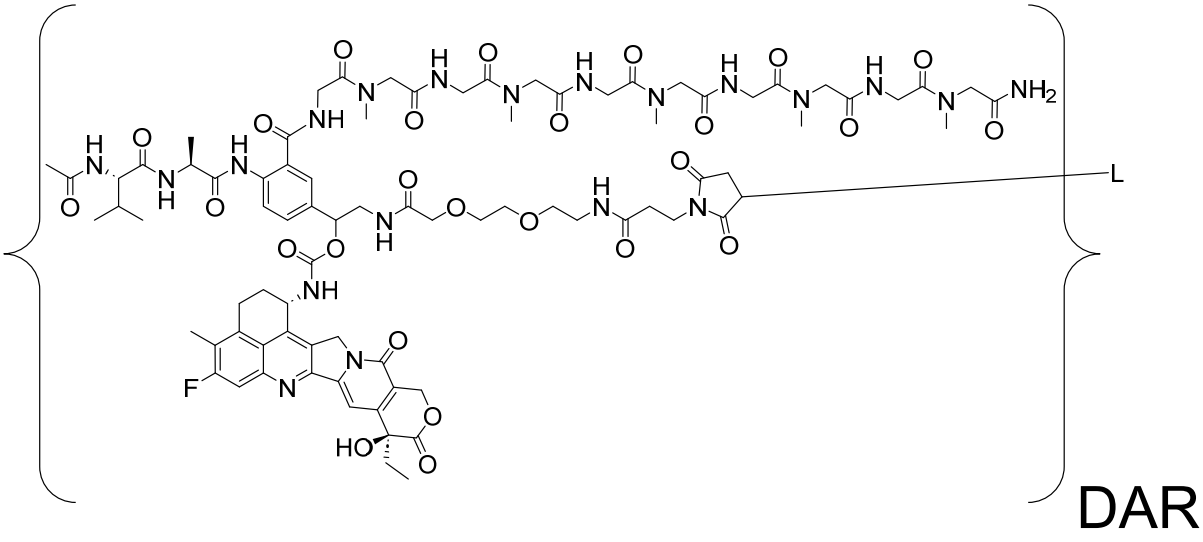
(SEQ ID NO: 29),



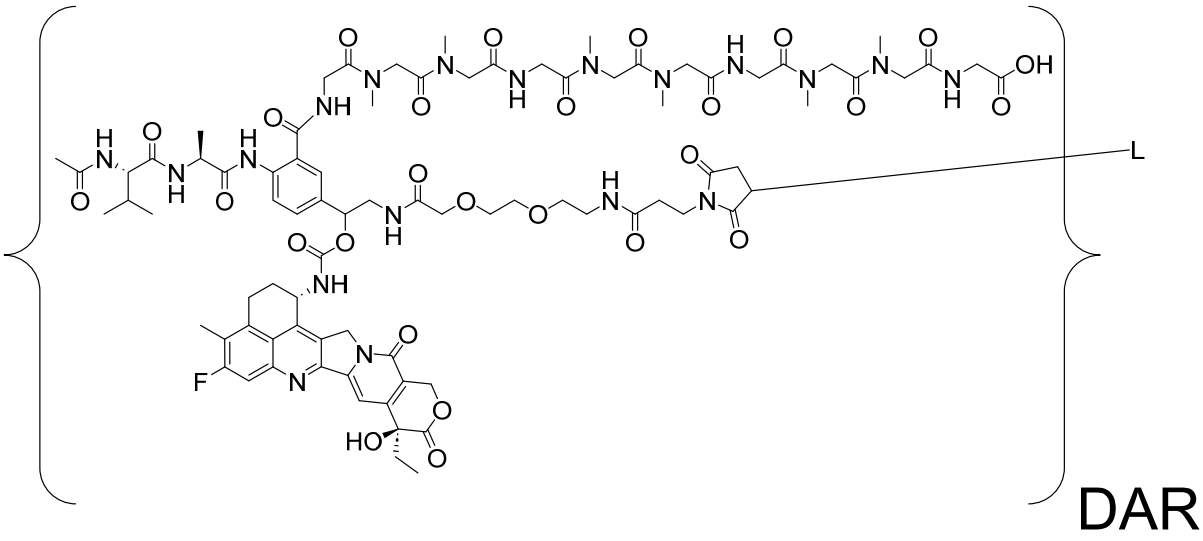
(SEQ ID NO: 29),



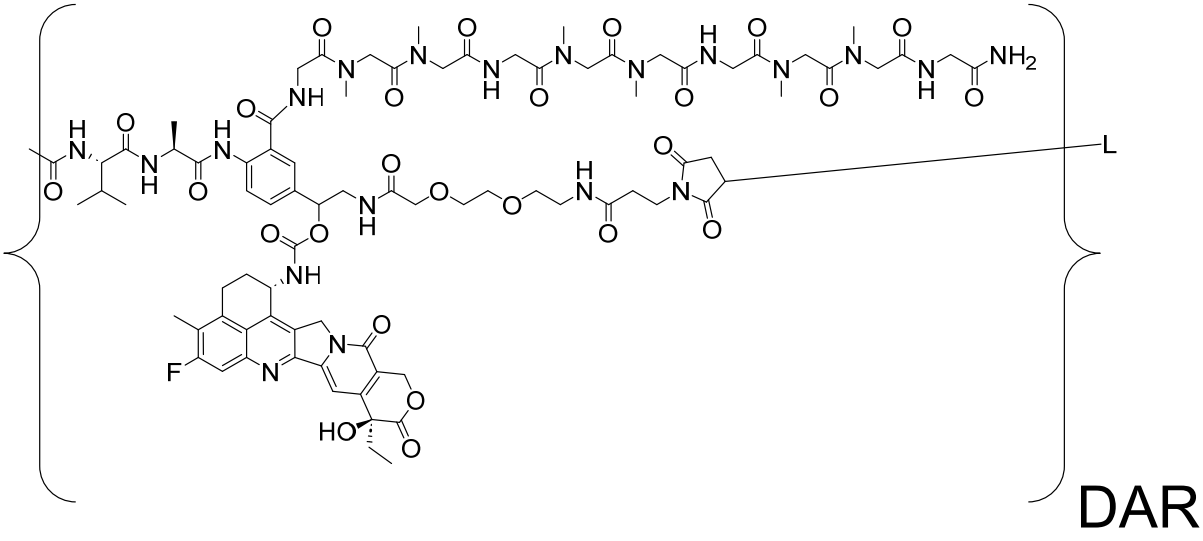
(SEQ ID NO: 30),



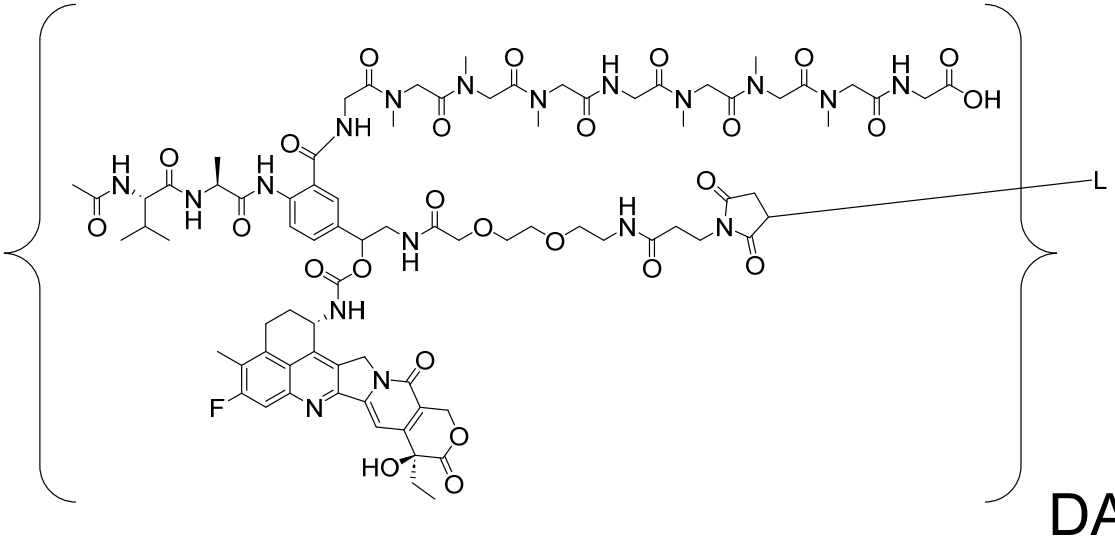
(SEQ ID NO: 30),



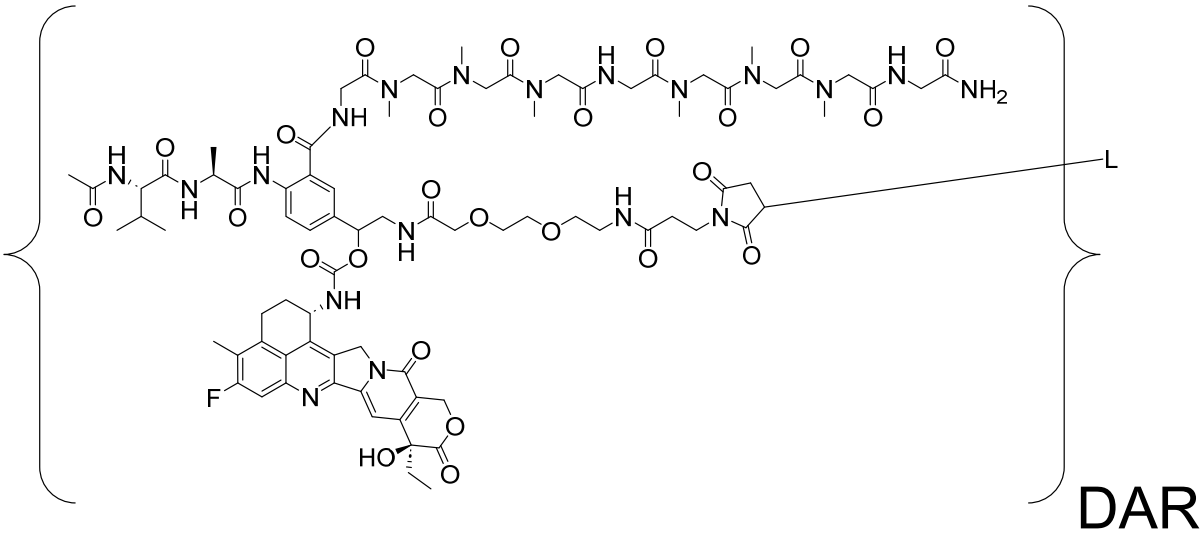
(SEQ ID NO: 33),



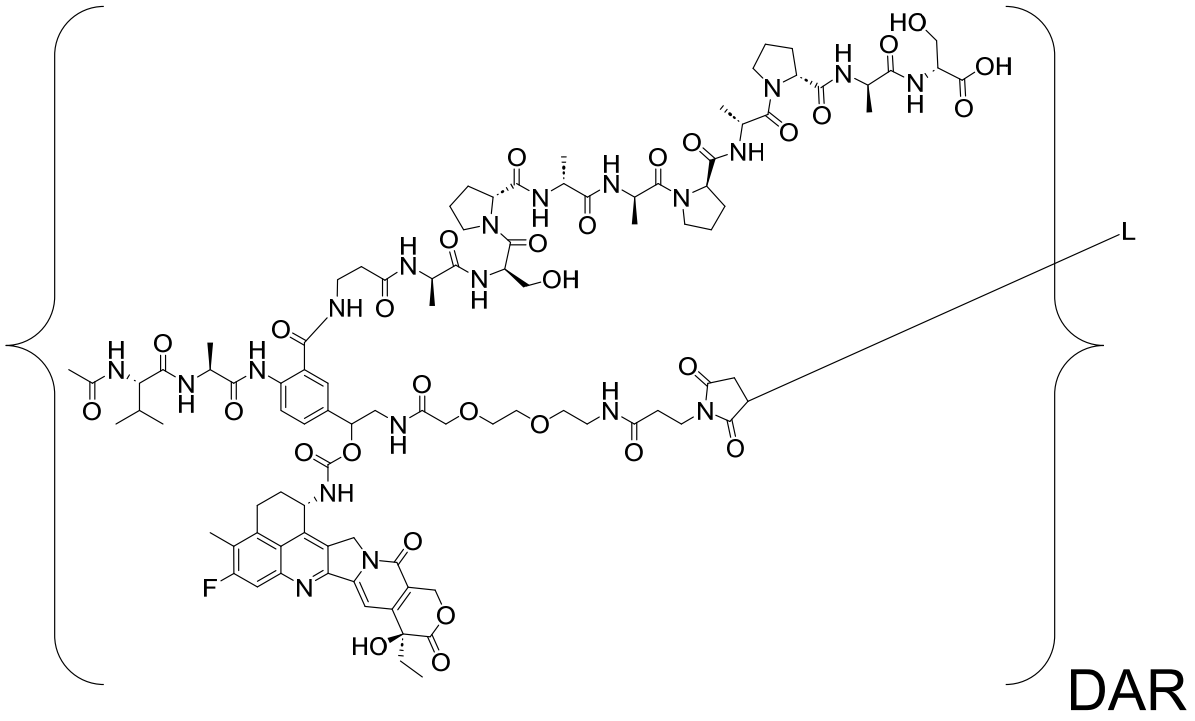
(SEQ ID NO: 33),



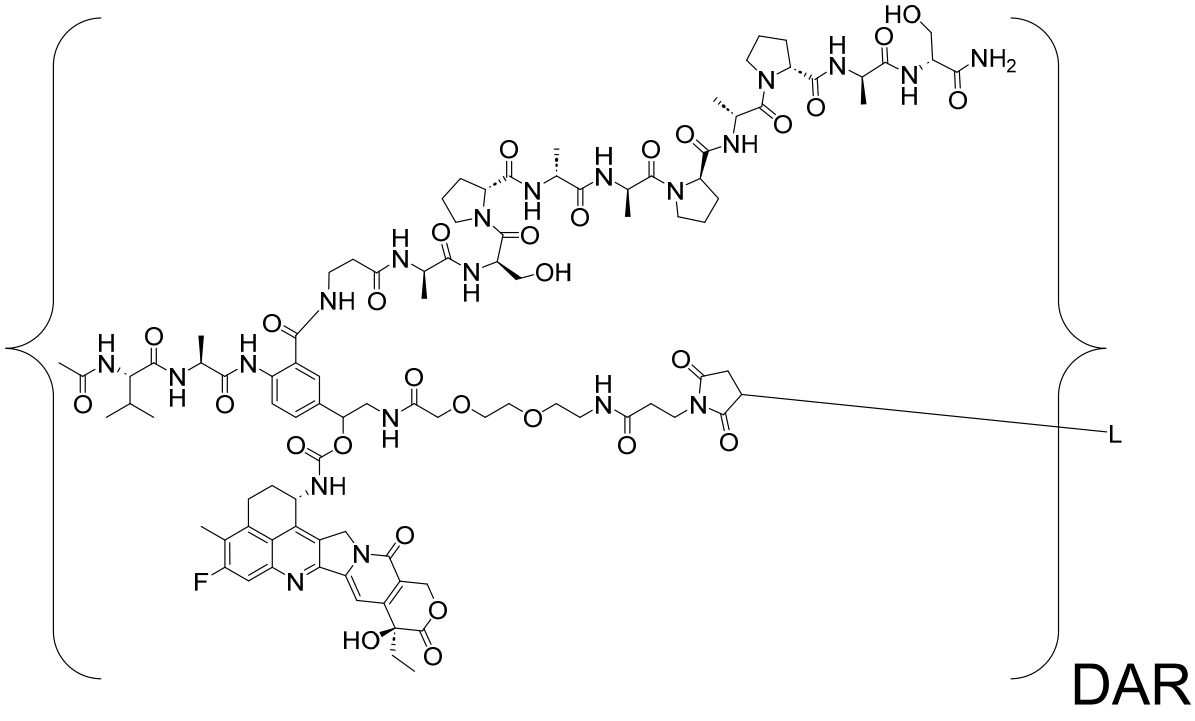
(SEQ ID NO: 34),



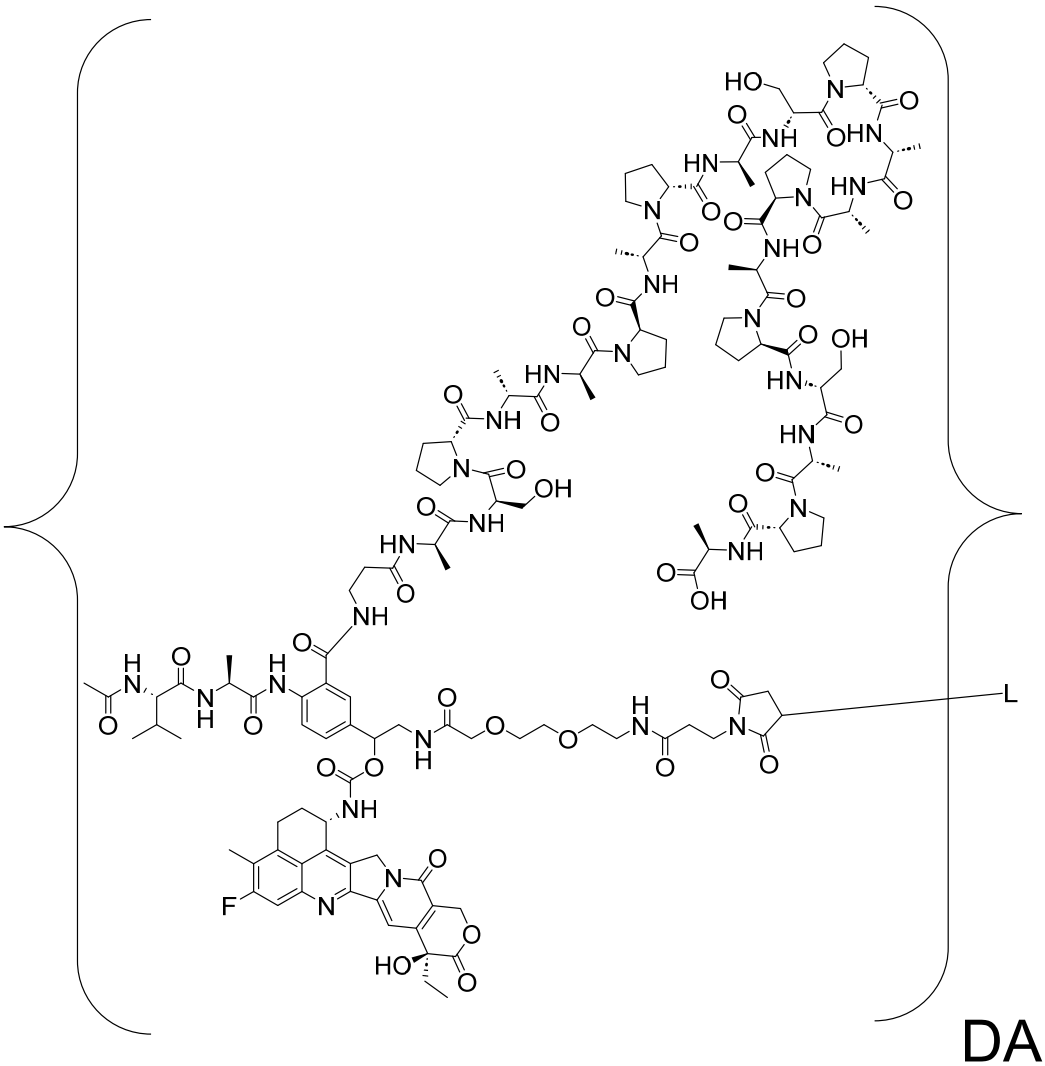
(SEQ ID NO: 34),



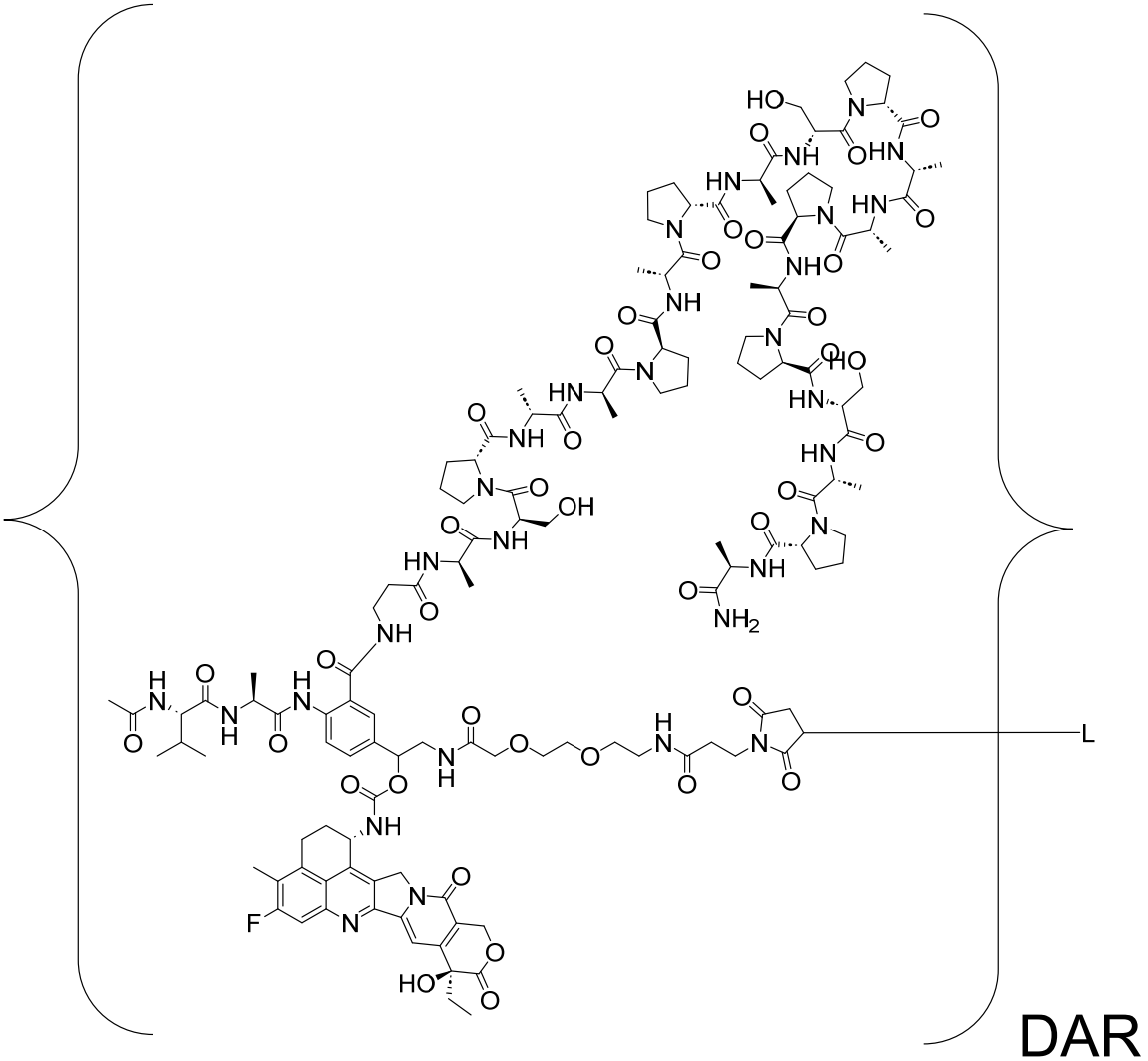
(SEQ ID NO: 35),



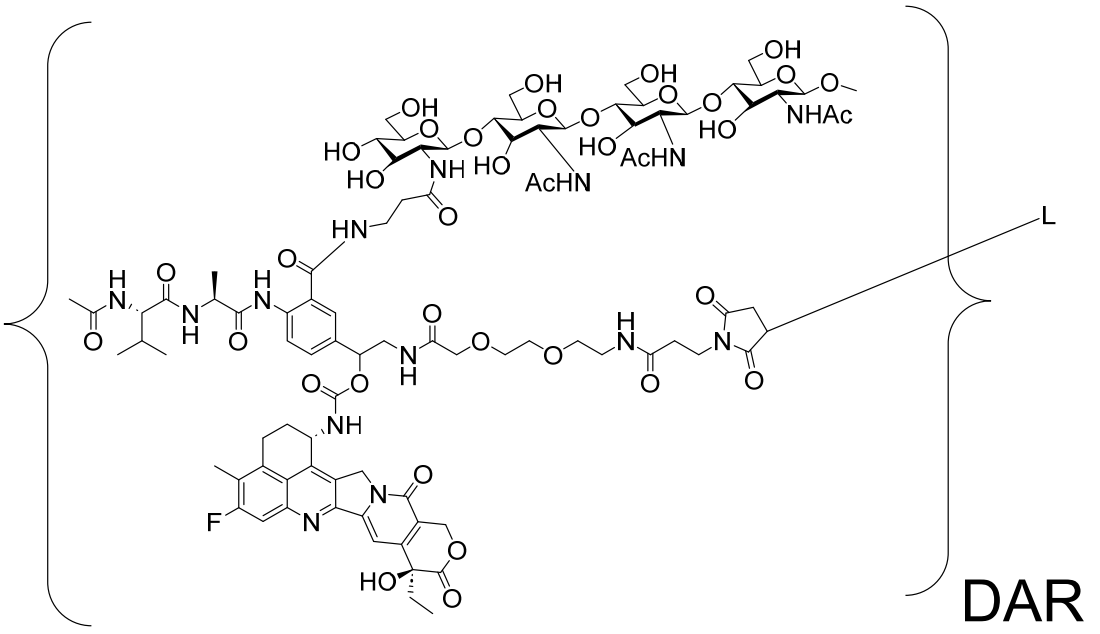
(SEQ ID NO: 35),



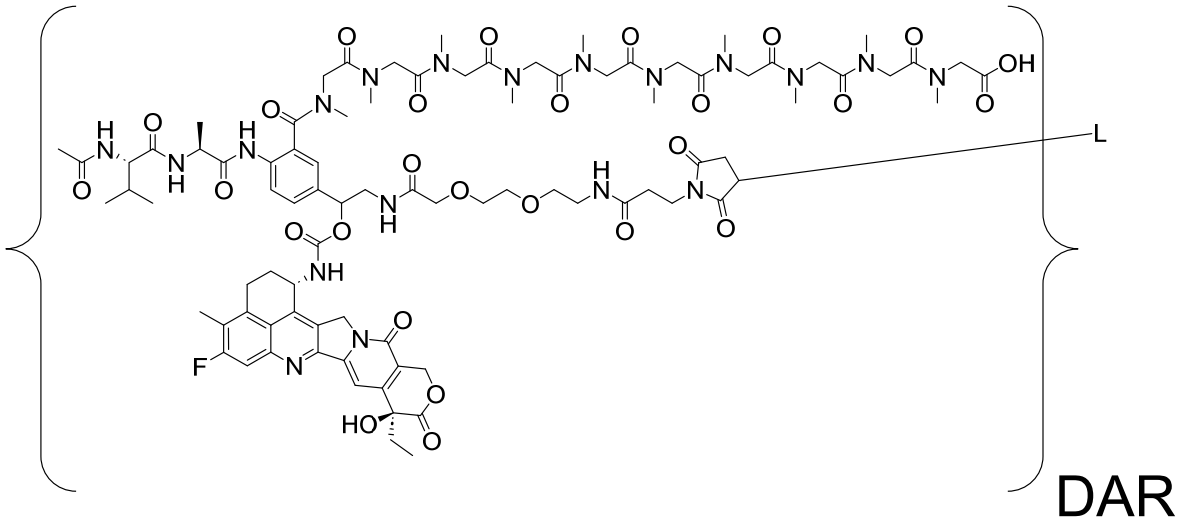
DAR (SEQ ID NO: 36),



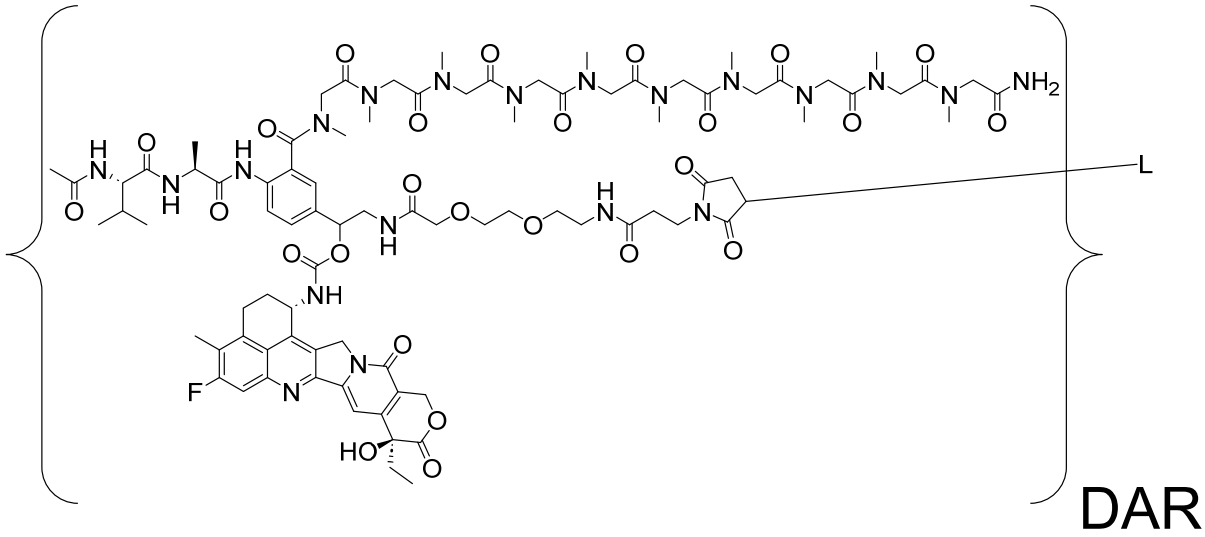
(SEQ ID NO: 36),



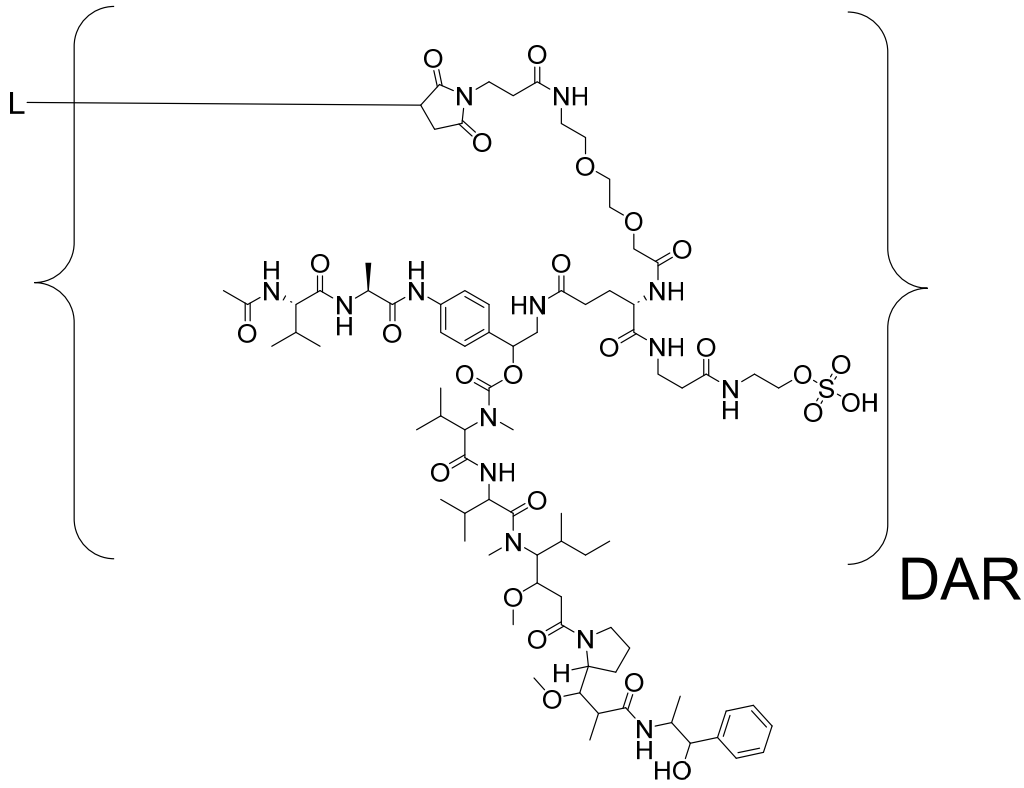
,



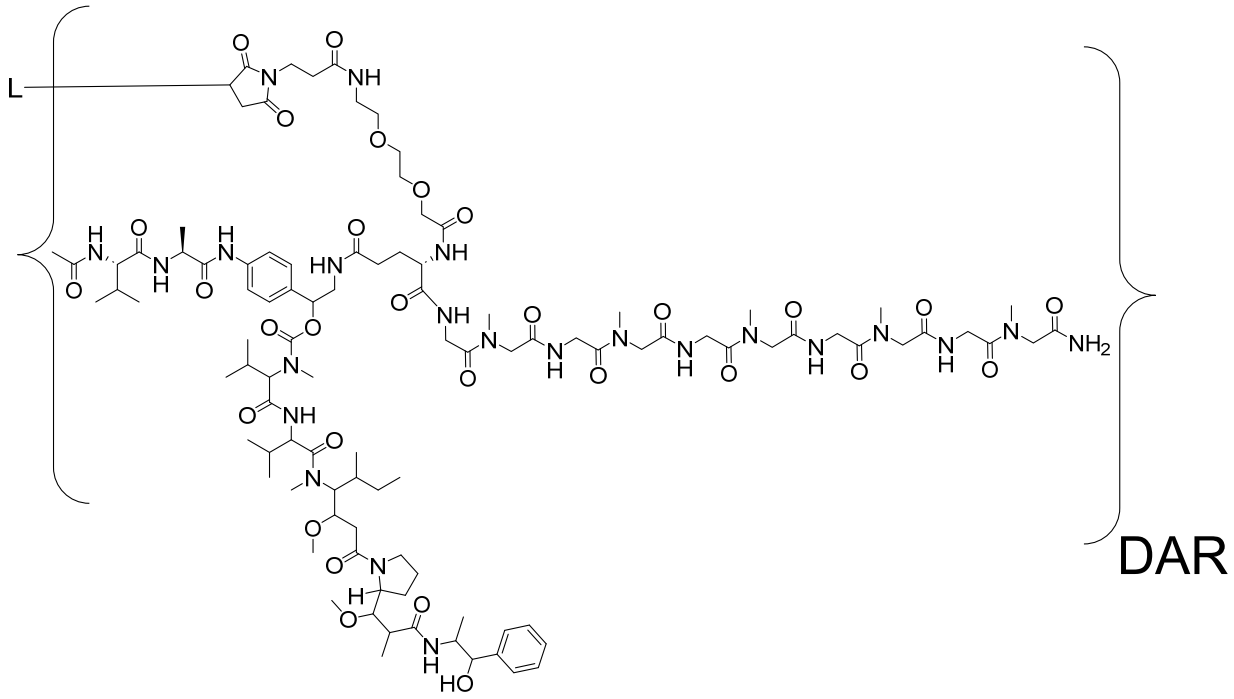
(SEQ ID NO: 29),



(SEQ ID NO: 29);

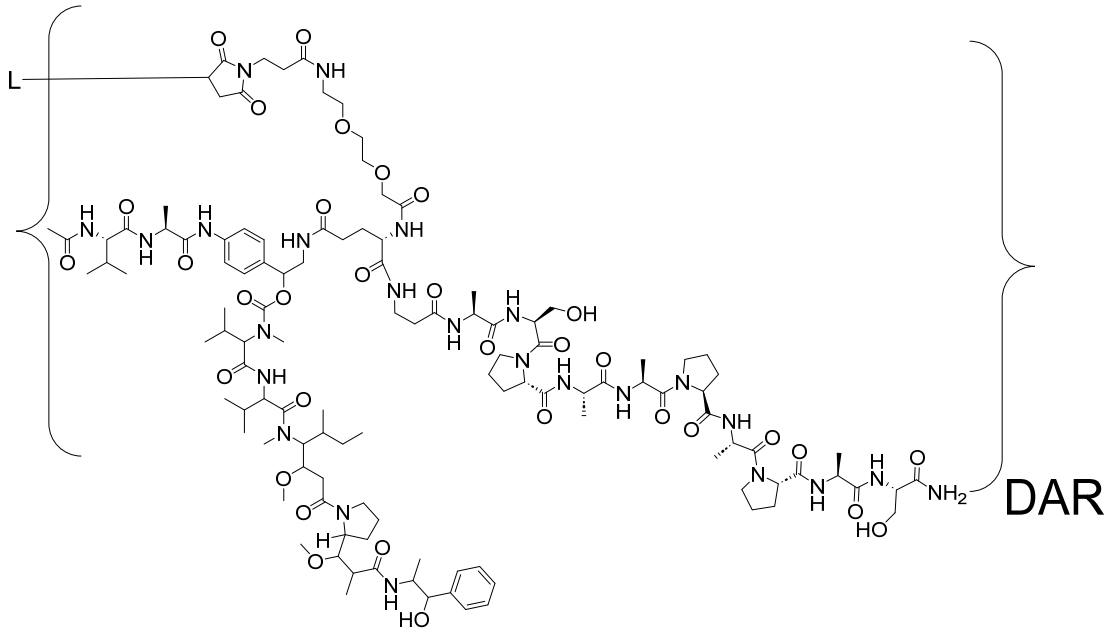


(SEQ ID NO: 22);



(SEQ ID NOS 26 and 22, respectively, in order of appearance)

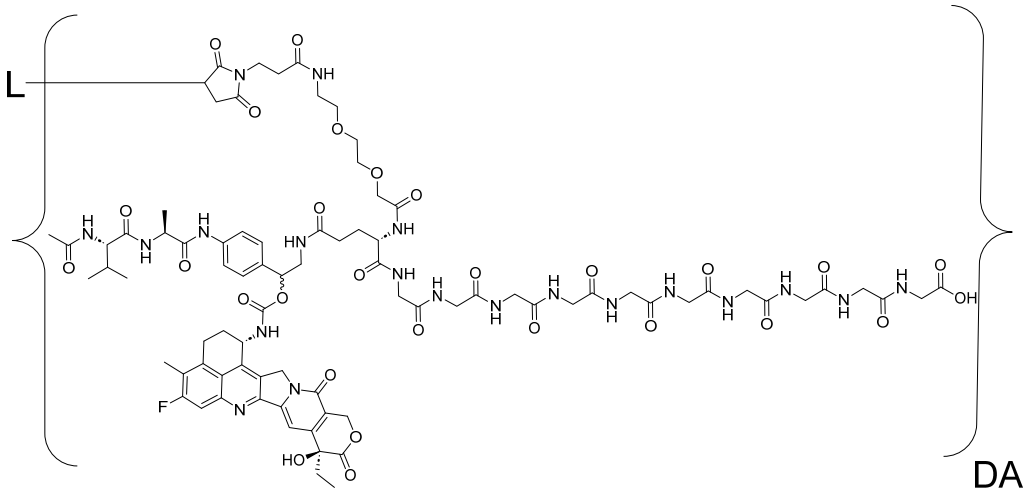
, and



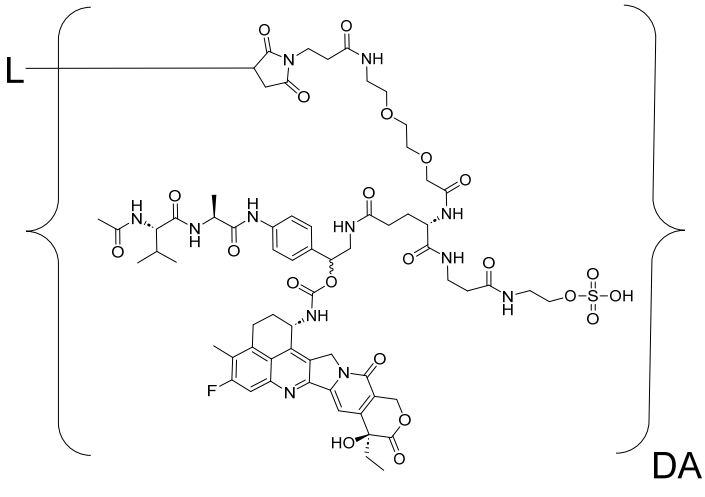
(SEQ ID NOS 27 and 22, respectively, in order of appearance);

wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, the DAR is determined using RP-HPLC. In some cases, the DAR is determined using RP-HPLC as in example 31. In some cases, the DAR is at most about 16. In some cases, the DAR is about 8. In some cases, the DAR is most about 10. In some cases, the DAR is at least about 1. In some cases, the DAR is at least about 2. In some cases, the DAR is at least about 4. In some cases, the DAR is at least about 8. In some cases, the DAR is at most about 8. In some cases, the DAR is from about 1 to about 16. In some cases, the DAR is from about 4 to about 12. In some cases, the DAR is from about 6 to about 10. In some cases, the DAR is from about 7 to about 9. In some cases, the DAR is from about 8 to about 10. In some cases, the DAR is from about 6 to about 8. In some cases, L is UC-961 antibody. In some cases, L is ROR2 antibody. In some cases, L is an antibody or antigen binding portion thereof. In some cases, L is an antibody. In some cases, L is a peptide. In some cases, L includes one or more amino acids.

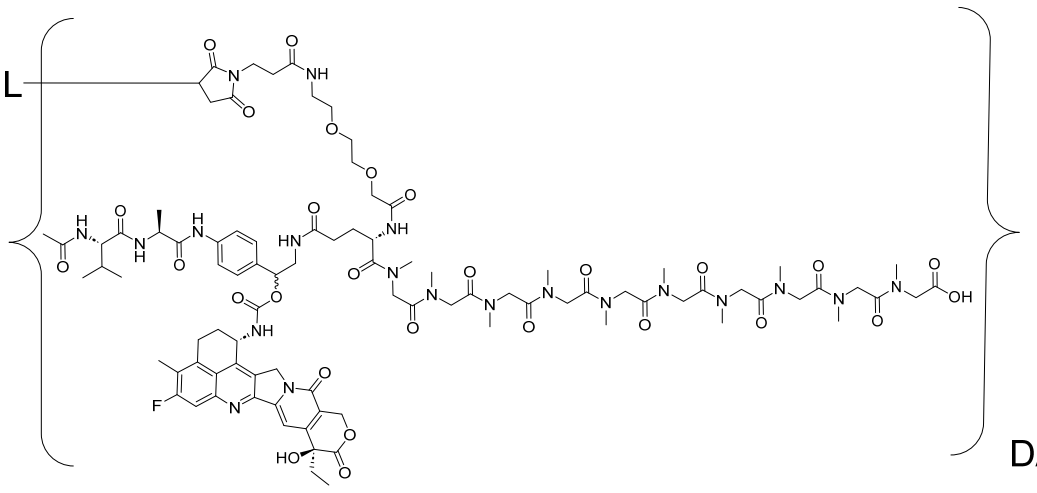
[00199] In some embodiments, a conjugate of Formula (A), is represented by:



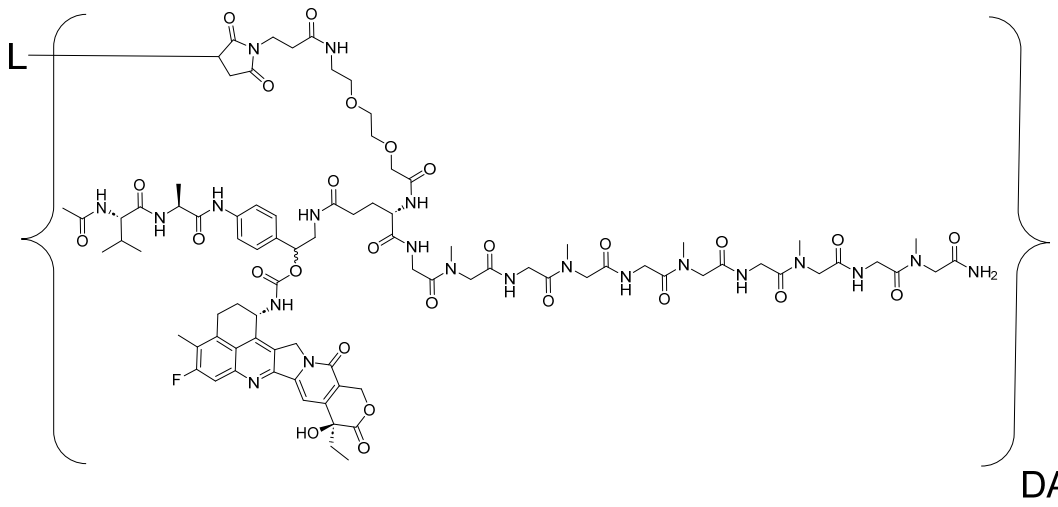
(SEQ ID NO: 24);



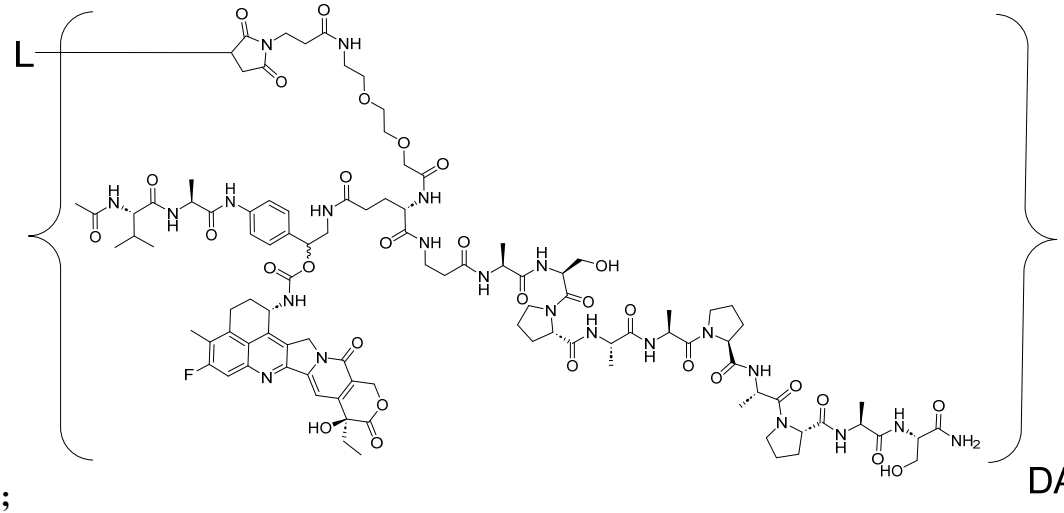
;



(SEQ ID NO: 25);

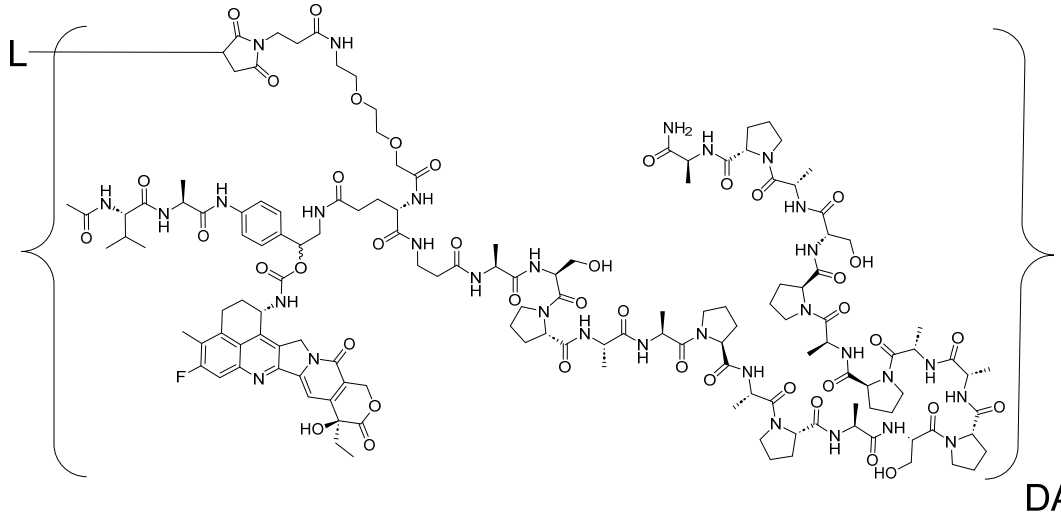


(SEQ ID NO: 26)

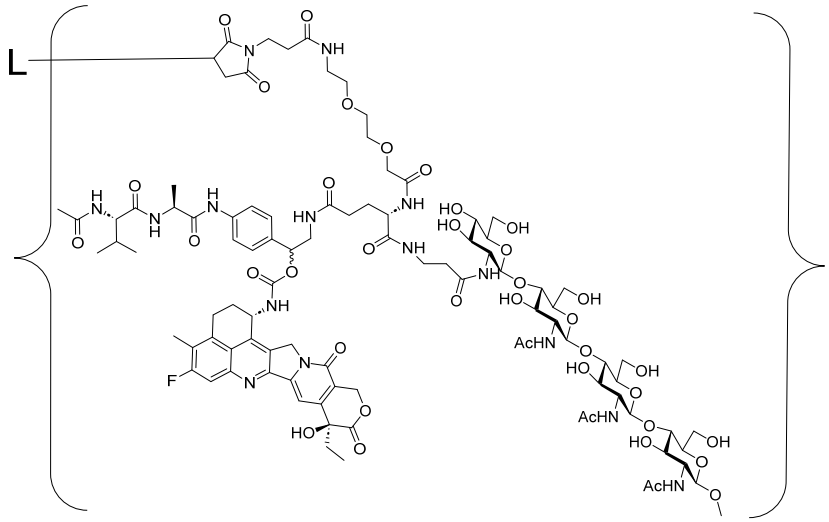


;

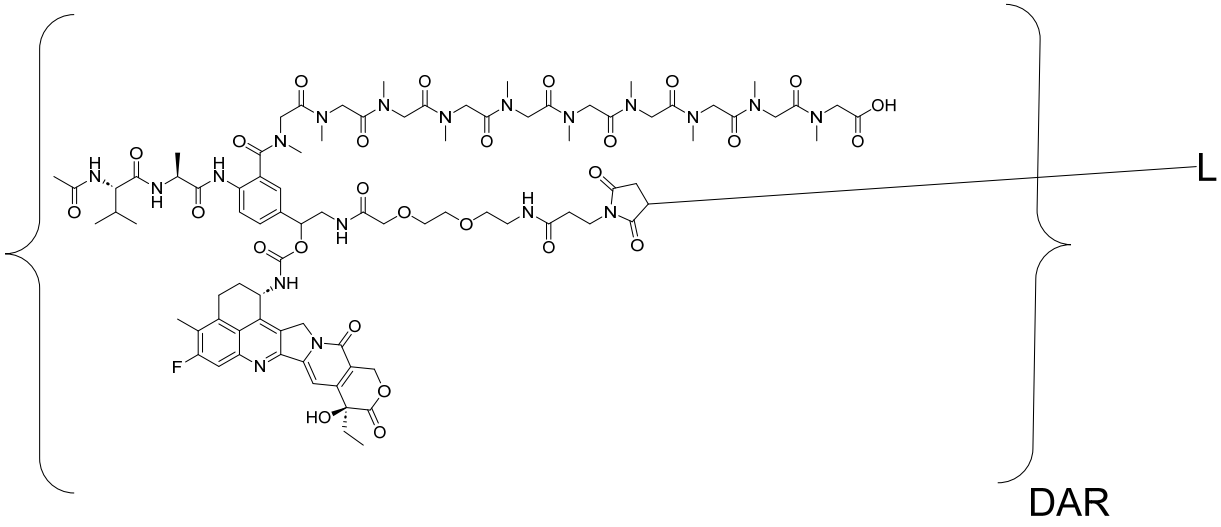
(SEQ ID NO: 27);



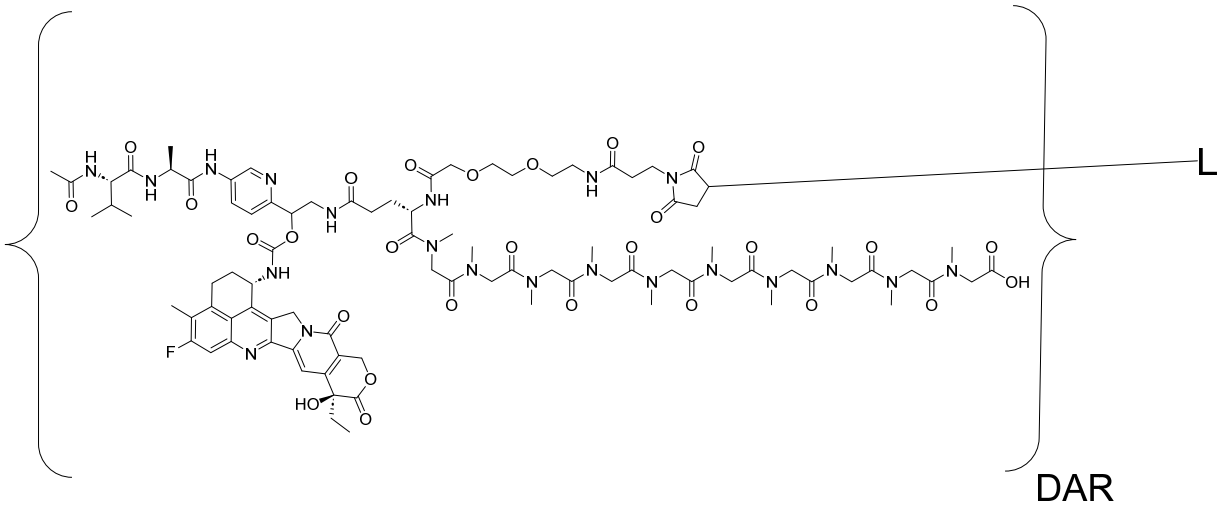
(SEQ ID NO: 28)



; or ; wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, a conjugate of Formula (A), is represented by:



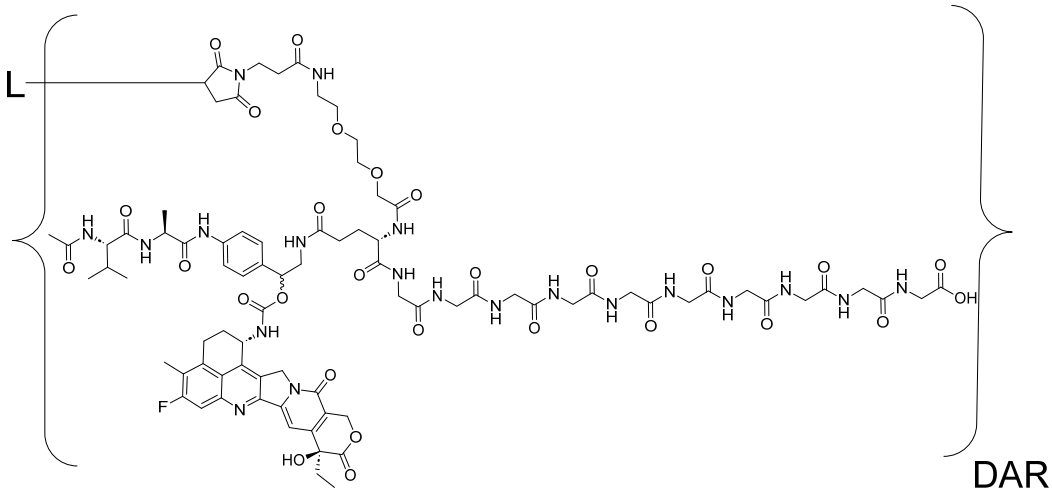
(SEQ ID NO: 29) wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, a conjugate of Formula (A), is represented by:



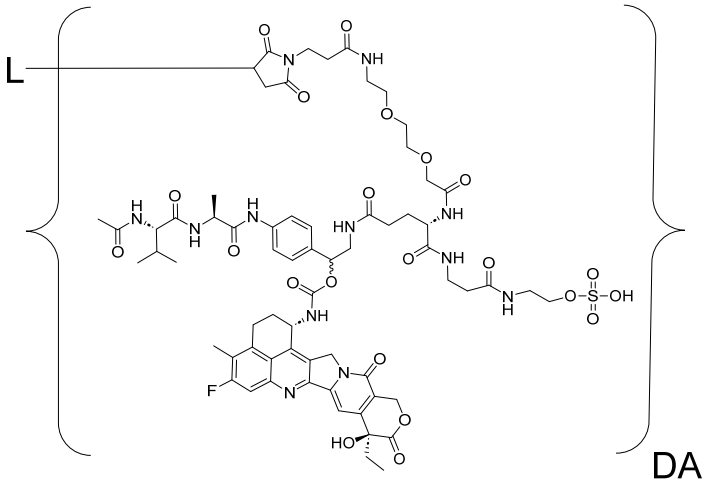
(SEQ ID NO: 25)

wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, the DAR is determined using RP-HPLC. In some cases, the DAR is determined using RP-HPLC as in example 31. In some cases, the DAR is at most about 16. In some cases, the DAR is about 8. In some cases, the DAR is most about 10. In some cases, the DAR is at least about 1. In some cases, the DAR is at least about 2. In some cases, the DAR is at least about 4. In some cases, the DAR is at least about 8. In some cases, the DAR is at most about 8. In some cases, the DAR is from about 1 to about 16. In some cases, the DAR is from about 4 to about 12. In some cases, the DAR is from about 6 to about 10. In some cases, the DAR is from about 7 to about 9. In some cases, the DAR is from about 8 to about 10. In some cases, the DAR is from about 6 to about 8. In some cases, the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:1 and the light chain variable region is SEQ ID NO:2. In some cases the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:3 and the light chain variable region is SEQ ID NO:4. In some cases, L is UC-961 antibody. In some cases, L is ROR2 antibody.

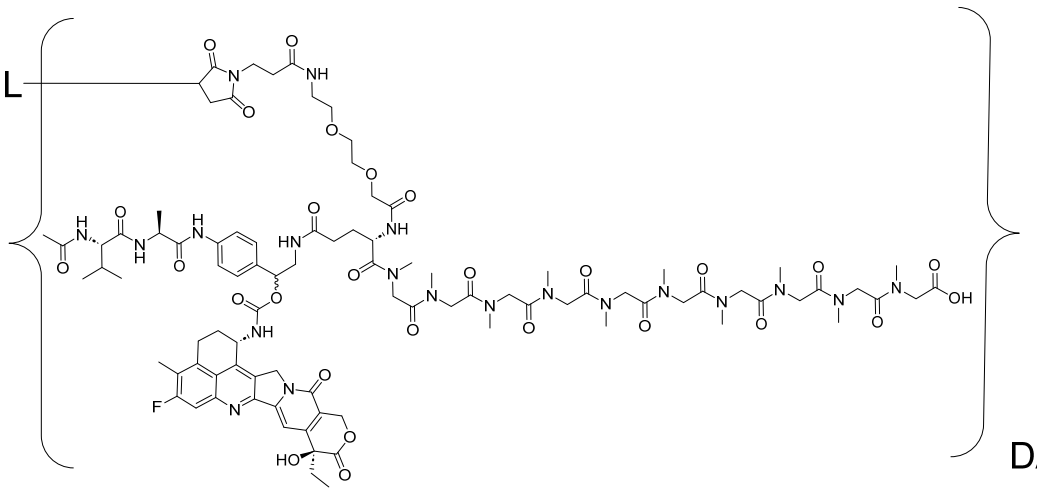
[00200] In some embodiments, a conjugate of Formula (A), is represented by:



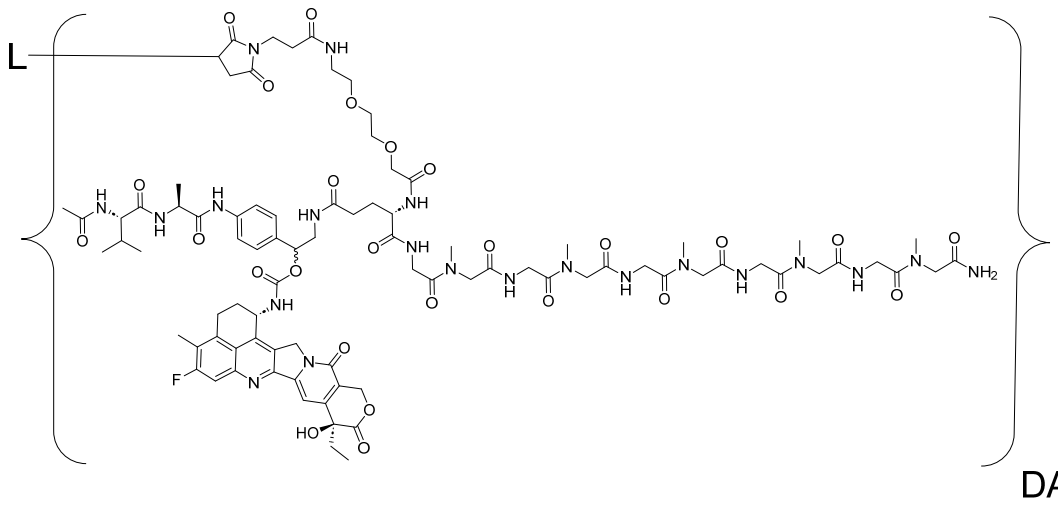
(SEQ ID NO: 24);



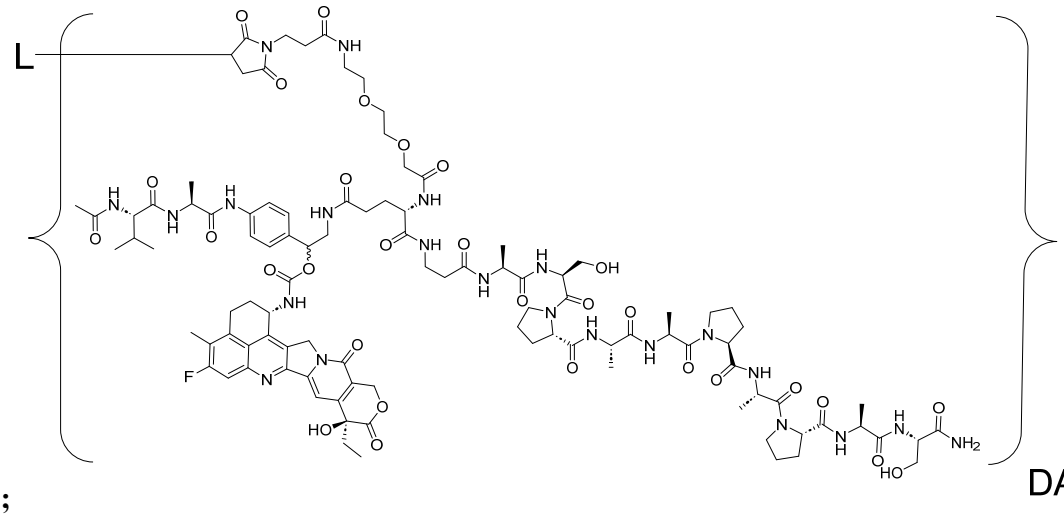
;



(SEQ ID NO: 25);

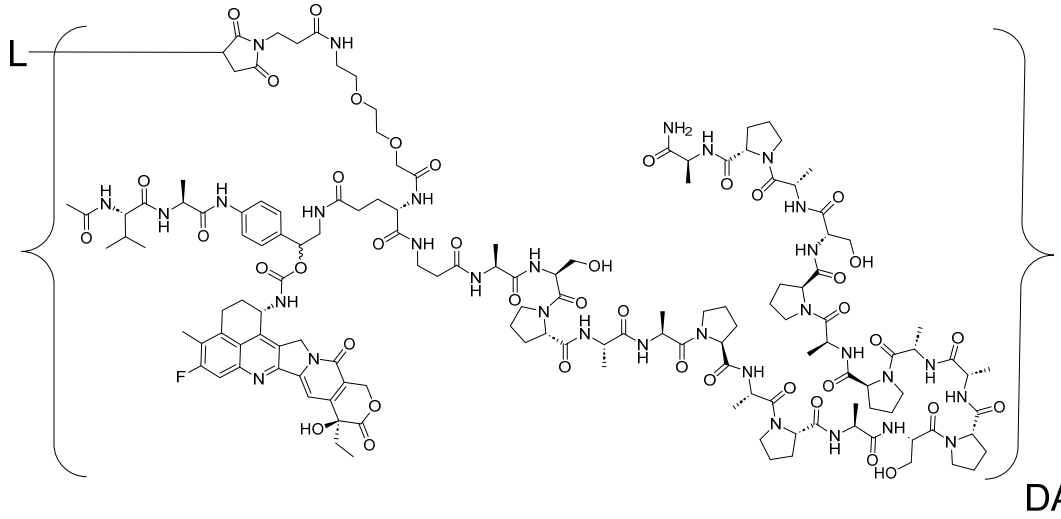


(SEQ ID NO: 26)

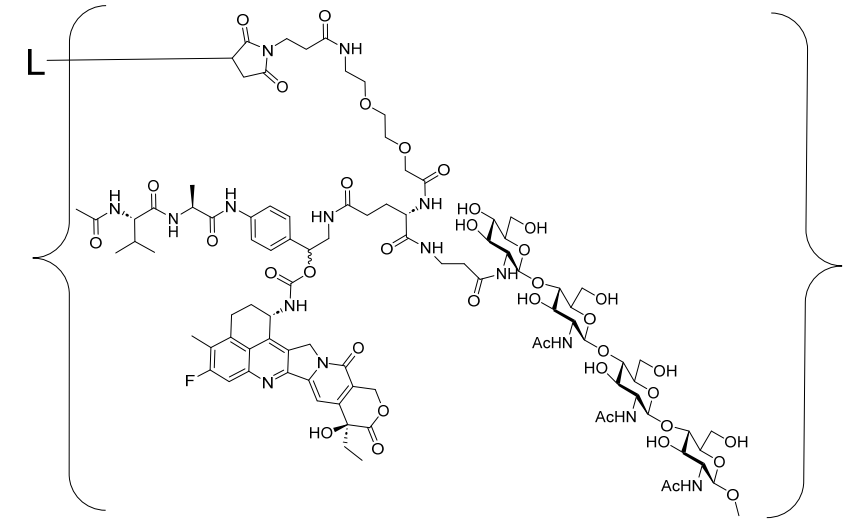


;

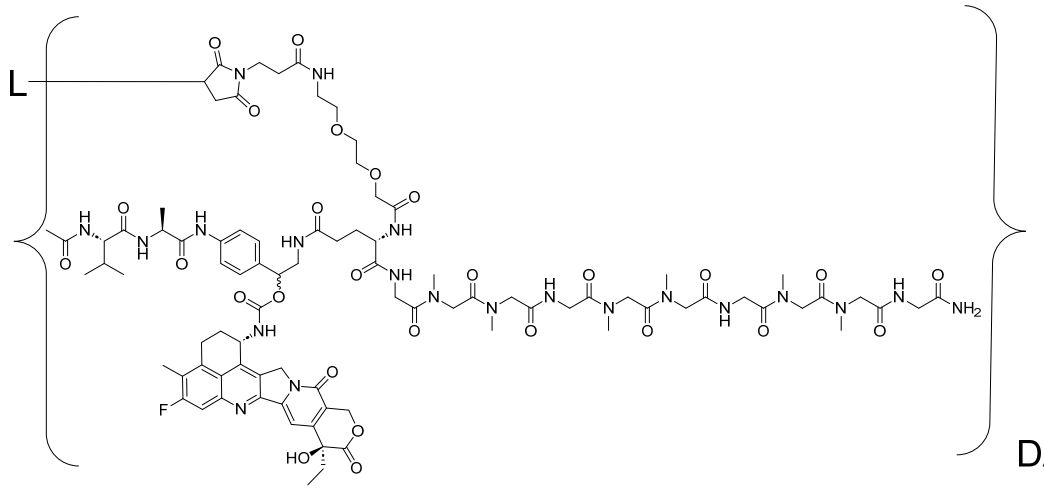
(SEQ ID NO: 27);



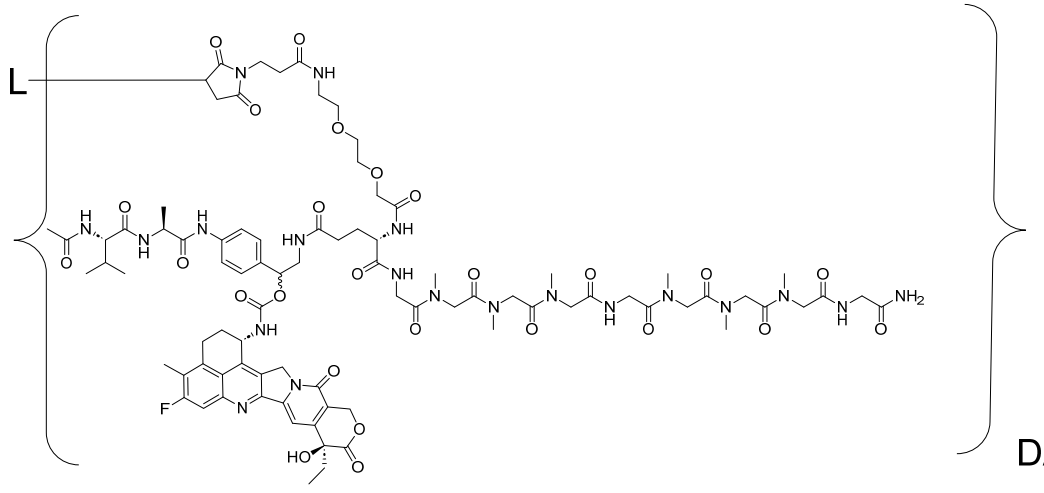
(SEQ ID NO: 28)



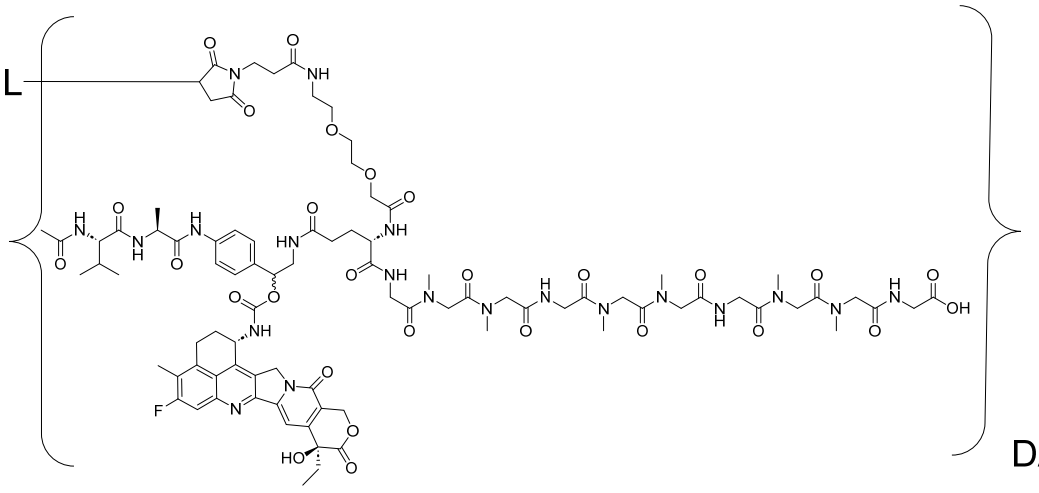
; DAR;



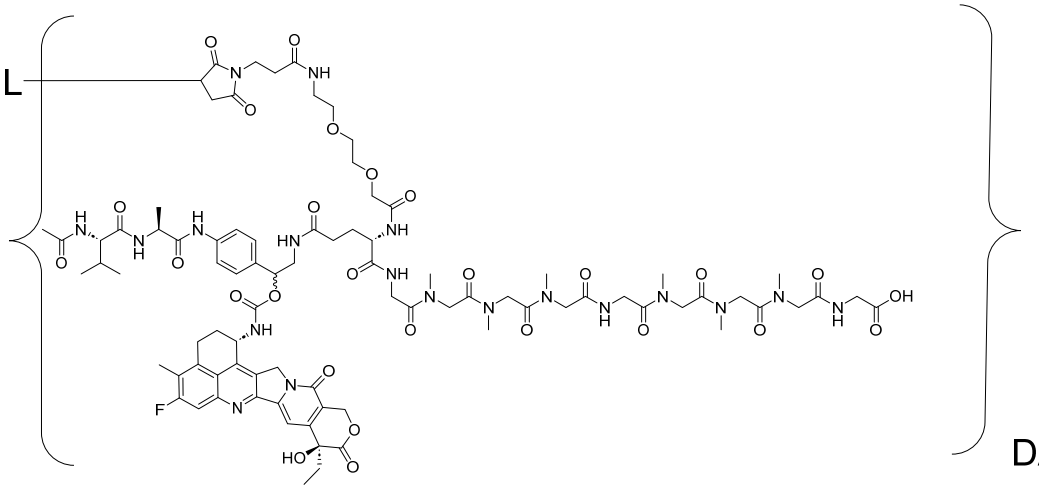
DAR (SEQ ID NO: 31);



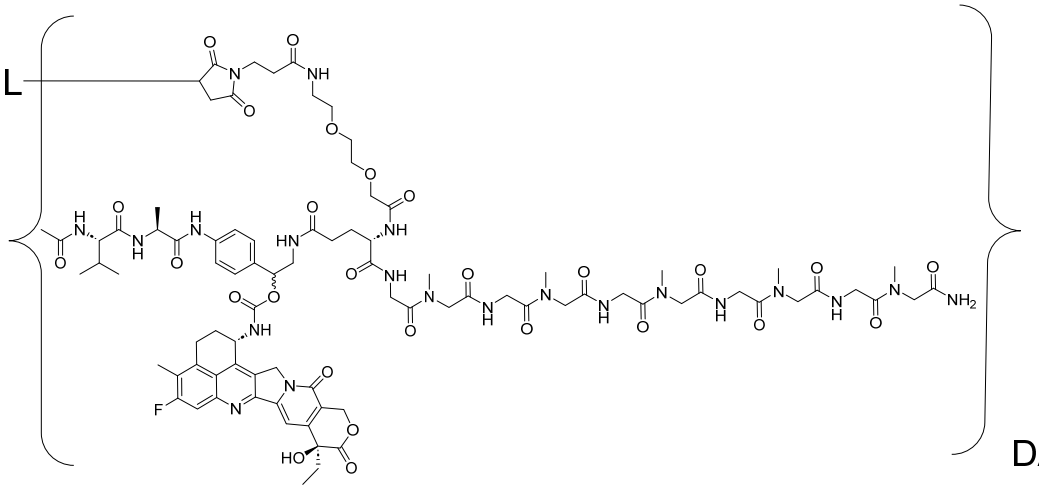
DAR (SEQ ID NO: 32);



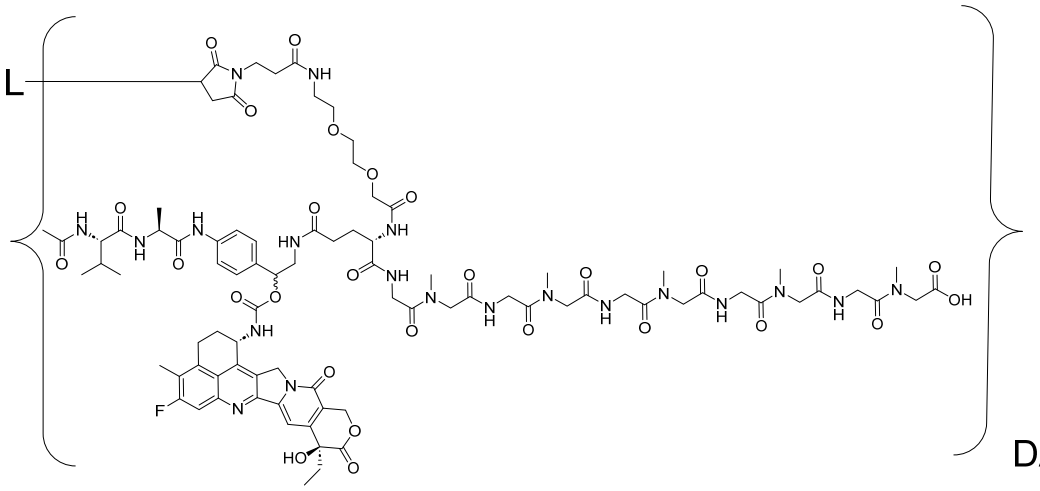
DAR (SEQ ID NO: 31);



DAR (SEQ ID NO: 32);

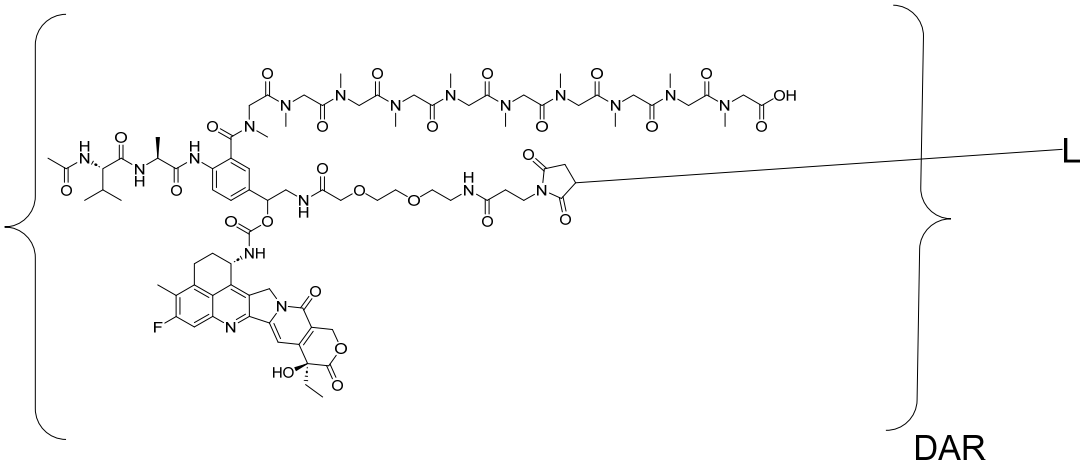


DAR (SEQ ID NO: 26);

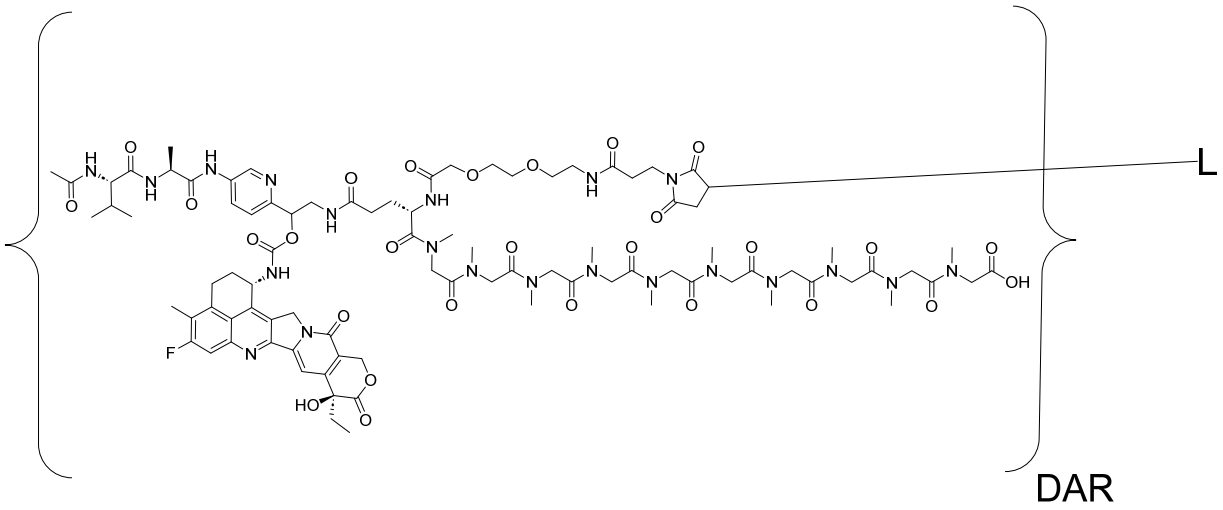


or

(SEQ ID NO: 26); wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, a conjugate of Formula (A), is represented by:

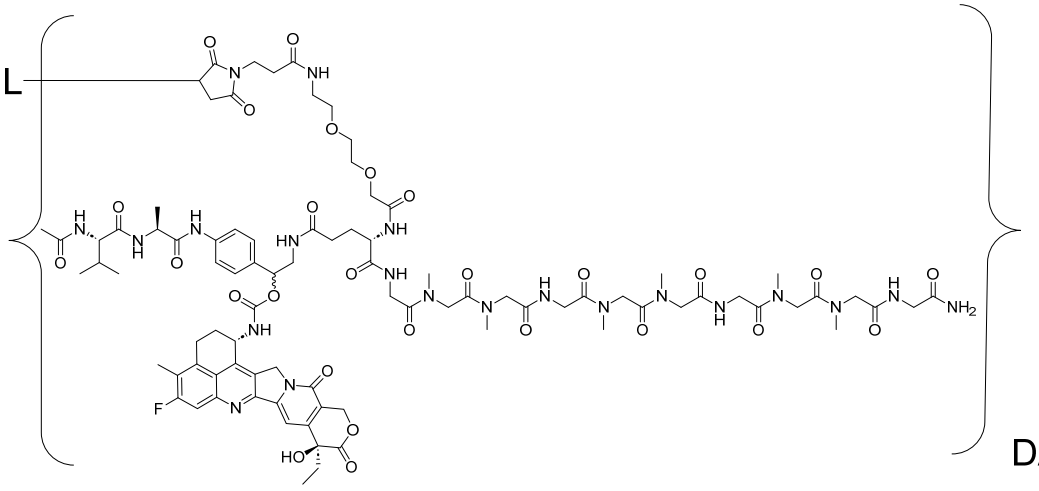


(SEQ ID NO: 29) wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, a conjugate of Formula (A), is represented by:

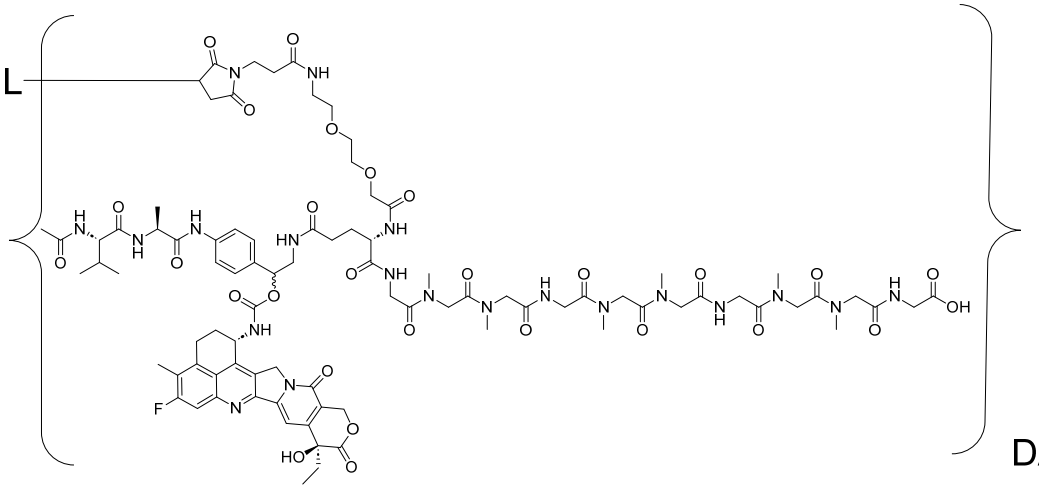


(SEQ ID NO: 25)

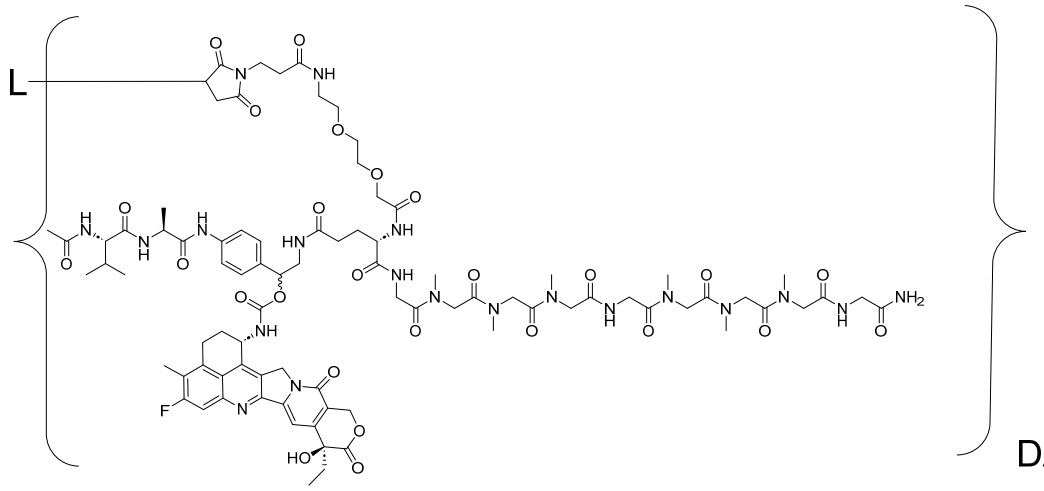
wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, a conjugate of Formula (A), is represented by:



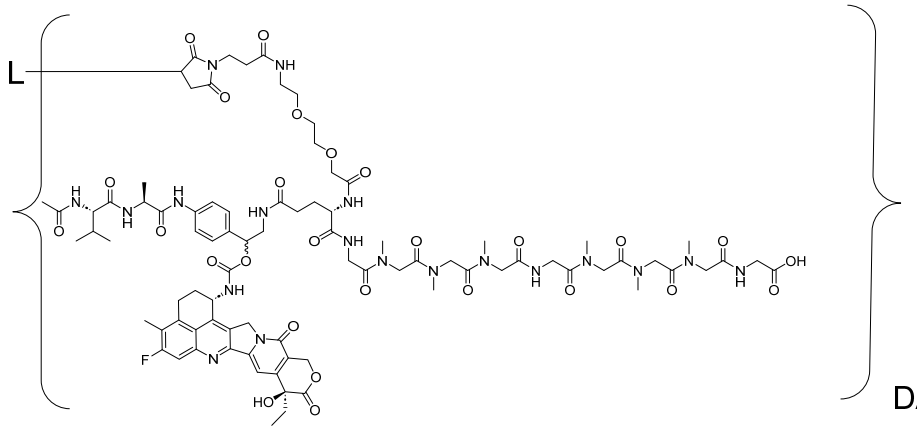
(SEQ ID NO: 31) wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, a conjugate of Formula (A), is represented by:



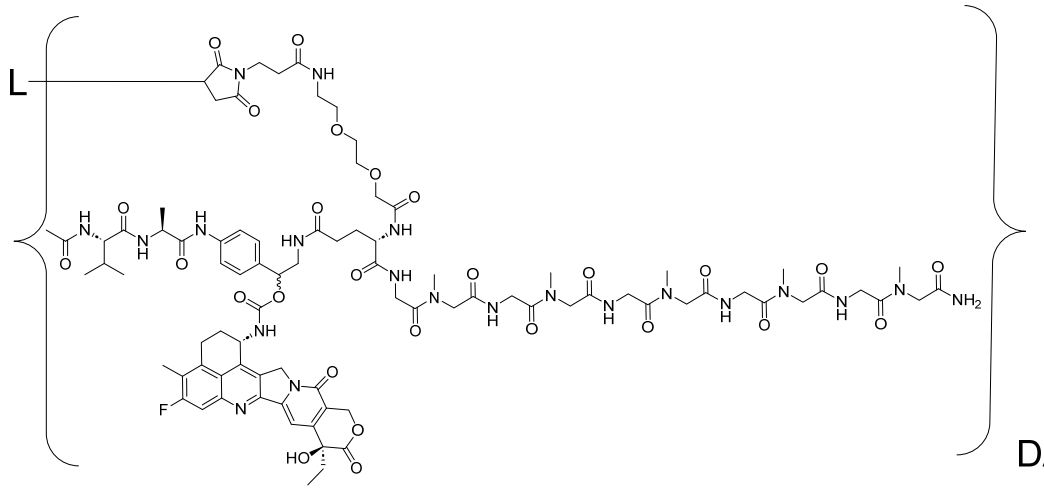
(SEQ ID NO: 31) wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, a conjugate of Formula (A), is represented by:



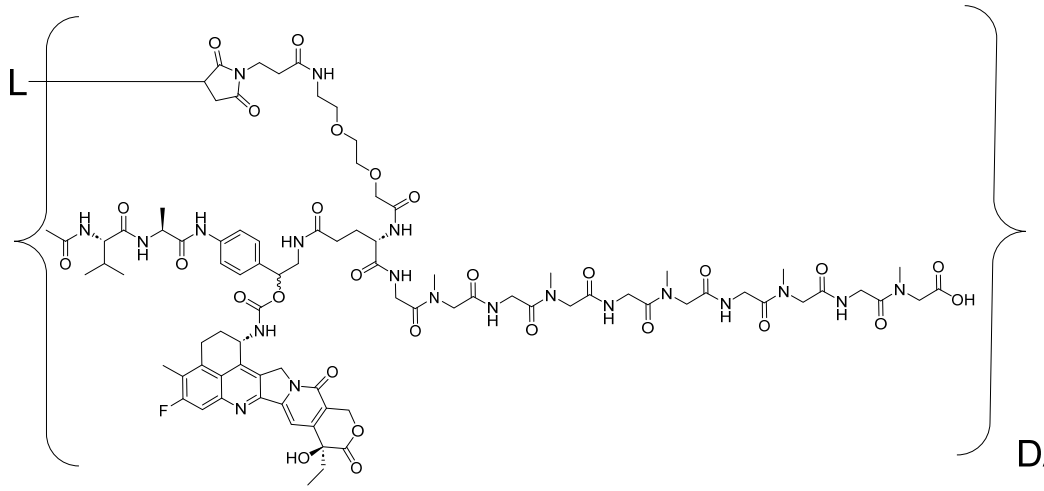
(SEQ ID NO: 32) wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, a conjugate of Formula (A), is represented by:



(SEQ ID NO: 32) wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, a conjugate of Formula (A), is represented by:

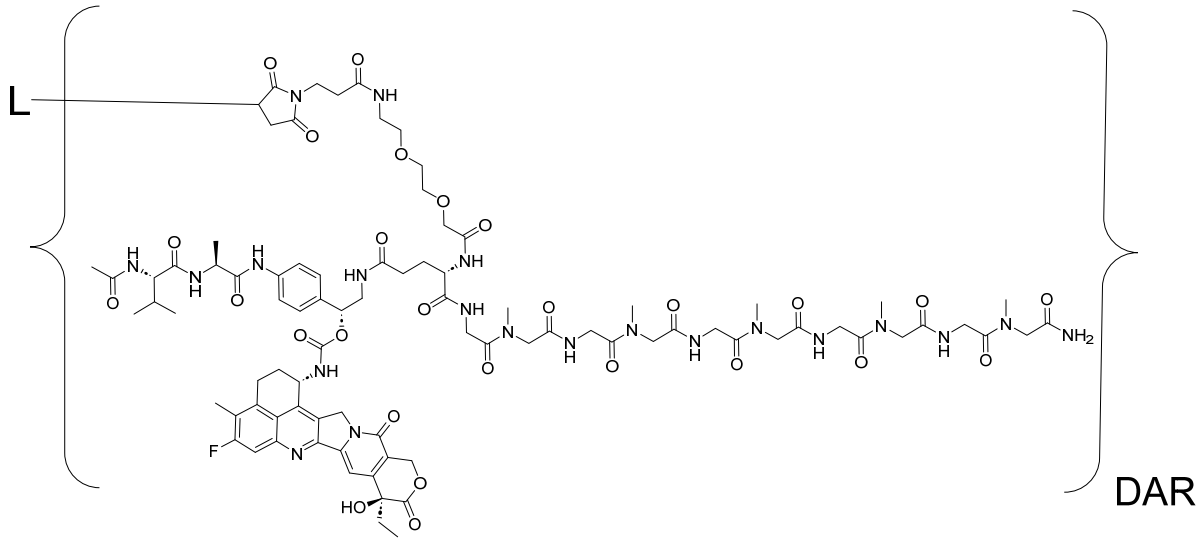


(SEQ ID NO: 26) wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, a conjugate of Formula (A), is represented by:



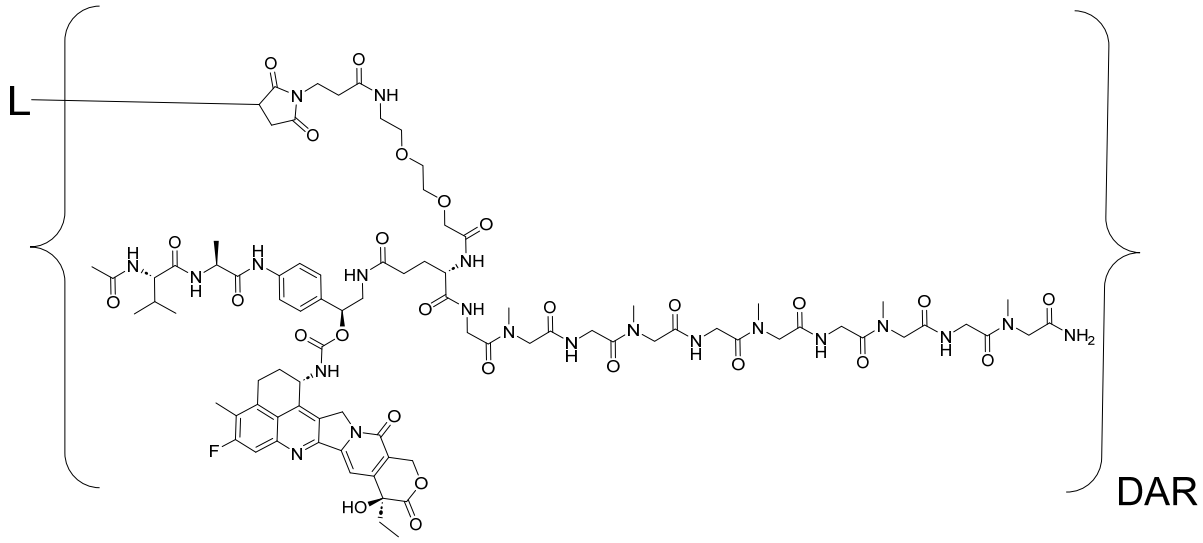
(SEQ ID NO: 26) wherein each L is a Targeting Unit; and each DAR is a drug to antibody ratio. In some cases, the DAR is determined using RP-HPLC. In some cases, the DAR is determined using RP-HPLC as in example 37. In some cases, the DAR is at most about 16. In some cases, the DAR is about 8. In some cases, the DAR is most about 10. In some cases, the DAR is at least about 1. In some cases, the DAR is at least about 2. In some cases, the DAR is at least about 4. In some cases, the DAR is at least about 8. In some cases, the DAR is at most about 8. In some cases, the DAR is from about 1 to about 16. In some cases, the DAR is from about 4 to about 12. In some cases, the DAR is from about 6 to about 10. In some cases, the DAR is from about 7 to about 9. In some cases, the DAR is from about 8 to about 10. In some cases, the DAR is from about 6 to about 8. In some cases, the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:1 and the light chain variable region is SEQ ID NO:2. In some cases the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:3 and the light chain variable region is SEQ ID NO:4. In some cases, L is UC-961 antibody. In some cases, L is ROR2 antibody.

[00201] In some embodiments, the conjugate or salt of Formula (Aa) is represented by:



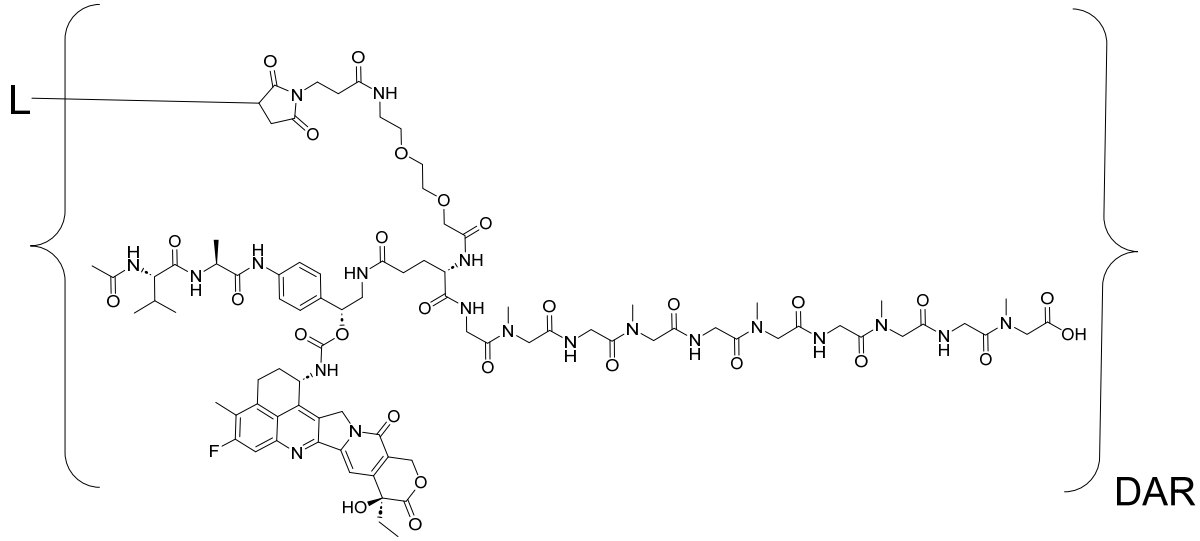
(SEQ ID NO: 26) in some cases, the DAR is determined using RP-HPLC. In some cases, the DAR is determined using RP-HPLC as in example 31. In some cases, the DAR is at most about 16. In some cases, the DAR is about 8. In some cases, the DAR is most about 10. In some cases, the DAR is at least about 1. In some cases, the DAR is at least about 2. In some cases, the DAR is at least about 4. In some cases, the DAR is at least about 8. In some cases, the DAR is at most about 8. In some cases, the DAR is from about 1 to about 16. In some cases, the DAR is from about 4 to about 12. In some cases, the DAR is from about 6 to about 10. In some cases, the DAR is from about 7 to about 9. In some cases, the DAR is from about 8 to about 10. In some cases, the DAR is from about 6 to about 8. In some cases, DAR is a drug (D) to antibody (L) ratio. In some cases, the drug of the DAR is exatecan. In some cases, the drug of the DAR is exatecan. In some cases, the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:1 and the light chain variable region is SEQ ID NO:2. In some cases the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:3 and the light chain variable region is SEQ ID NO:4. In some cases, L is UC-961. In some cases, L is ROR2 antibody. In some cases, L is UC-961 antibody.

[00202] In some embodiments, the conjugate or salt of Formula (Ab) is represented by:



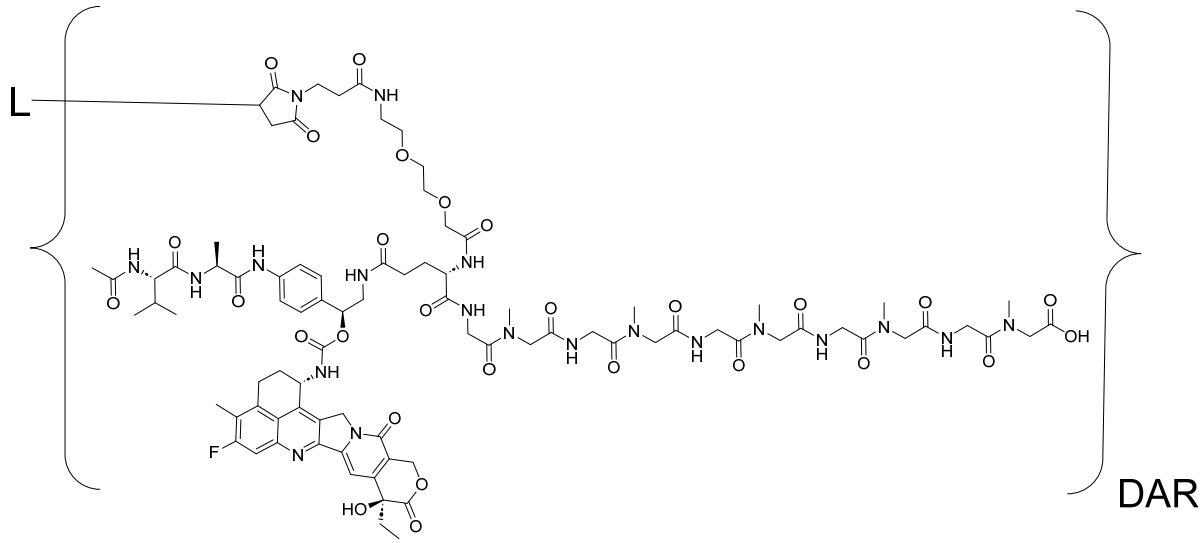
(SEQ ID NO: 26), wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the DAR is determined using RP-HPLC. In some cases, the DAR is determined using RP-HPLC as in example 37. In some cases, the DAR is at most about 16. In some cases, the DAR is about 8. In some cases, the DAR is most about 10. In some cases, the DAR is at least about 1. In some cases, the DAR is at least about 2. In some cases, the DAR is at least about 4. In some cases, the DAR is at least about 8. In some cases, the DAR is at most about 8. In some cases, the DAR is from about 1 to about 16. In some cases, the DAR is from about 4 to about 12. In some cases, the DAR is from about 6 to about 10. In some cases, the DAR is from about 7 to about 9. In some cases, the DAR is from about 8 to about 10. In some cases, the DAR is from about 6 to about 8. In some cases, DAR is a drug (D) to antibody (L) ratio. In some cases, the drug of the DAR is exatecan. In some cases, the drug of the DAR is exatecan. In some cases, the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:1 and the light chain variable region is SEQ ID NO:2. In some cases the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:3 and the light chain variable region is SEQ ID NO:4. In some cases, L is UC-961. In some cases, L is ROR2 antibody. In some cases, L is UC-961.

[00203] In some embodiments, the conjugate or salt of Formula (Aa) is represented by:



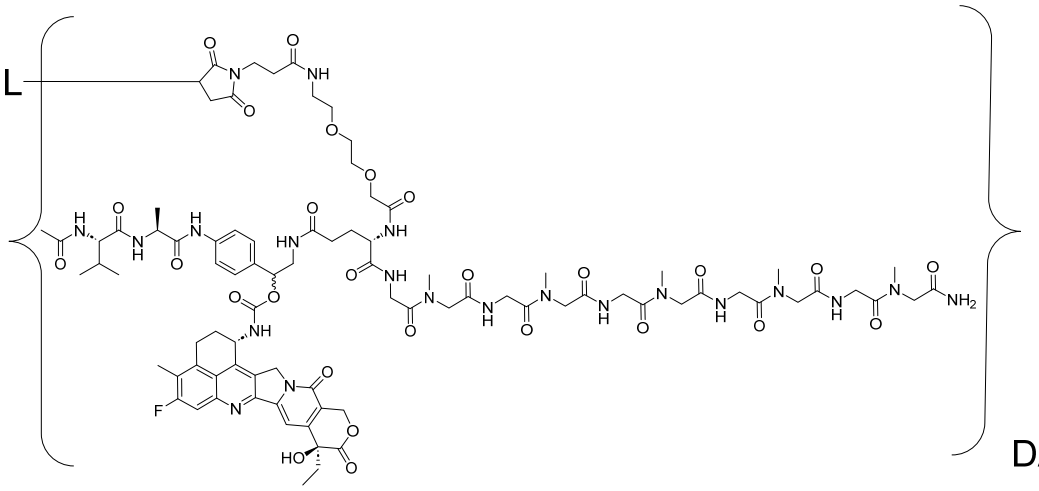
(SEQ ID NO: 26) in some cases, the DAR is determined using RP-HPLC. In some cases, the DAR is determined using RP-HPLC as in example 37. In some cases, the DAR is at most about 16. In some cases, the DAR is about 8. In some cases, the DAR is most about 10. In some cases, the DAR is at least about 1. In some cases, the DAR is at least about 2. In some cases, the DAR is at least about 4. In some cases, the DAR is at least about 8. In some cases, the DAR is at most about 8. In some cases, the DAR is from about 1 to about 16. In some cases, the DAR is from about 4 to about 12. In some cases, the DAR is from about 6 to about 10. In some cases, the DAR is from about 7 to about 9. In some cases, the DAR is from about 8 to about 10. In some cases, the DAR is from about 6 to about 8. In some cases, DAR is a drug (D) to antibody (L) ratio. In some cases, the drug of the DAR is exatecan. In some cases, the drug of the DAR is exatecan. In some cases, the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:1 and the light chain variable region is SEQ ID NO:2. In some cases the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:3 and the light chain variable region is SEQ ID NO:4. In some cases, L is UC-961. In some cases, L is ROR2 antibody. In some cases, the antibody is UC-961.

[00204] In some embodiments, the conjugate or salt of Formula (Ab) is represented by:



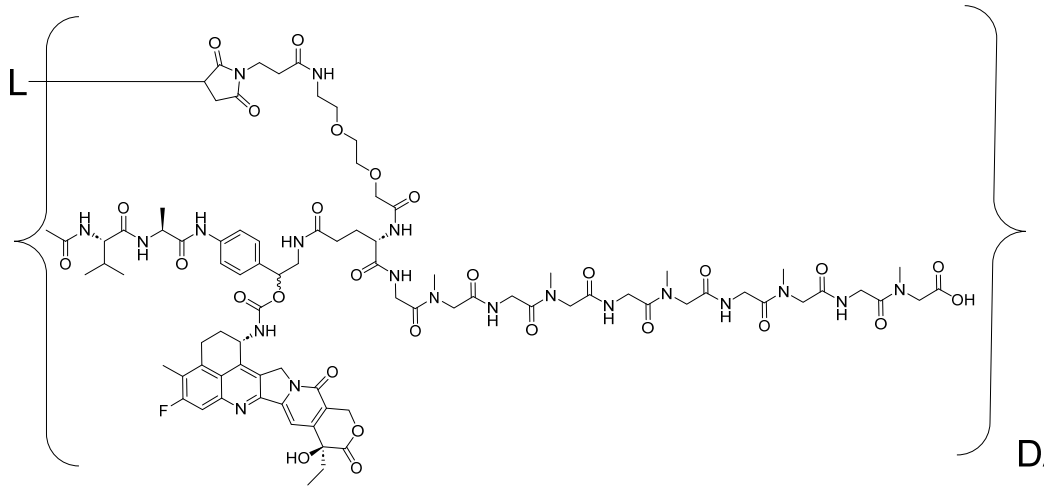
(SEQ ID NO: 26), wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the DAR is determined using RP-HPLC. In some cases, the DAR is determined using RP-HPLC as in example 37. In some cases, the DAR is at most about 16. In some cases, the DAR is about 8. In some cases, the DAR is most about 10. In some cases, the DAR is at least about 1. In some cases, the DAR is at least about 2. In some cases, the DAR is at least about 4. In some cases, the DAR is at least about 8. In some cases, the DAR is at most about 8. In some cases, the DAR is from about 1 to about 16. In some cases, the DAR is from about 4 to about 12. In some cases, the DAR is from about 6 to about 10. In some cases, the DAR is from about 7 to about 9. In some cases, the DAR is from about 8 to about 10. In some cases, the DAR is from about 6 to about 8. In some cases, DAR is a drug (D) to antibody (L) ratio. In some cases, the drug of the DAR is exatecan. In some cases, the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:1 and the light chain variable region is SEQ ID NO:2. In some cases the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:3 and the light chain variable region is SEQ ID NO:4. In some cases, L is UC-961. In some cases, L is ROR2 antibody. In some cases, the drug of the DAR is exatecan. In some cases, the antibody is UC-961.

[00205] In some embodiments, the conjugate or salt of Formula (Ab) is represented by:



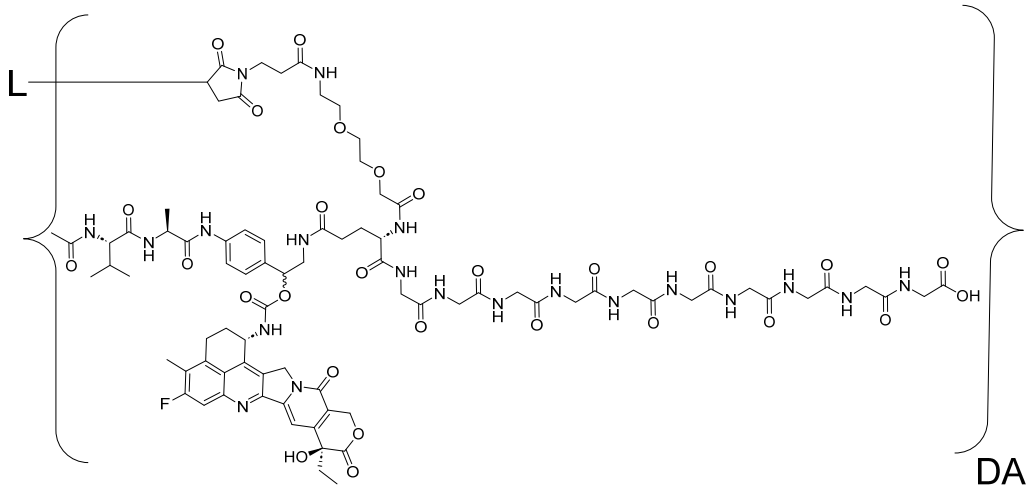
(SEQ ID NO: 26) in some cases, the DAR is determined using RP-HPLC. In some cases, the DAR is determined using RP-HPLC as in example 37. In some cases, the DAR is at most about 16. In some cases, the DAR is about 8. In some cases, the DAR is most about 10. In some cases, the DAR is at least about 1. In some cases, the DAR is at least about 2. In some cases, the DAR is at least about 4. In some cases, the DAR is at least about 8. In some cases, the DAR is at most about 8. In some cases, the DAR is from about 1 to about 16. In some cases, the DAR is from about 4 to about 12. In some cases, the DAR is from about 6 to about 10. In some cases, the DAR is from about 7 to about 9. In some cases, the DAR is from about 8 to about 10. In some cases, the DAR is from about 6 to about 8. In some cases, DAR is a drug (D) to antibody (L) ratio. In some cases, the drug of the DAR is exatecan. In some cases, the drug of the DAR is exatecan. In some cases, the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:1 and the light chain variable region is SEQ ID NO:2. In some cases the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:3 and the light chain variable region is SEQ ID NO:4. In some cases, L is UC-961. In some cases, L is ROR2 antibody. In some cases, the antibody is UC-961.

[00206] In some embodiments, the conjugate or salt of Formula (Ab) is represented by:

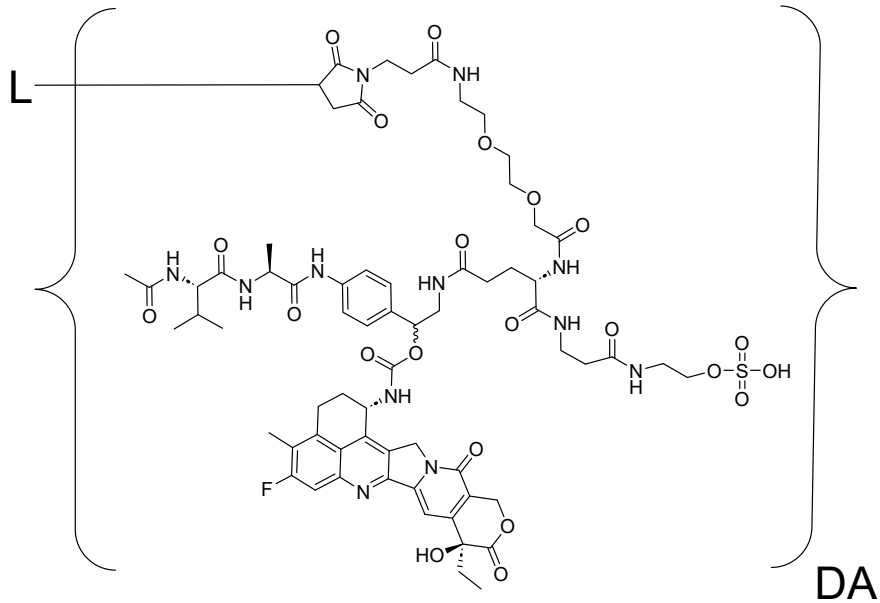


(SEQ ID NO: 26), wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the DAR is determined using RP-HPLC. In some cases, the DAR is determined using RP-HPLC as in example 37. In some cases, the DAR is at most about 16. In some cases, the DAR is about 8. In some cases, the DAR is most about 10. In some cases, the DAR is at least about 1. In some cases, the DAR is at least about 2. In some cases, the DAR is at least about 4. In some cases, the DAR is at least about 8. In some cases, the DAR is at most about 8. In some cases, the DAR is from about 1 to about 16. In some cases, the DAR is from about 4 to about 12. In some cases, the DAR is from about 6 to about 10. In some cases, the DAR is from about 7 to about 9. In some cases, the DAR is from about 8 to about 10. In some cases, the DAR is from about 6 to about 8. In some cases, DAR is a drug (D) to antibody (L) ratio. In some cases, the drug of the DAR is exatecan. In some cases, the drug of the DAR is exatecan. In some cases, the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:1 and the light chain variable region is SEQ ID NO:2. In some cases the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:3 and the light chain variable region is SEQ ID NO:4. In some cases, L is UC-961. In some cases, L is ROR2 antibody. In some cases, the antibody is UC-961.

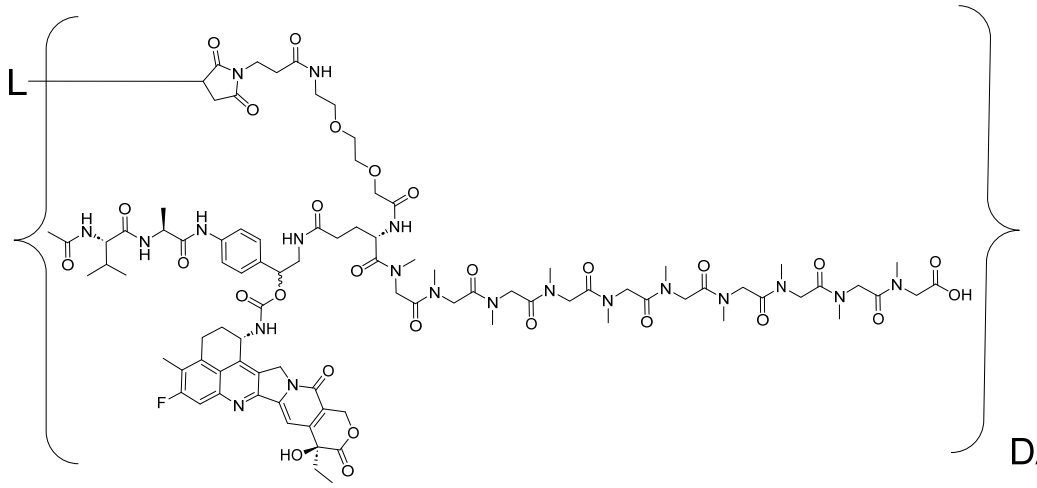
[00207] In some embodiments, the conjugate or salt of Formula (XX), Formula (XXIII), or Formula (A), the conjugate is represented by



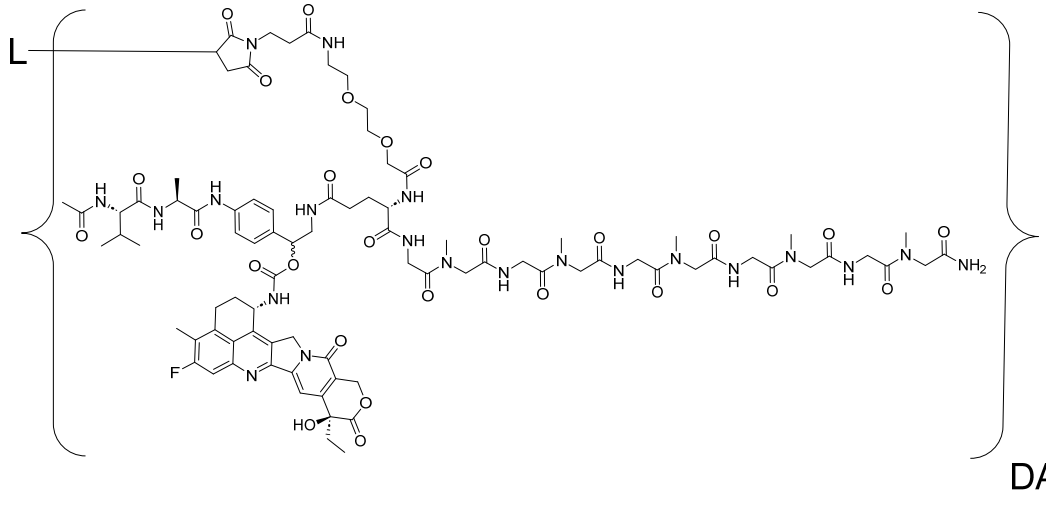
DAR (SEQ ID NO: 24), wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the conjugate is represented by



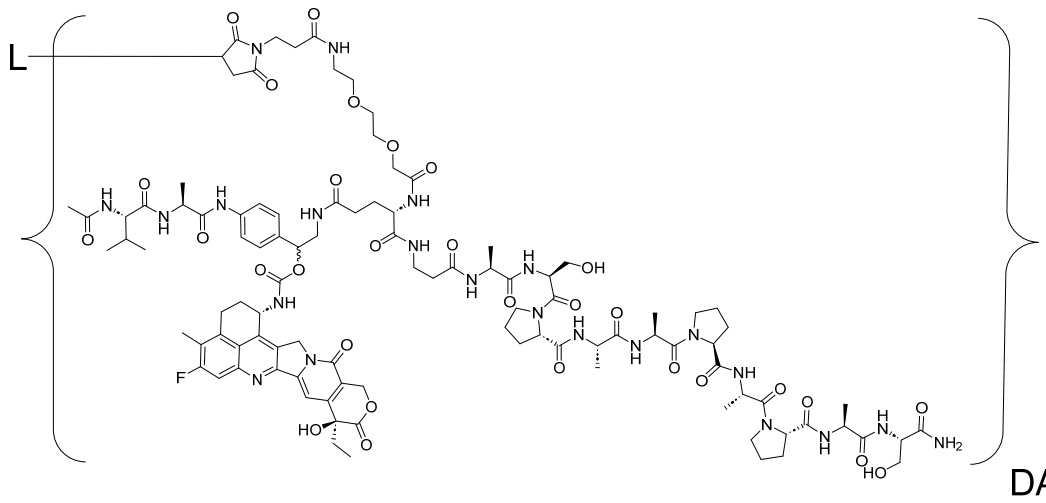
DAR, wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the conjugate is represented by



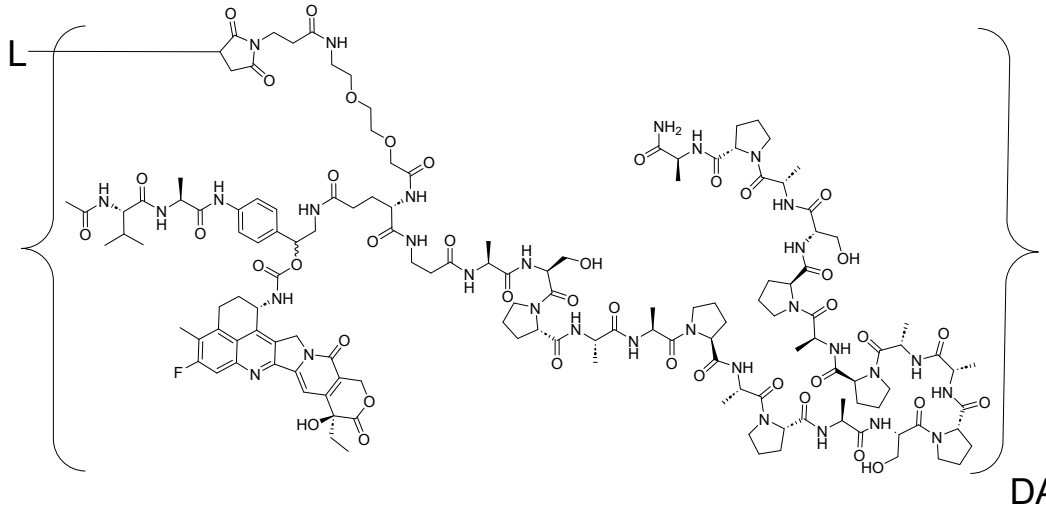
(SEQ ID NO: 25), wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the conjugate is represented by



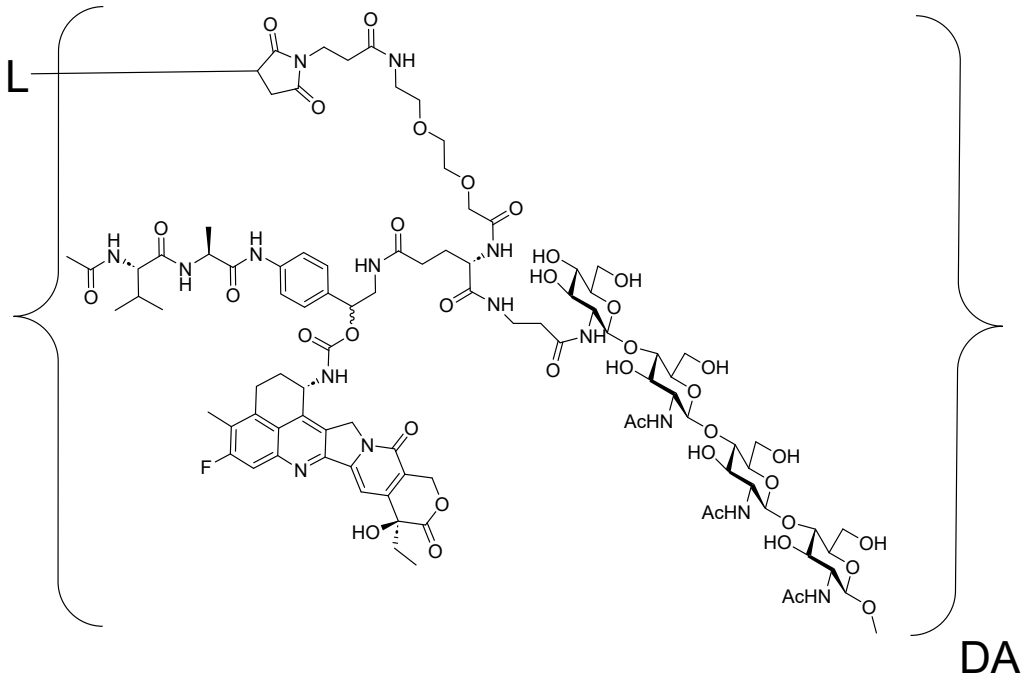
(SEQ ID NO: 26), wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the conjugate is represented by



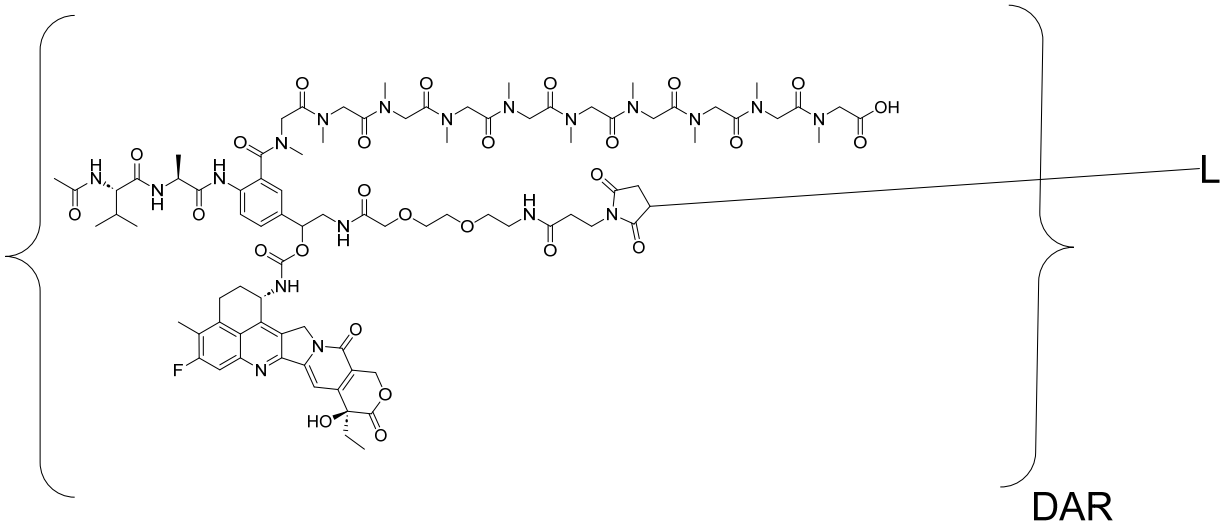
DAR (SEQ ID NO: 27), wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the conjugate is represented by



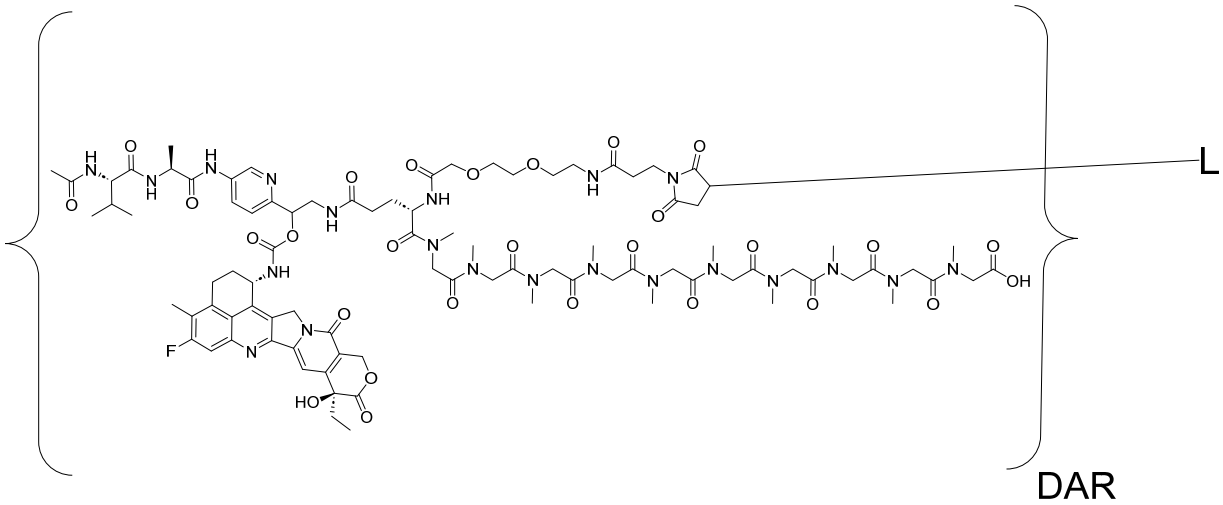
DAR (SEQ ID NO: 28), wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the conjugate is represented by



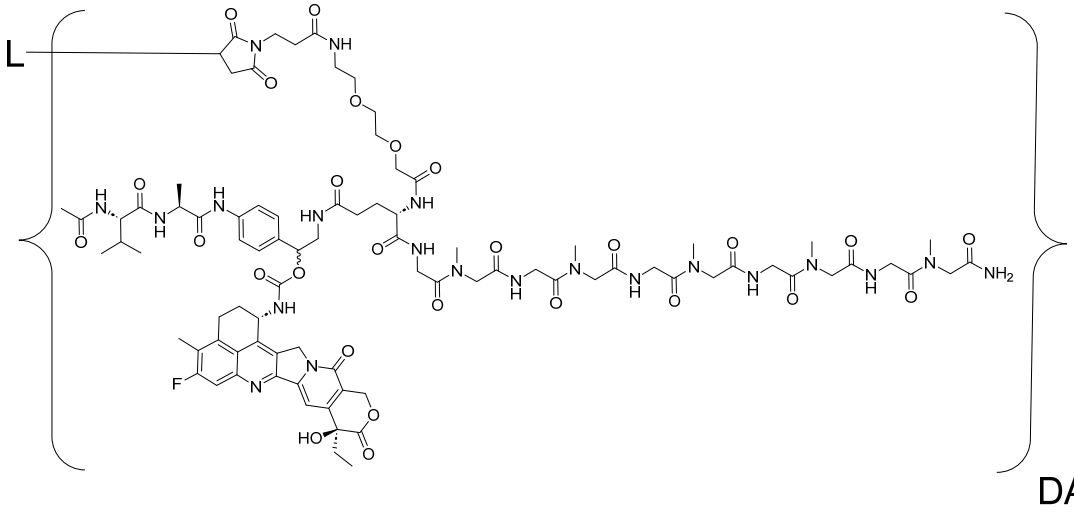
, wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the conjugate is represented by



(SEQ ID NO: 29), wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the conjugate is represented by



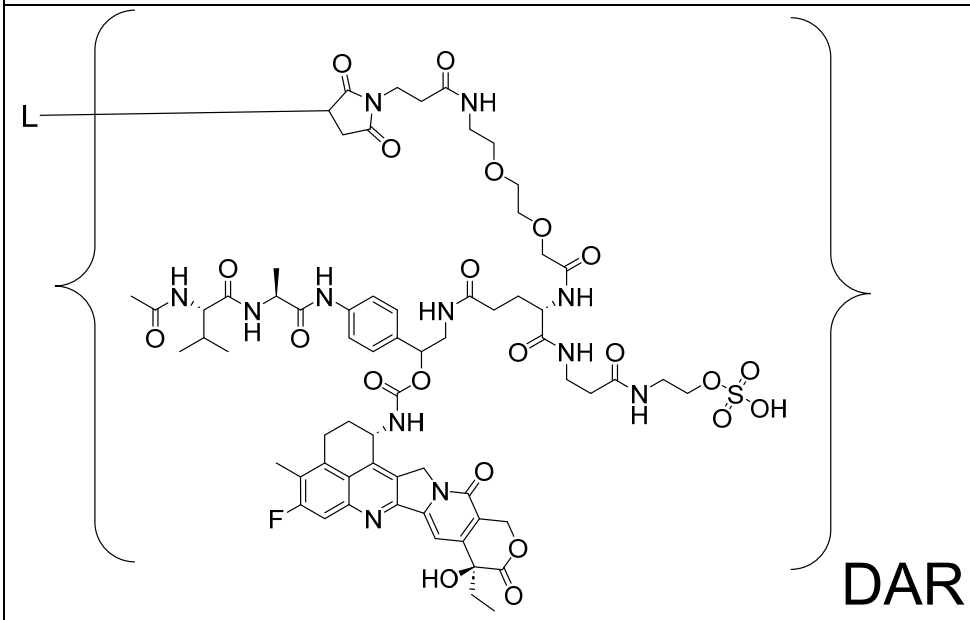
(SEQ ID NO: 25), wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the conjugate is represented by

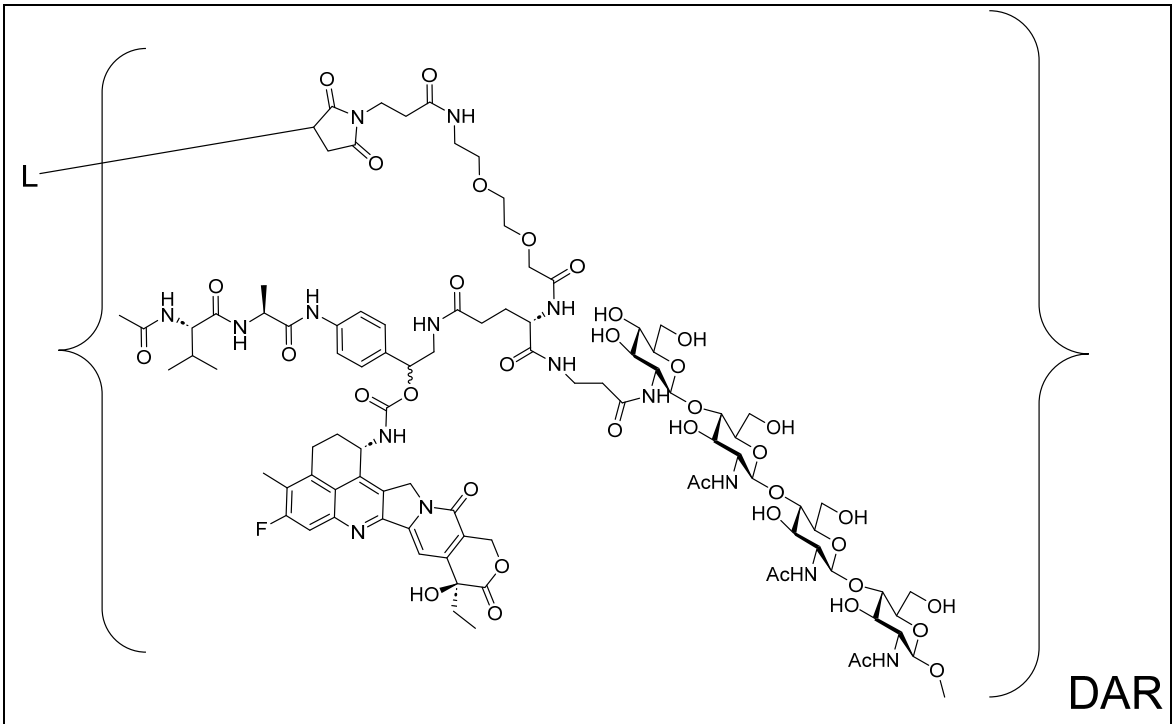


(SEQ ID NO: 26), wherein L is the Targeting Unit; and DAR is a drug to antibody ratio. In some cases, the DAR is determined using RP-HPLC. In some cases, the DAR is determined using RP-HPLC as in example 37. In some cases, the DAR is at most about 16. In some cases, the DAR is about 8. In some cases, the DAR is most about 10. In some cases, the DAR is at least about 1. In some cases, the DAR is at least about 2. In some cases, the DAR is at least about 4. In some cases, the DAR is at least about 8. In some cases, the DAR is at most about 8. In some cases, the DAR is from about 1 to about 16. In some cases, the DAR is from about 4 to about 12. In some cases, the DAR is from about 6 to about 10. In some cases, the DAR is from about 7 to about 9. In some cases, the DAR is from about 8 to about 10. In some cases, the DAR is from about 6 to about 8. In some cases, DAR is a drug (D) to antibody (L) ratio. In some cases, the drug of the DAR is exatecan. In some cases, the drug of the DAR is exatecan. In some cases, the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable

(VL) region, wherein the heavy chain variable region is SEQ ID NO:1 and the light chain variable region is SEQ ID NO:2. In some cases the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:3 and the light chain variable region is SEQ ID NO:4. In some cases, L is UC-961. In some cases, L is ROR2 antibody. In some cases, L is UC-961 antibody.

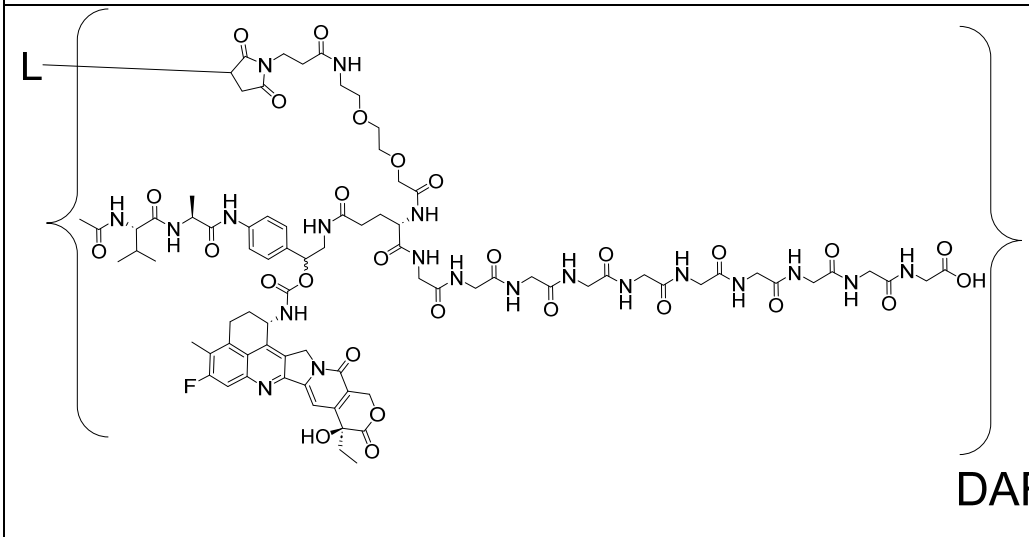
Table A: Specific Conjugates of the Disclosure

Conjugates
 1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or 2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



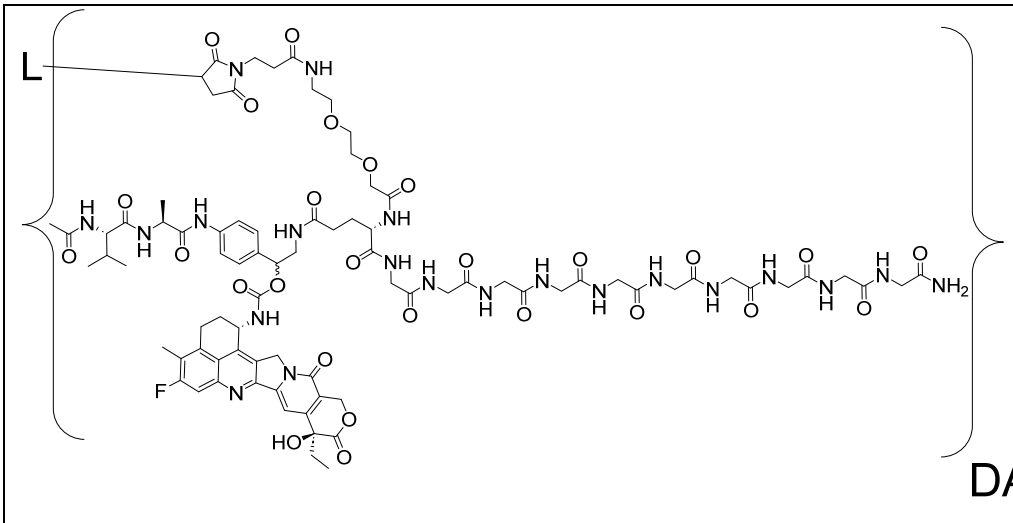
,

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



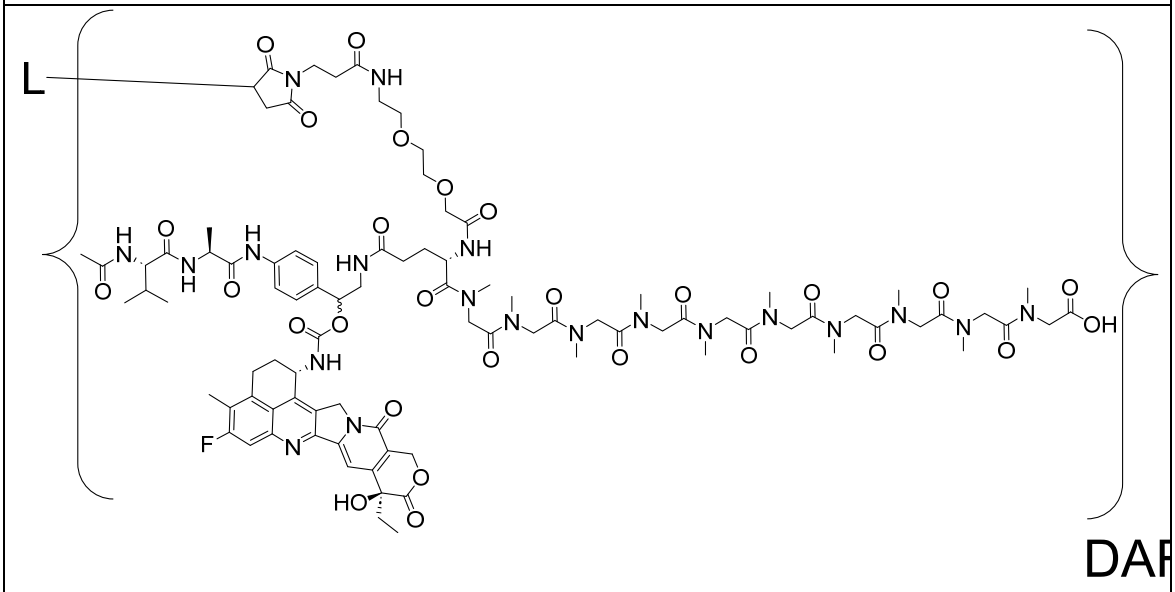
(SEQ ID NO: 24)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



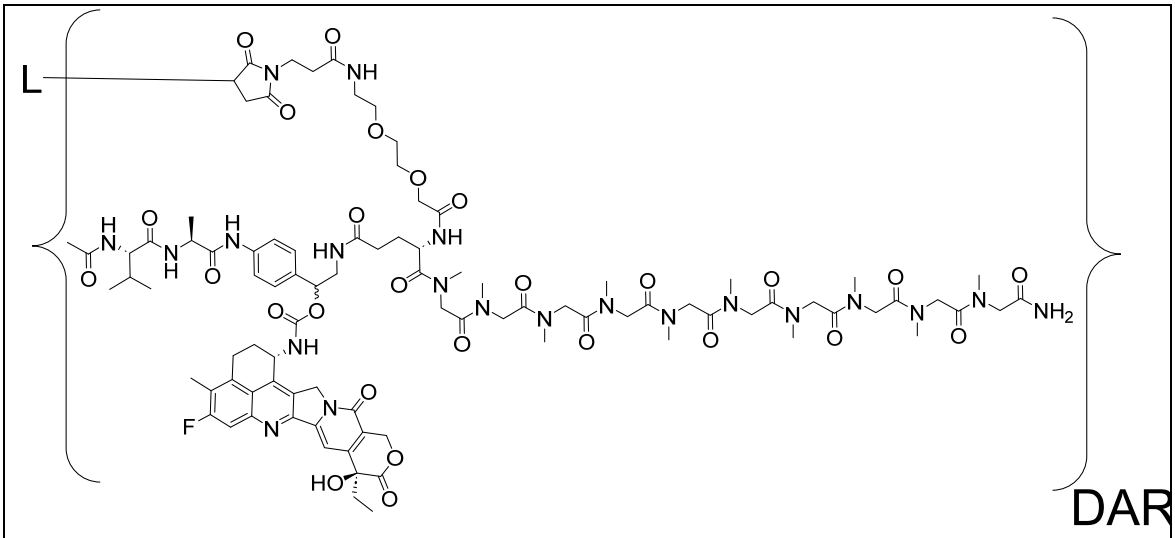
(SEQ ID NO: 24)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



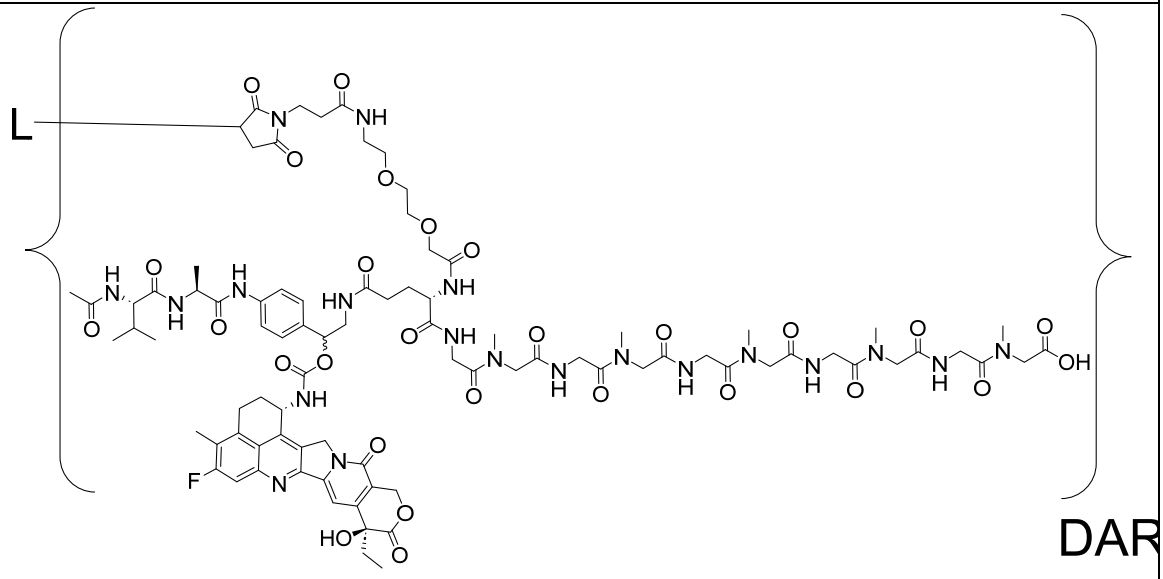
(SEQ ID NO: 25)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



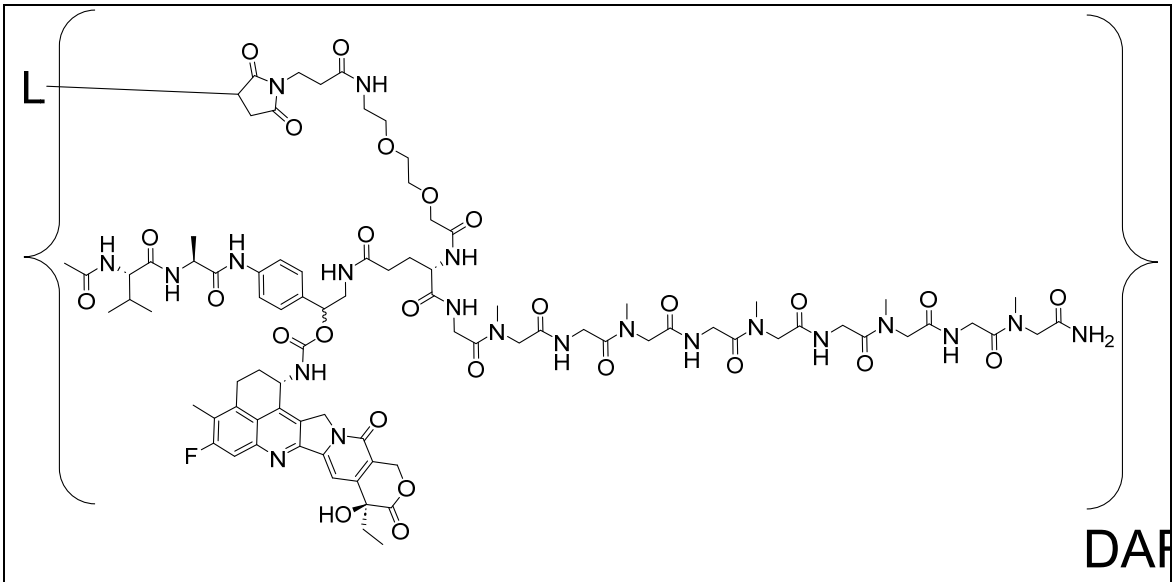
(SEQ ID NO: 25)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



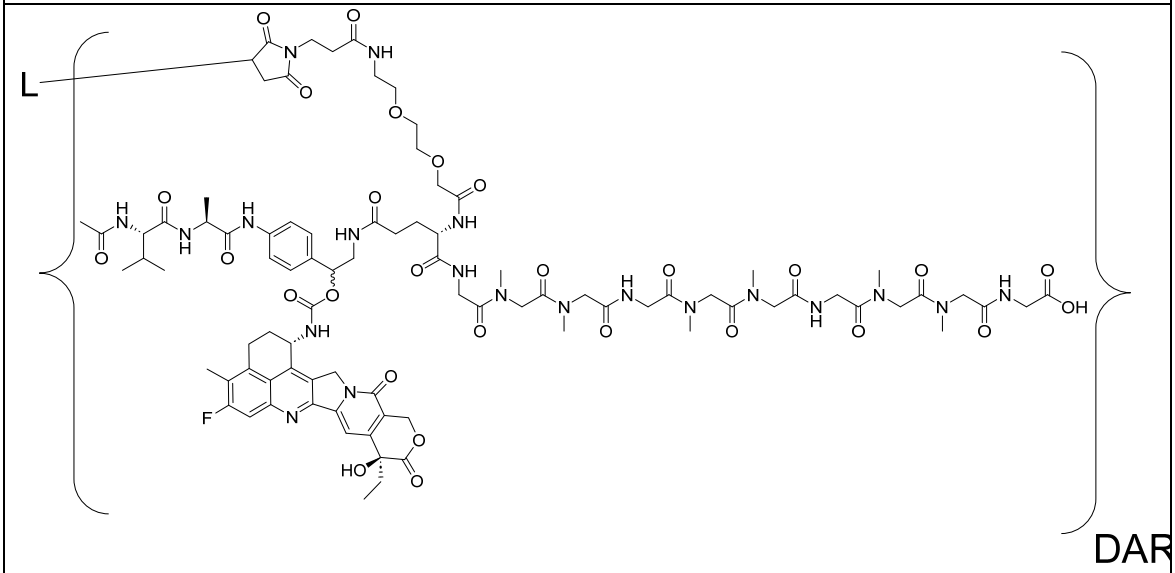
(SEQ ID NO: 26)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



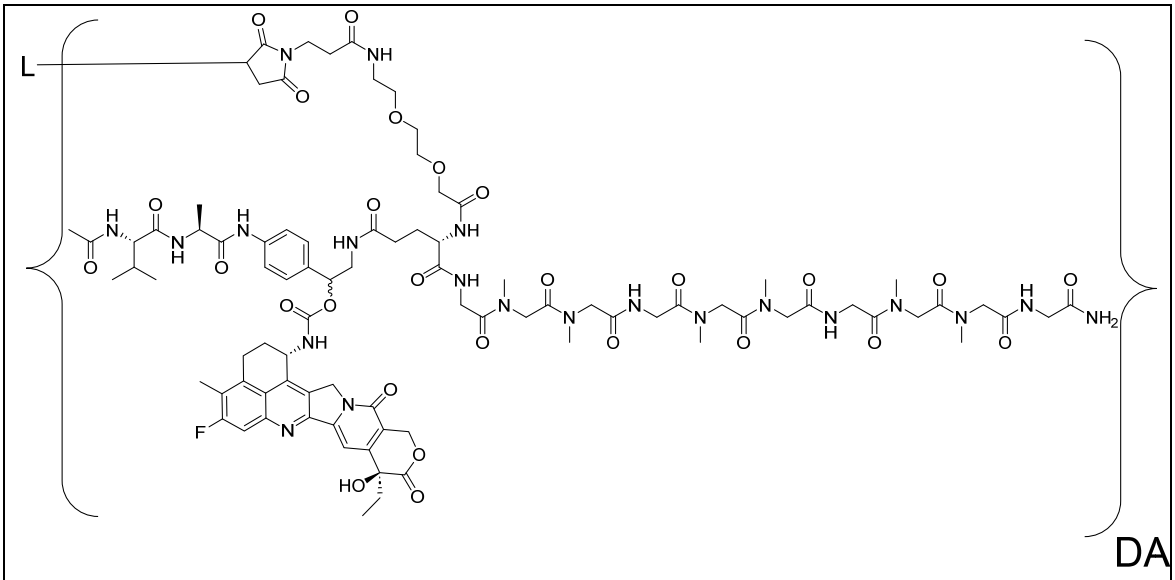
(SEQ ID NO: 26)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



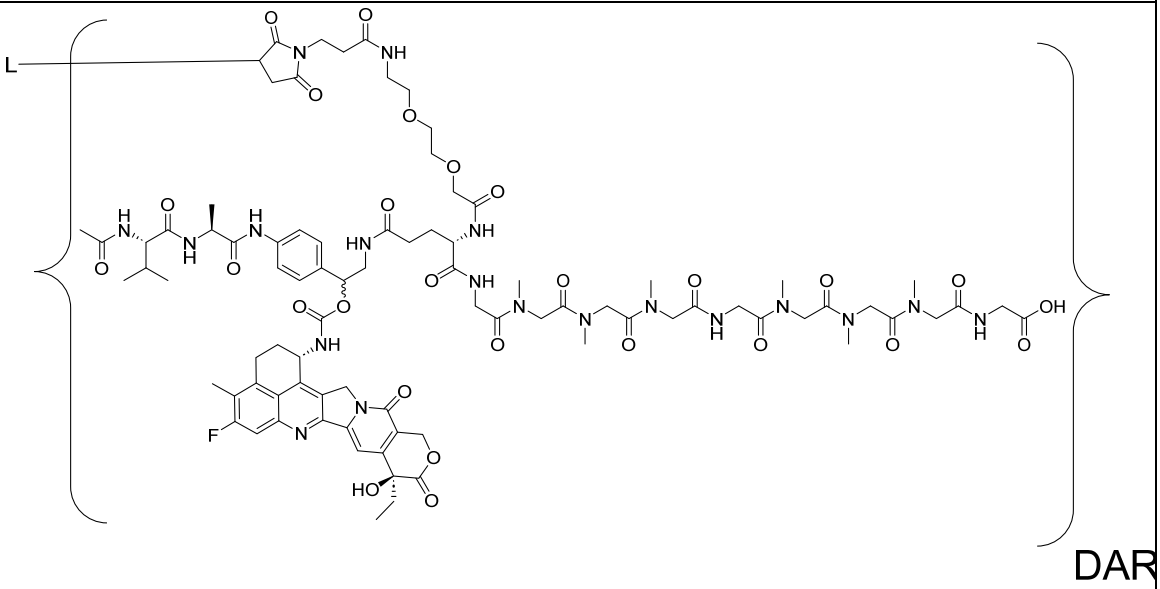
(SEQ ID NO: 31)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



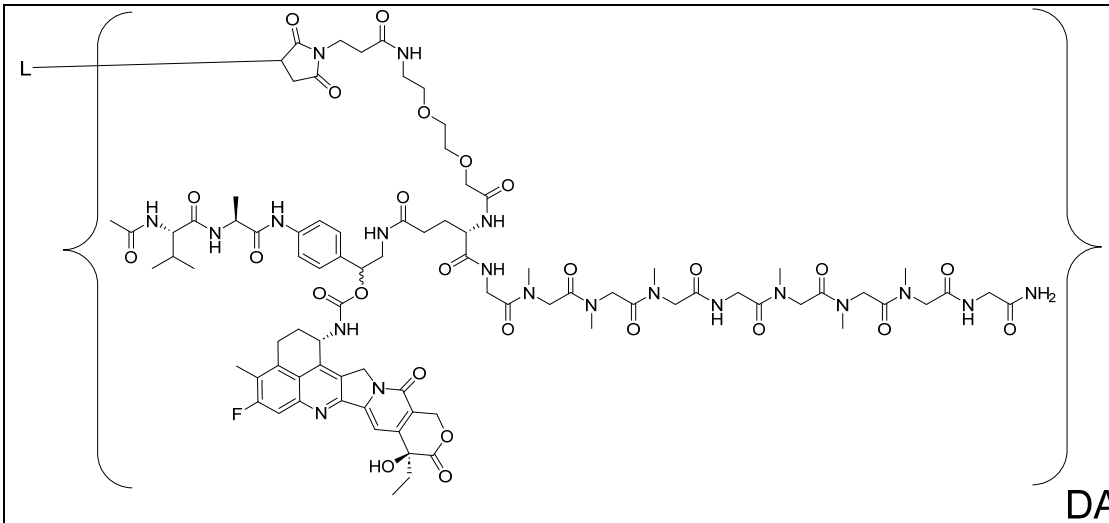
(SEQ ID NO: 31)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



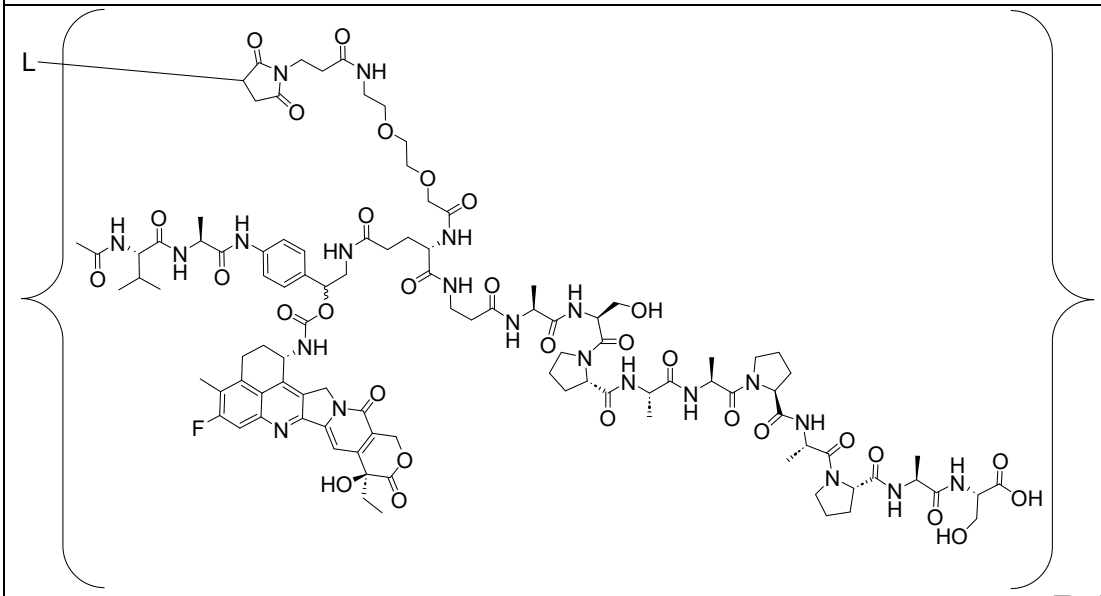
(SEQ ID NO: 32)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



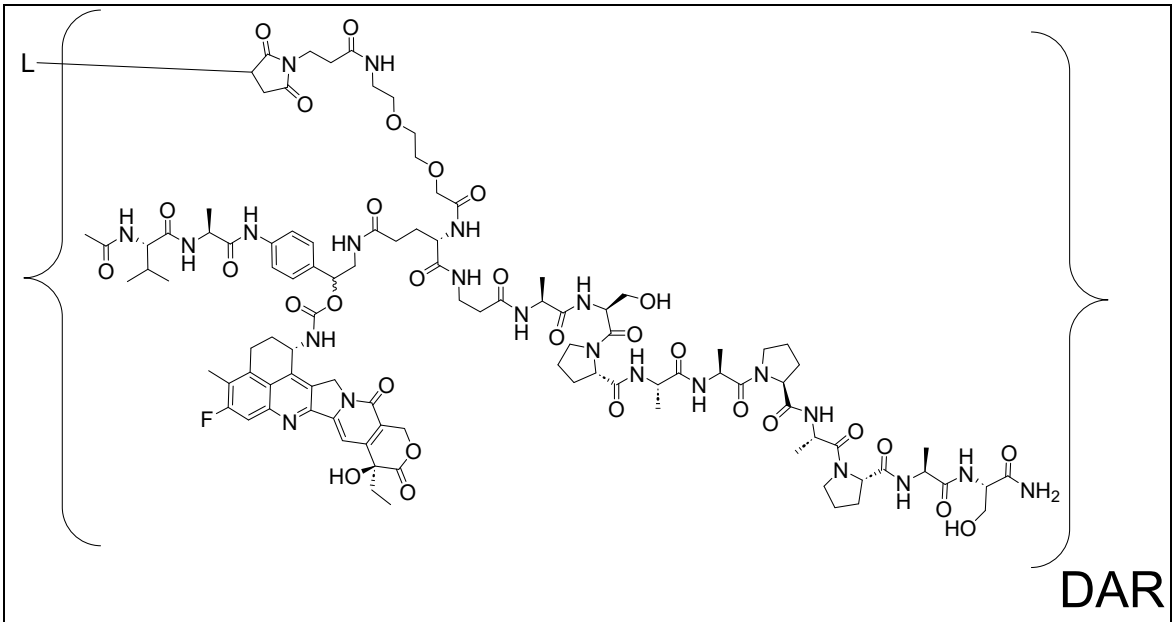
(SEQ ID NO: 32)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



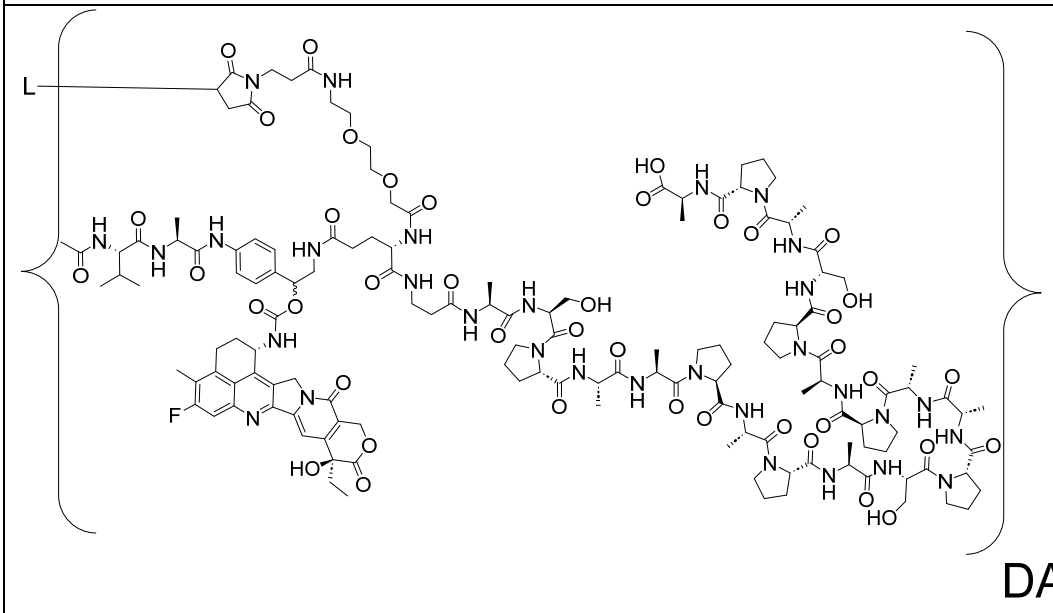
(SEQ ID NO: 27)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



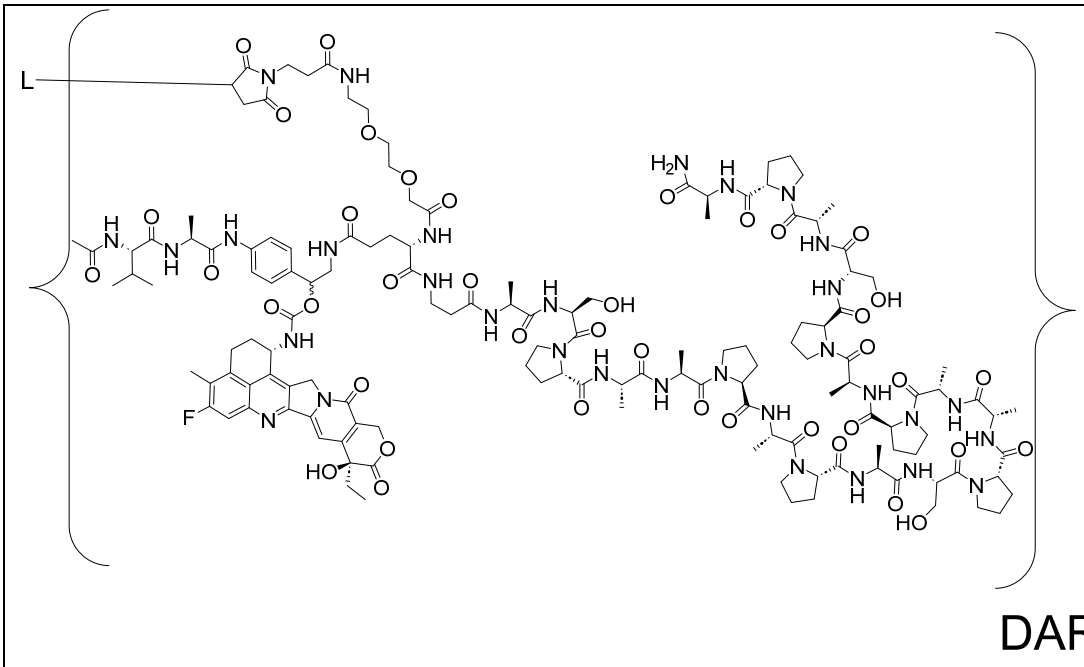
(SEQ ID NO: 27)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



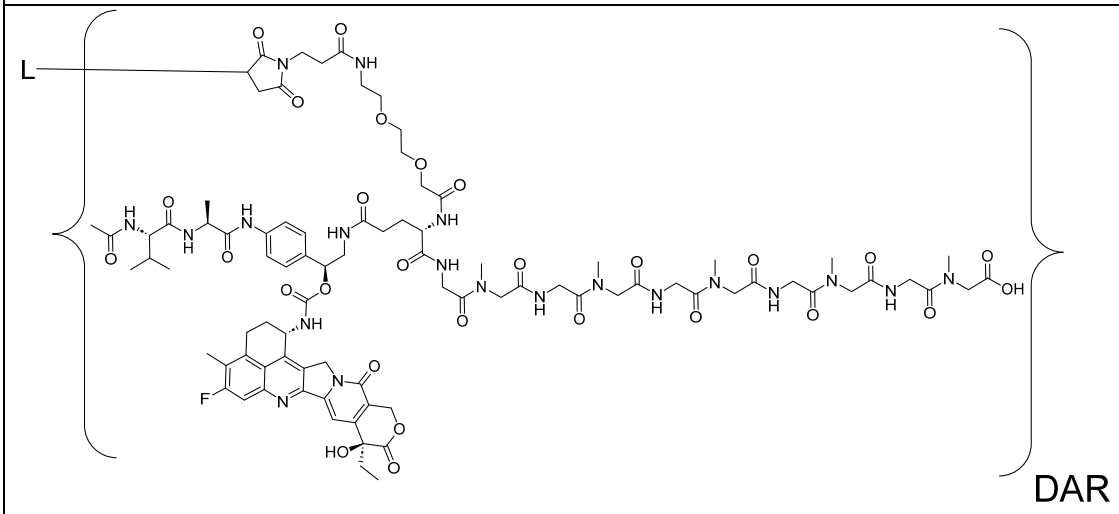
(SEQ ID NO: 28)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



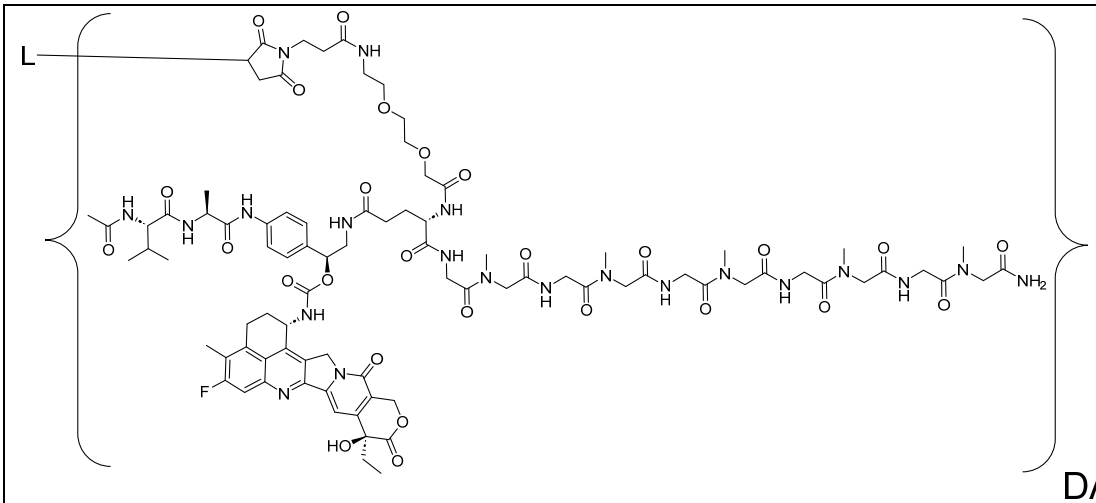
(SEQ ID NO: 28)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



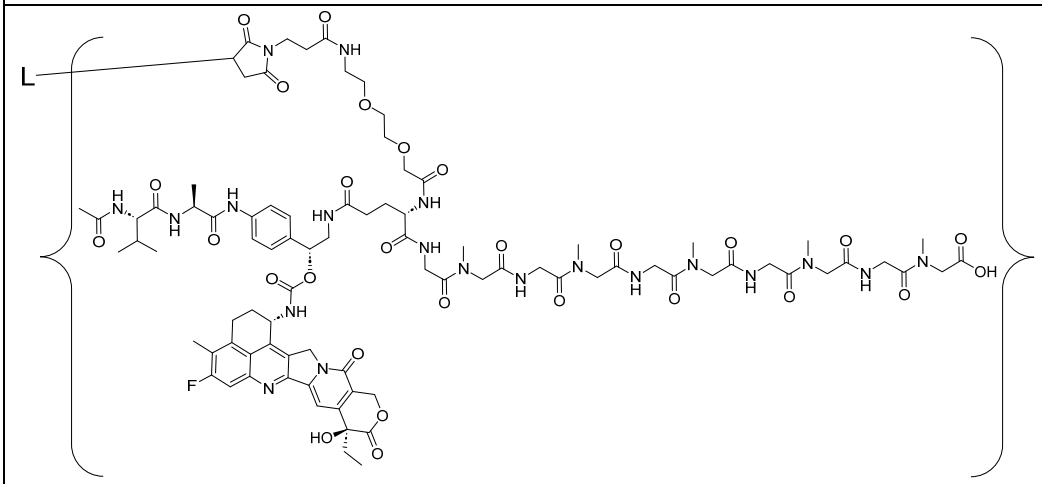
(SEQ ID NO: 26)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



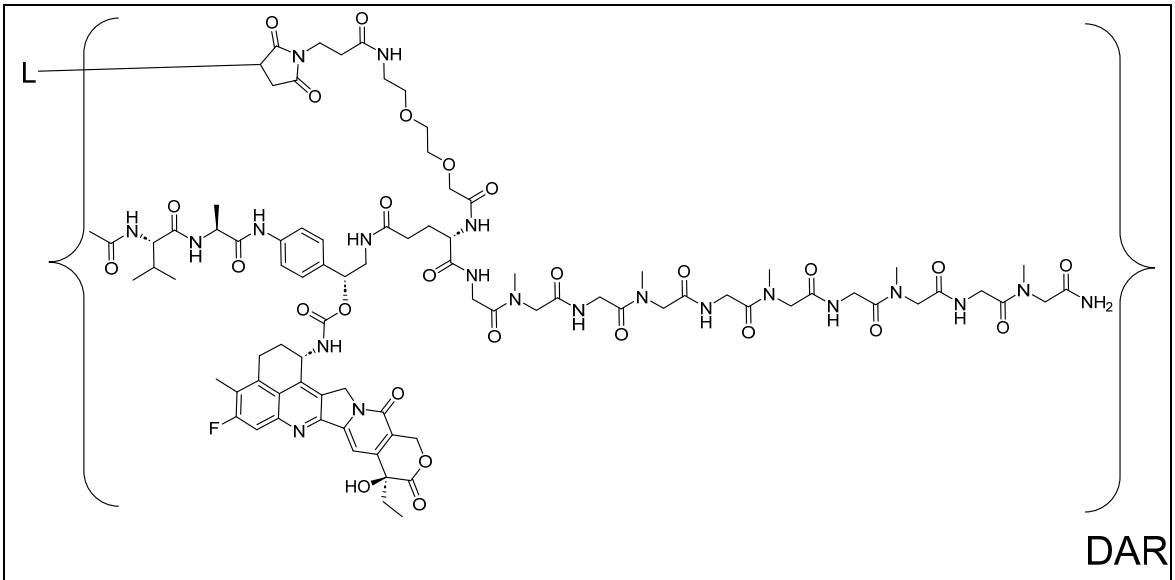
(SEQ ID NO: 26)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



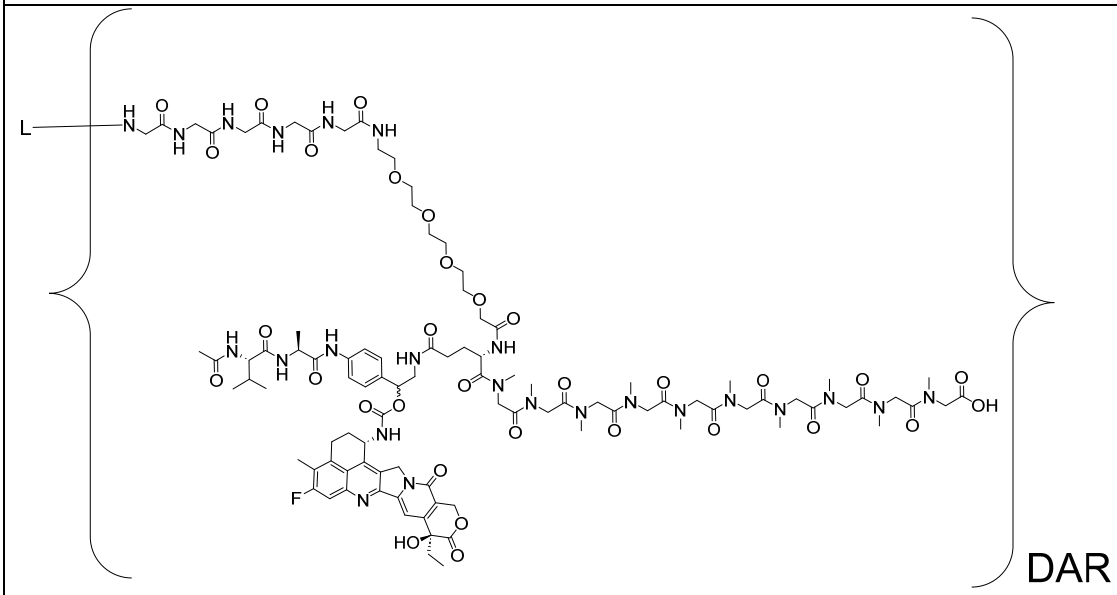
(SEQ ID NO: 26)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



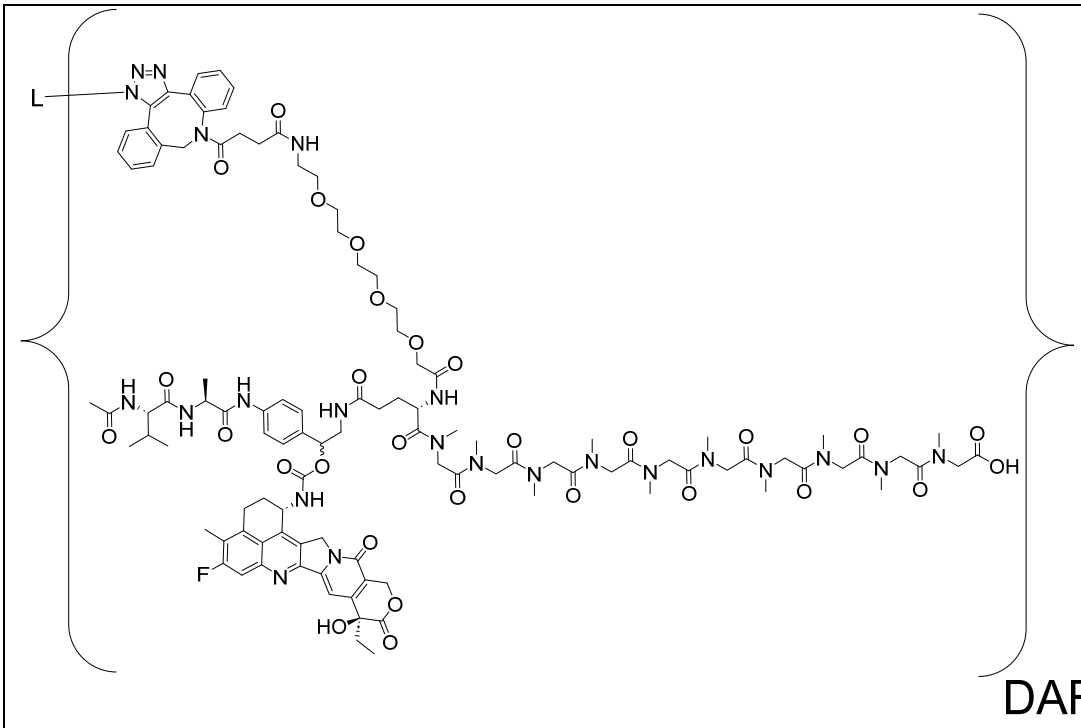
(SEQ ID NO: 26)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



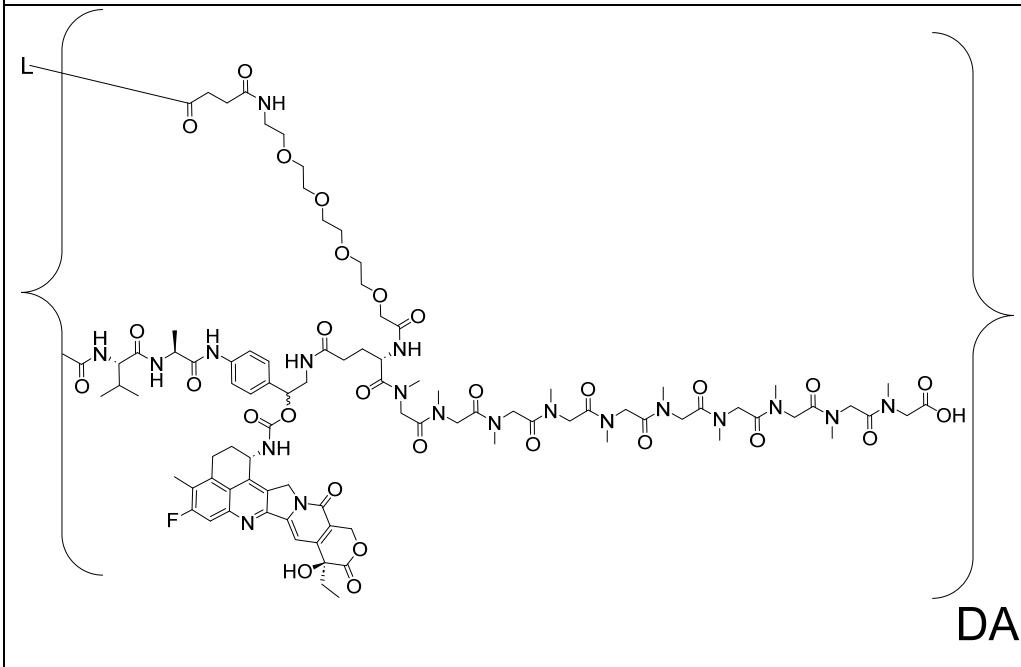
(SEQ ID NOS 39 and 25, respectively, in order of appearance)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



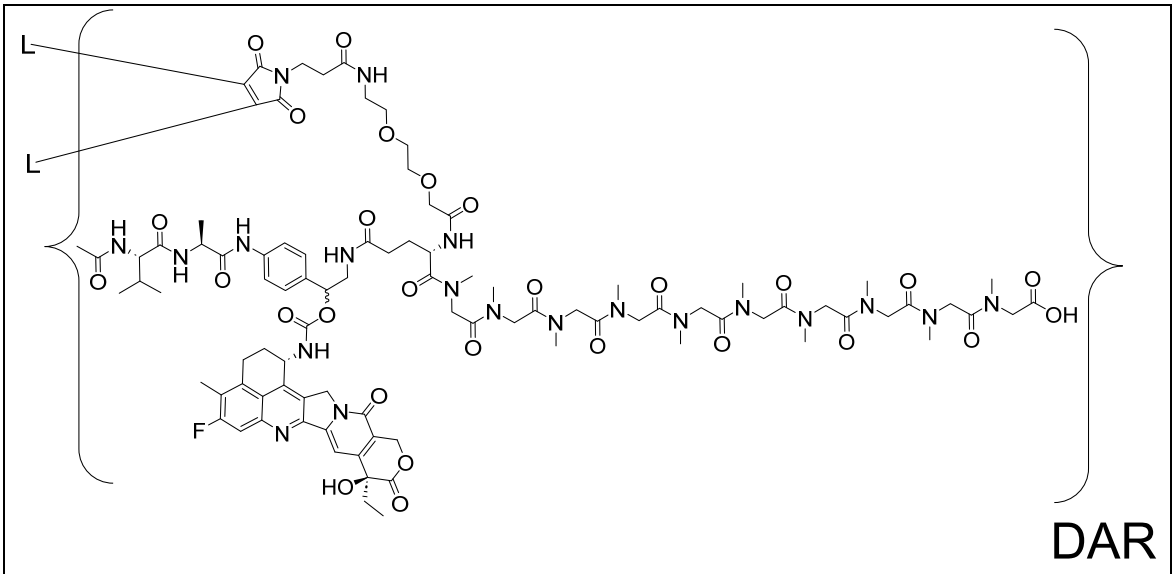
(SEQ ID NO: 25)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



(SEQ ID NO: 25)

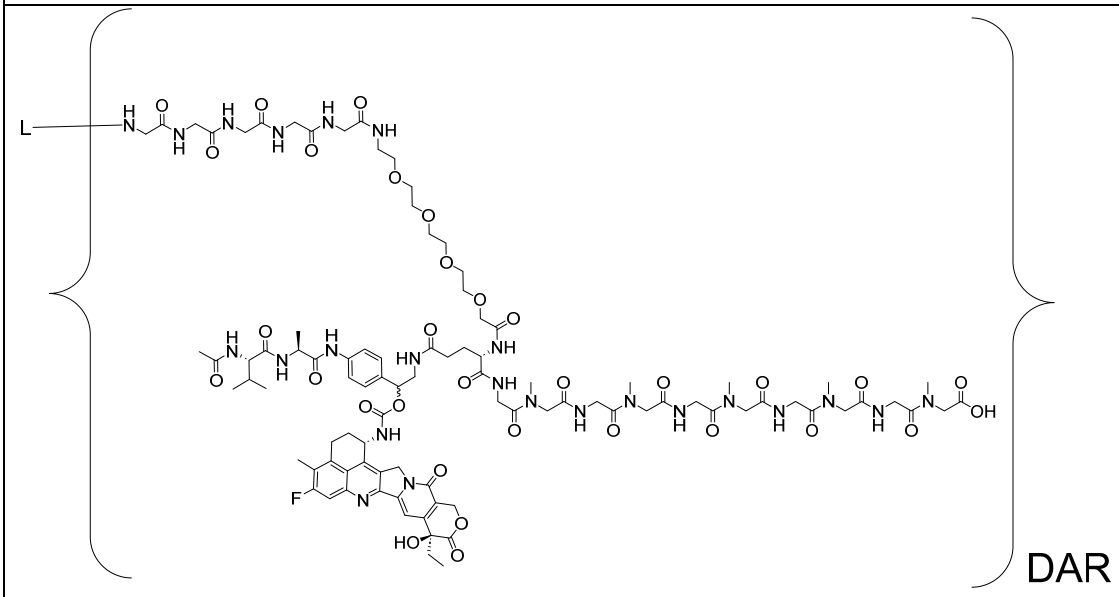
1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



(SEQ ID NO: 25)

3) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or

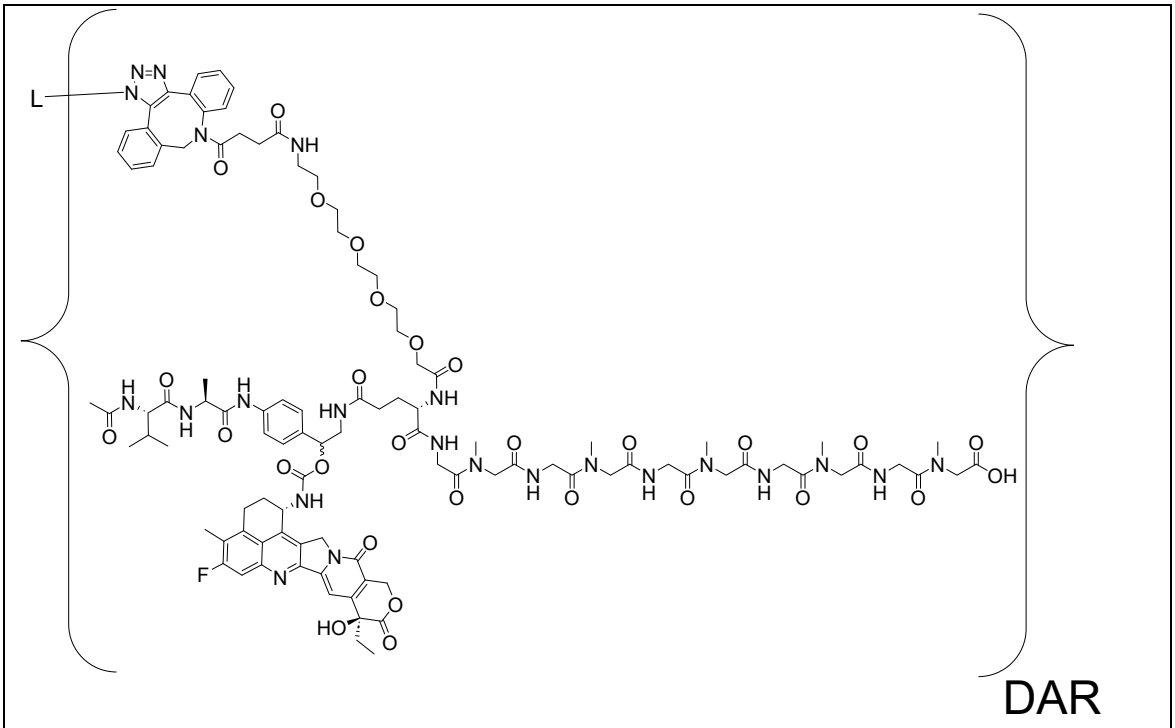
4) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



(SEQ ID NOS 39 and 26, respectively, in order of appearance)

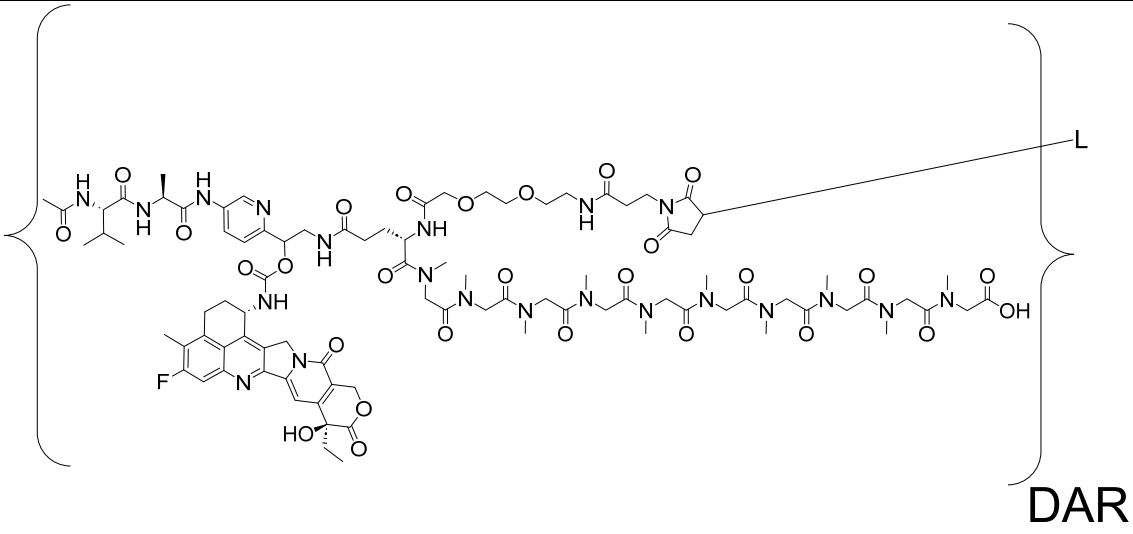
1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or

2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



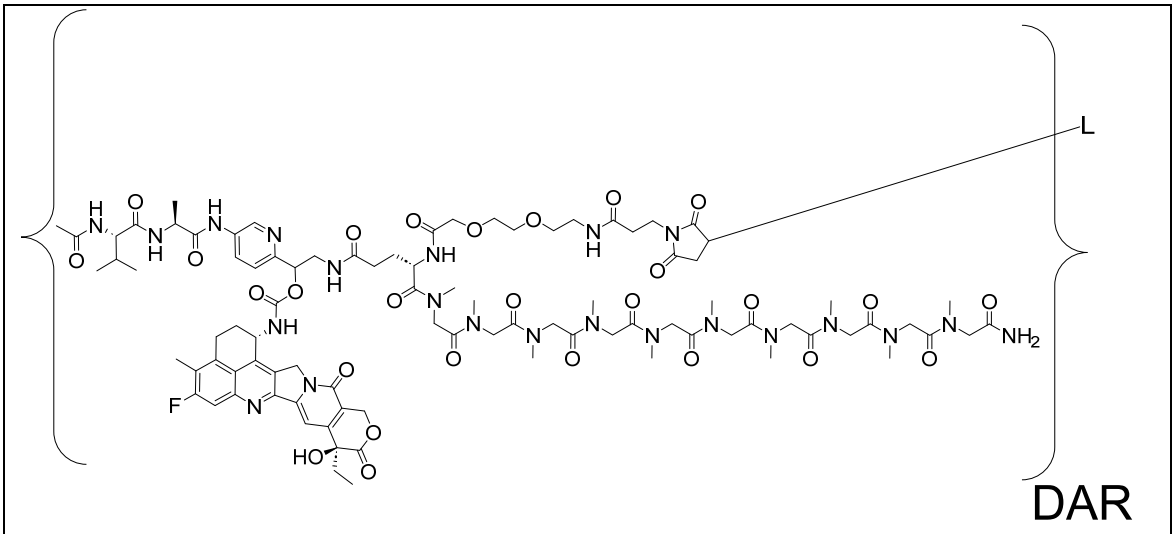
(SEQ ID NO: 26)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



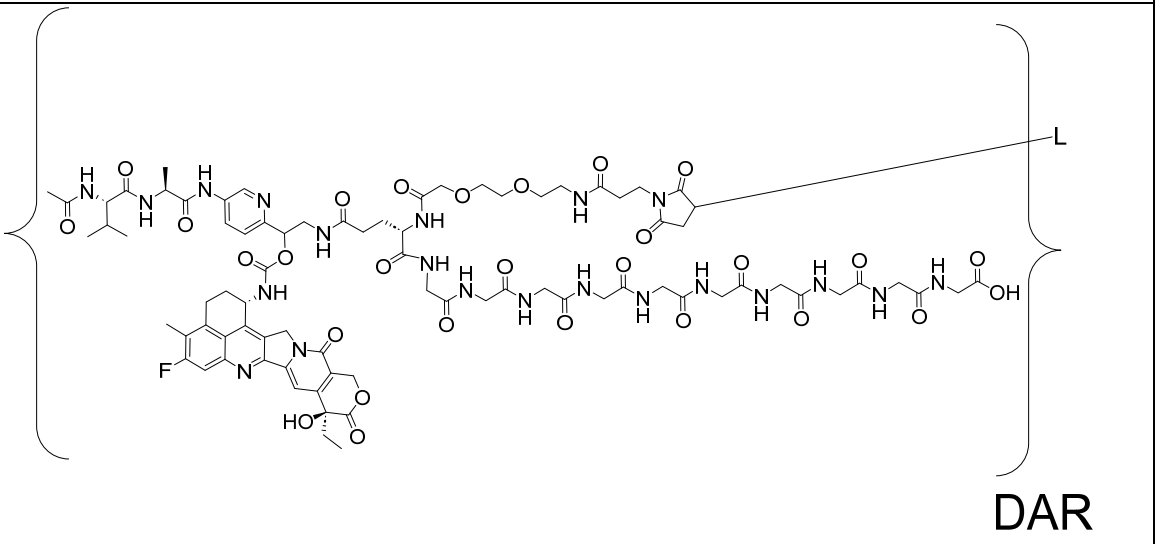
(SEQ ID NO: 25)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



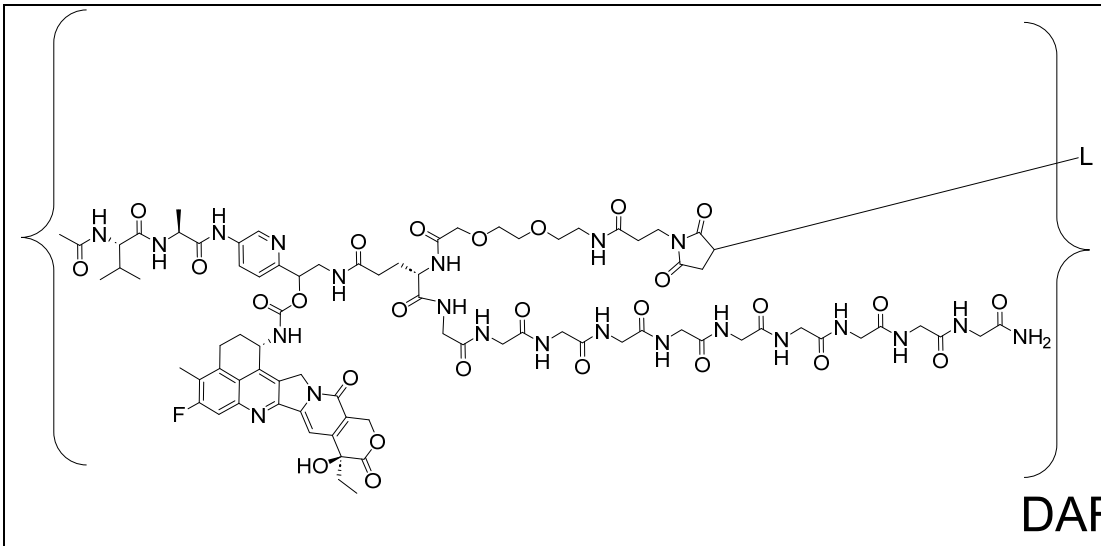
(SEQ ID NO: 25)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



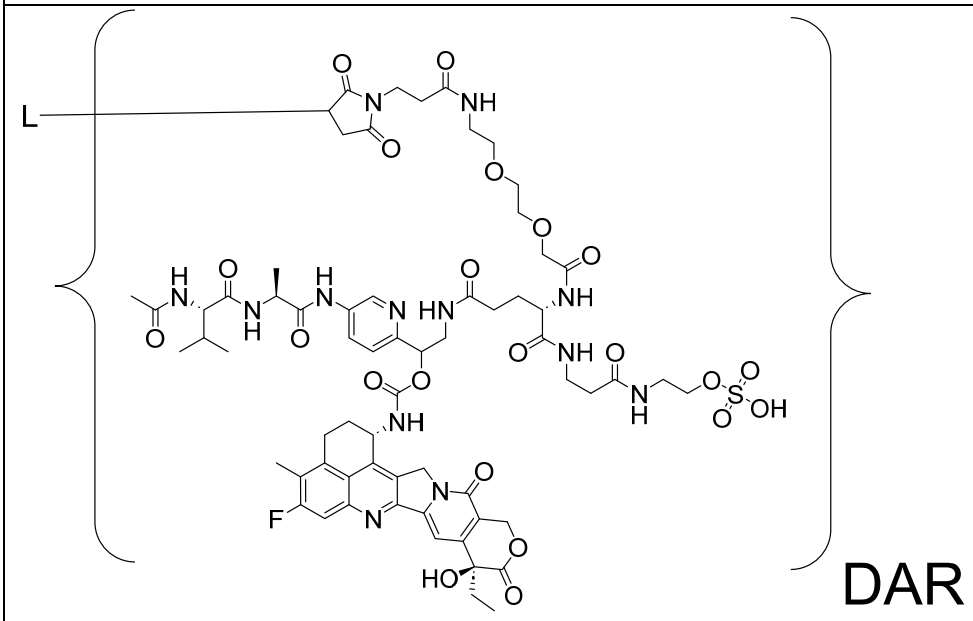
(SEQ ID NO: 24)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.

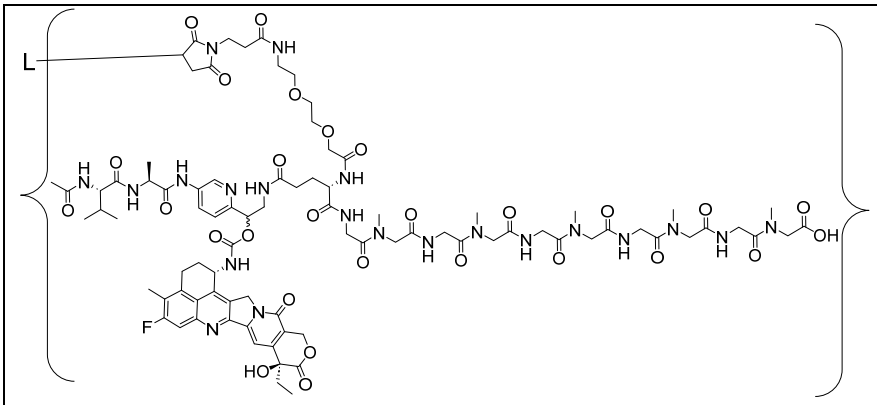


(SEQ ID NO: 24)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.

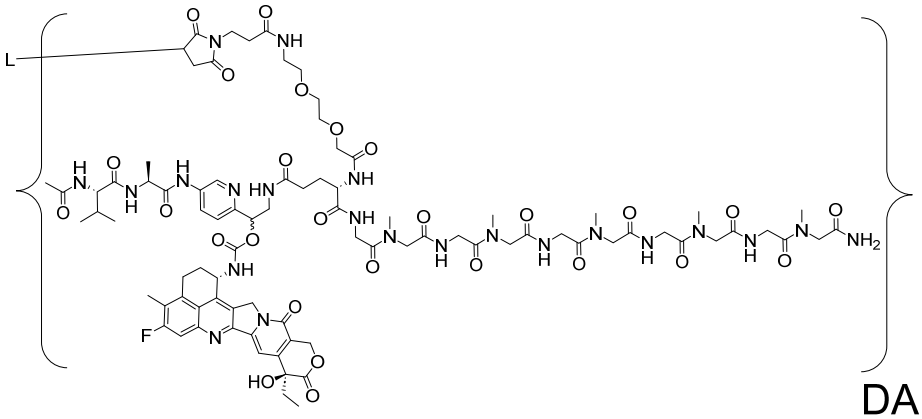


1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



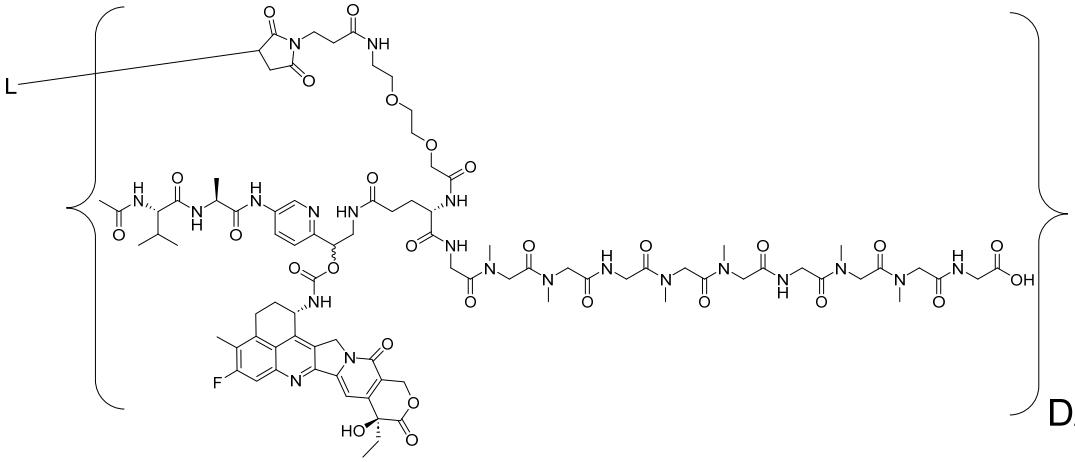
DAR (SEQ ID NO: 26)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



DAR (SEQ ID NO: 26)

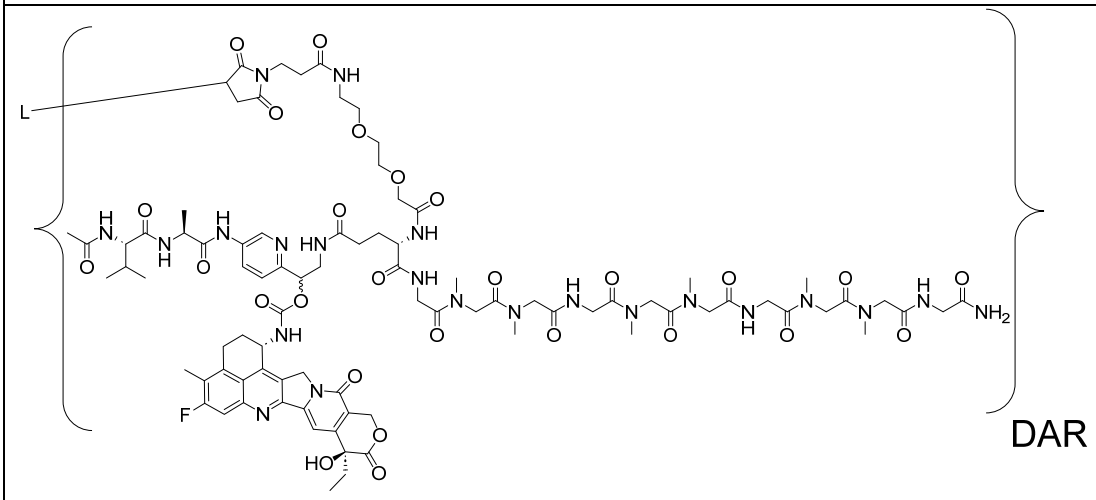
1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



DAR (SEQ ID NO: 31),

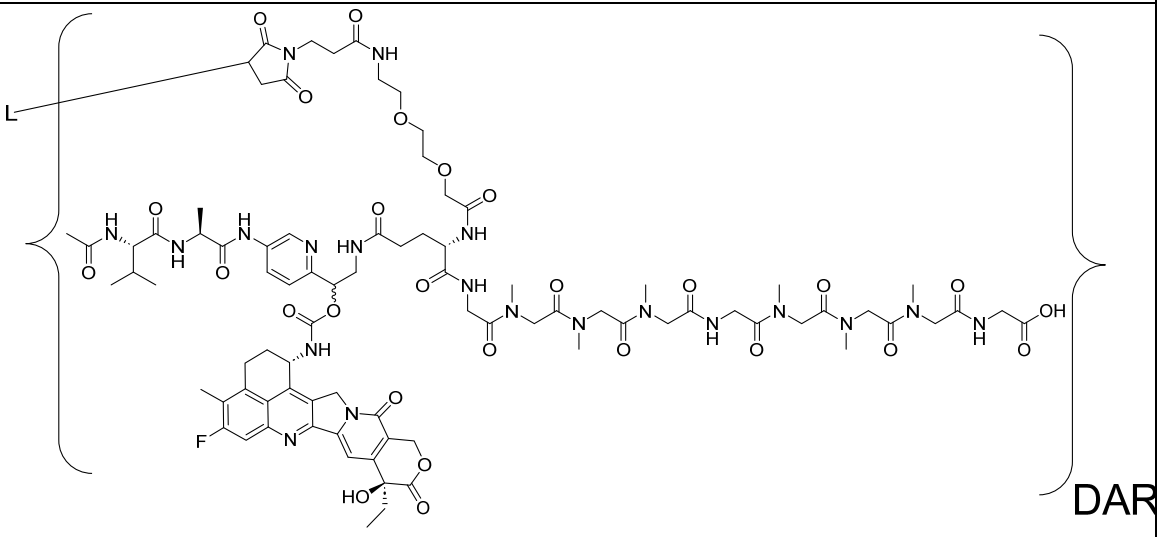
1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or

2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



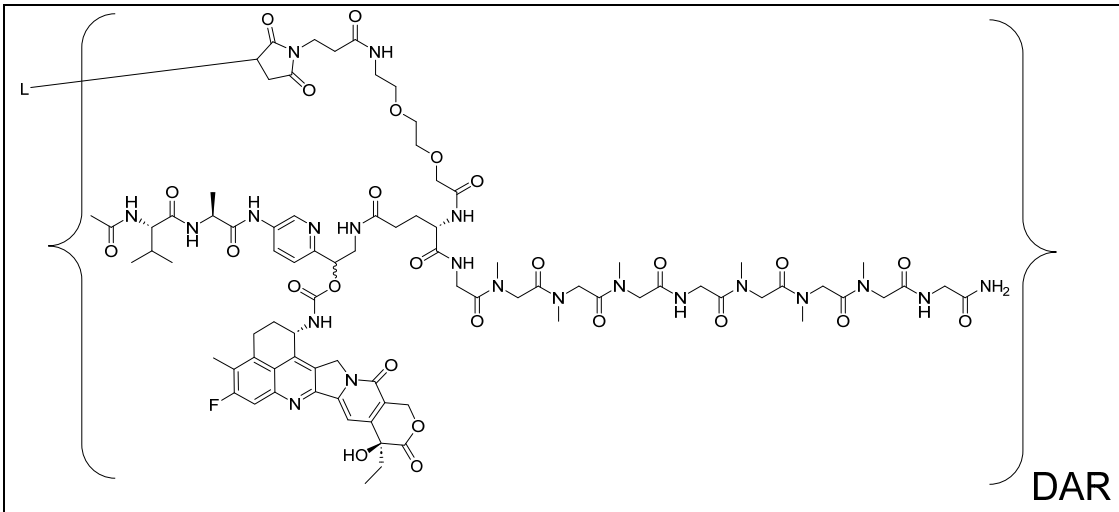
(SEQ ID NO: 31)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



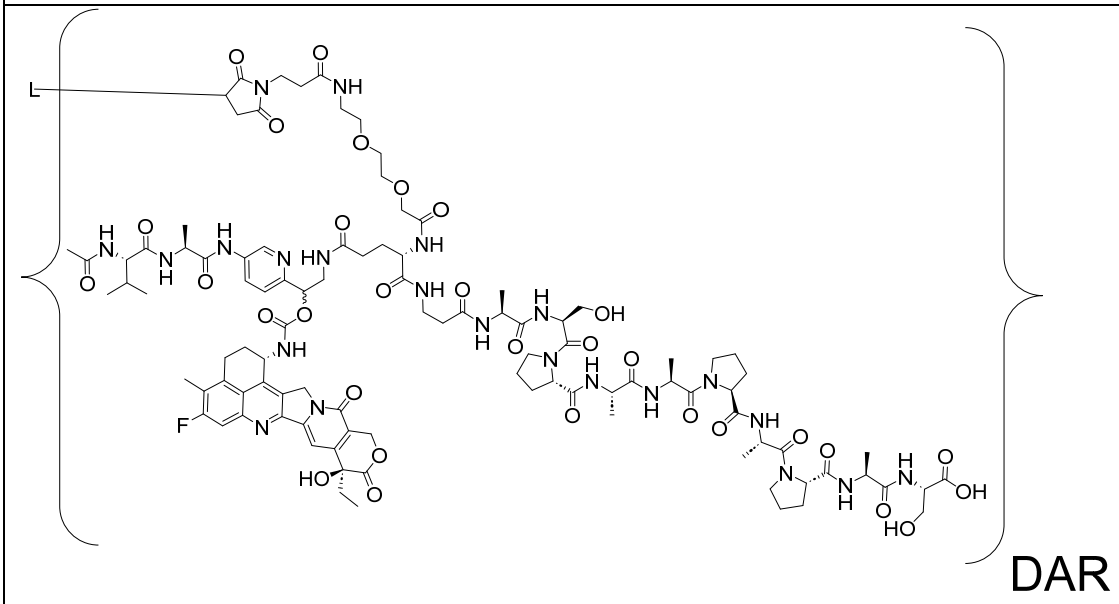
(SEQ ID NO: 32)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



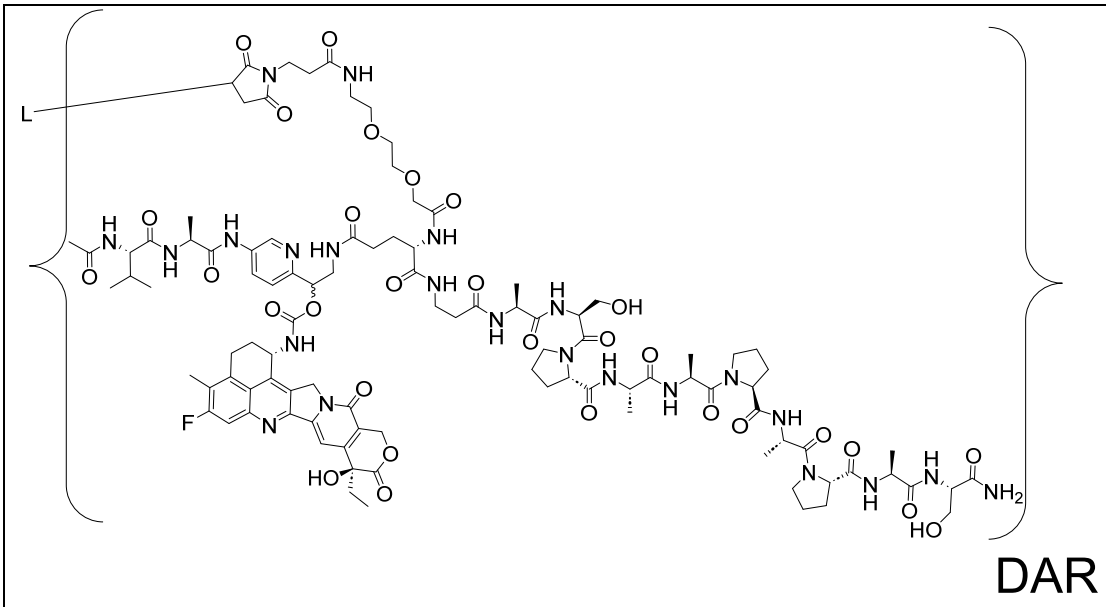
(SEQ ID NO: 32),

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



(SEQ ID NO: 27)

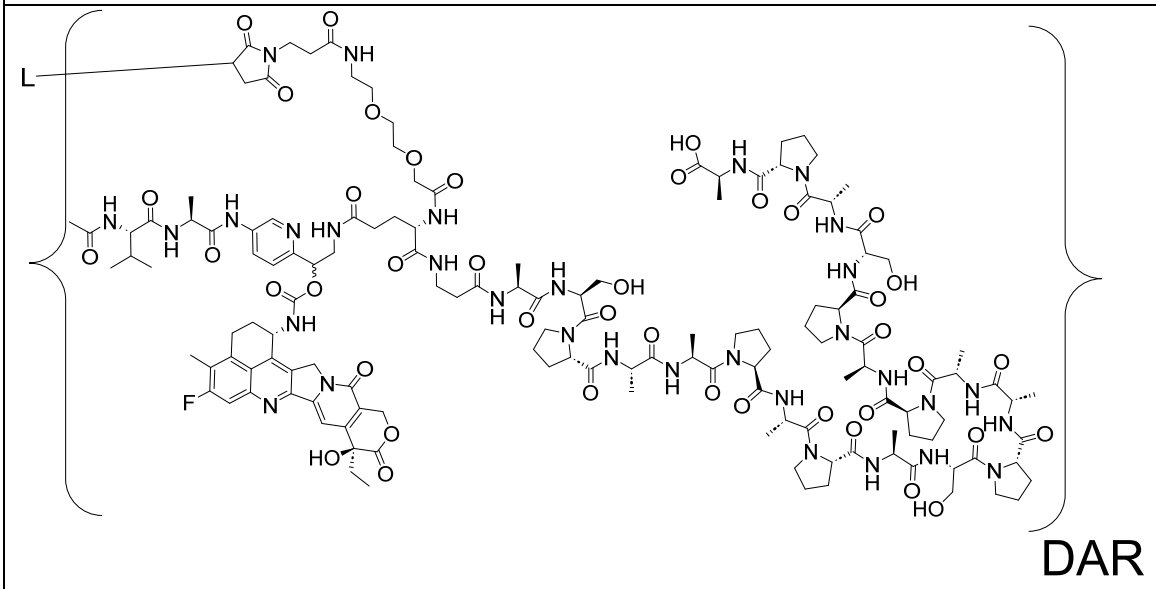
1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



DAR

(SEQ ID NO: 27)

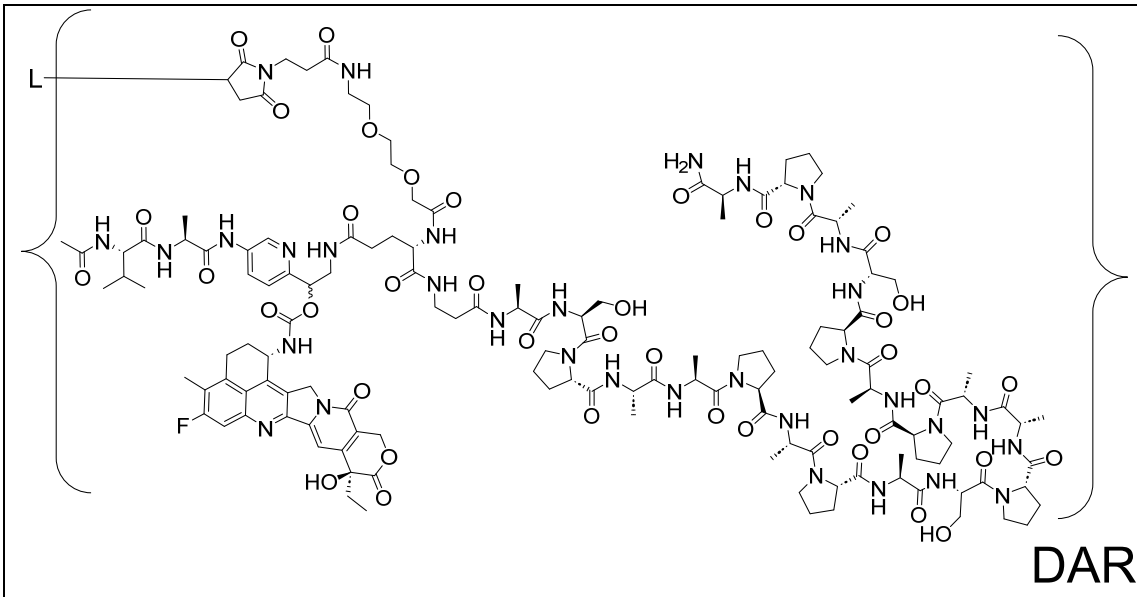
1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



DAR

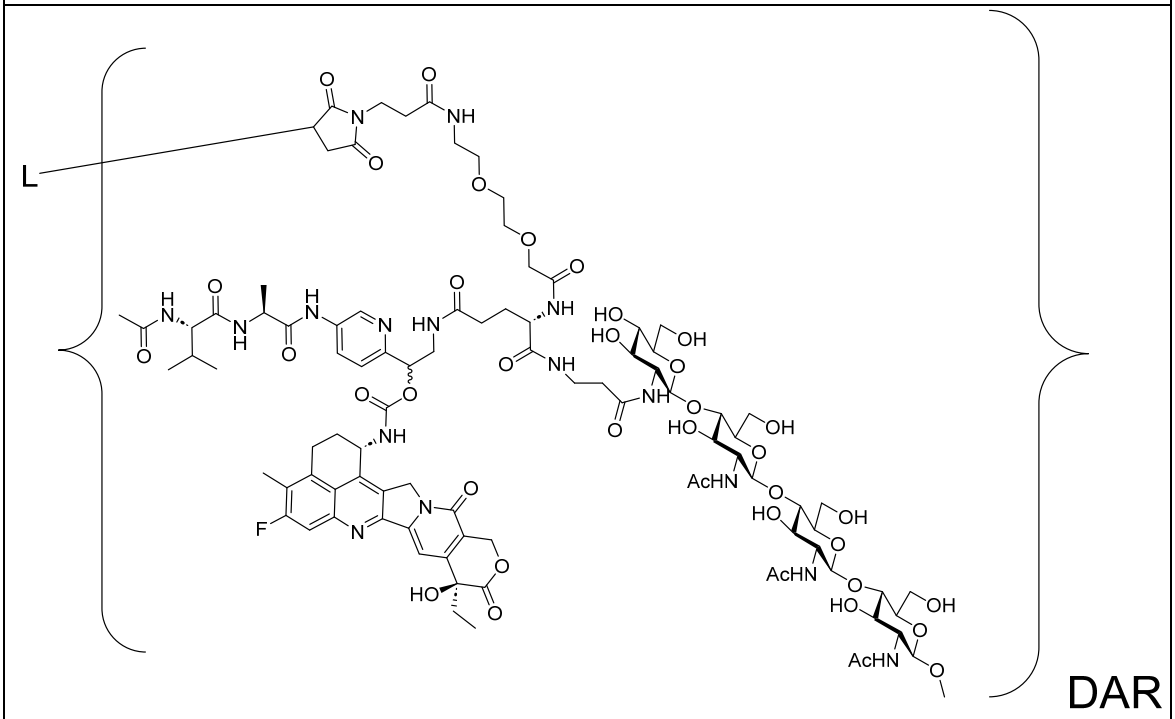
(SEQ ID NO: 28)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



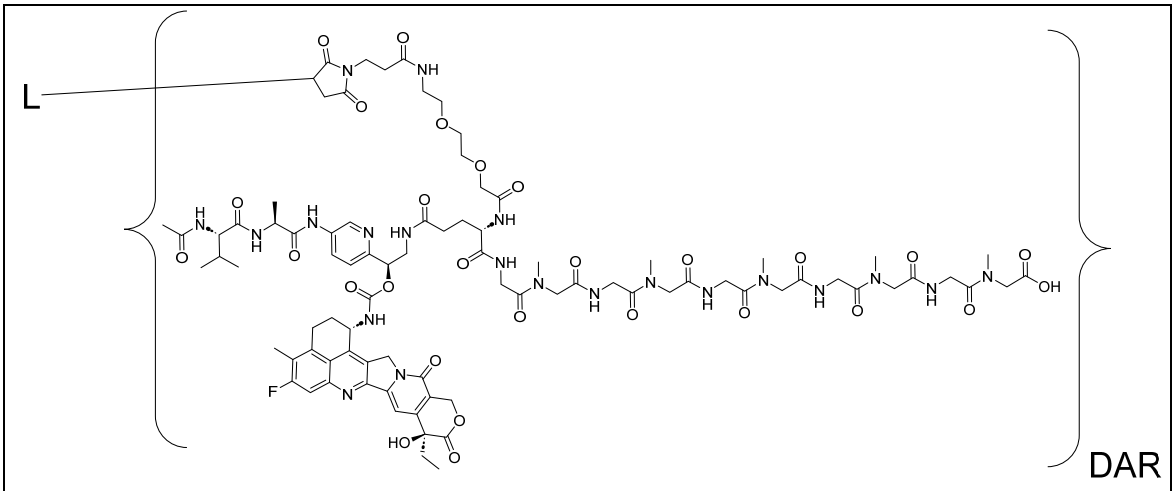
(SEQ ID NO: 28)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



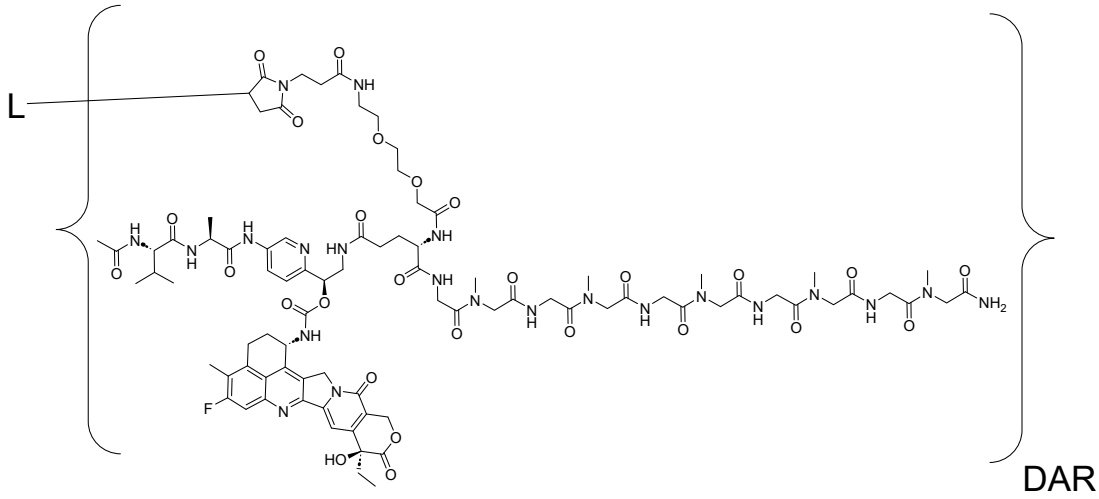
,

3) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
4) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



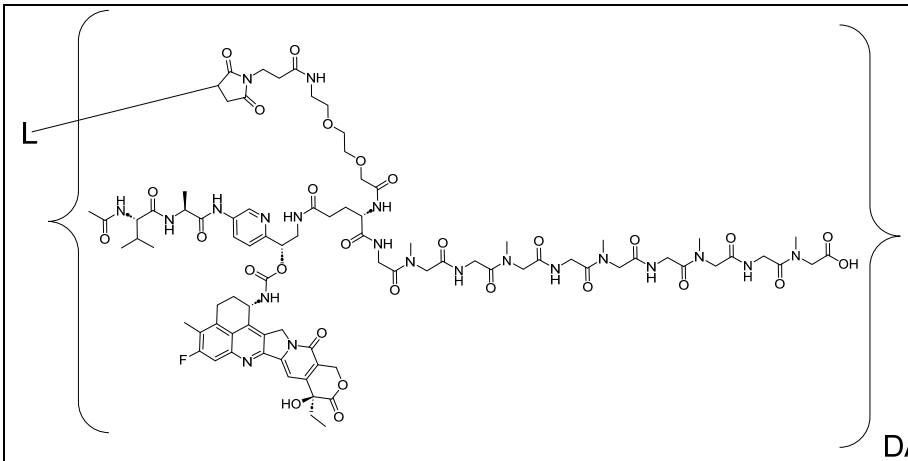
(SEQ ID NO: 26),

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



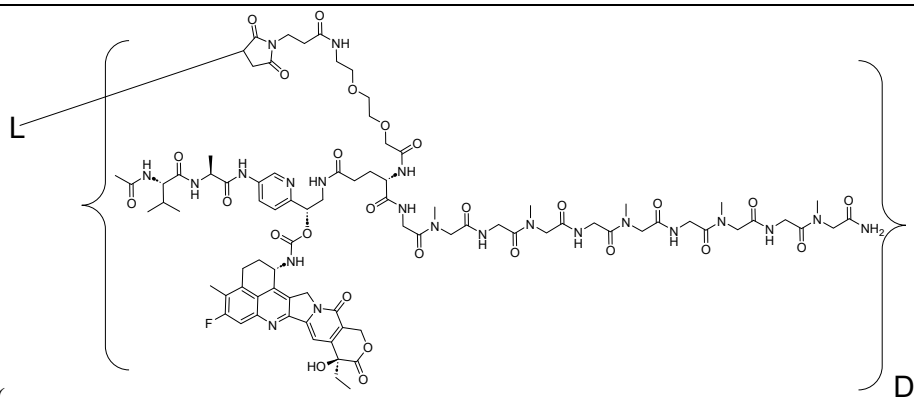
(SEQ ID NO: 26)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



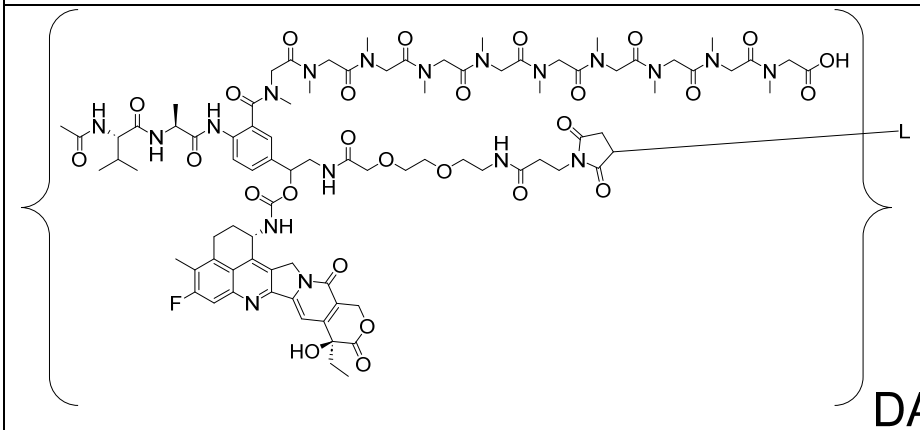
DAR (SEQ ID NO: 26),

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



(DAR SEQ ID NO: 26)

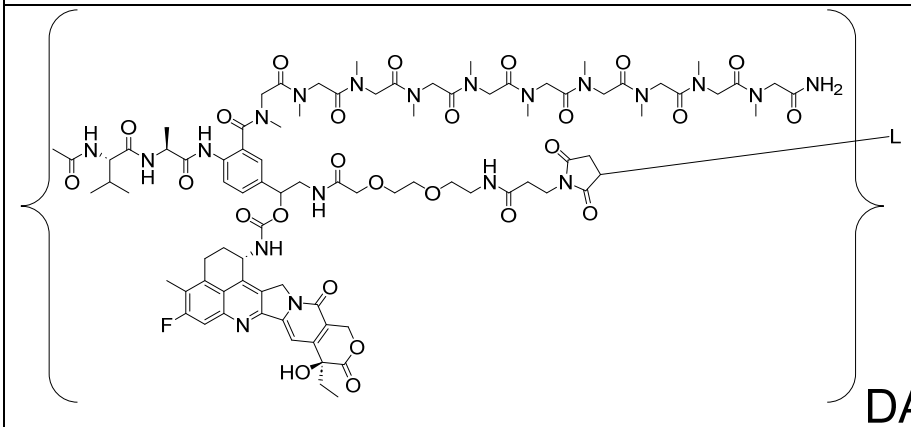
1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



DAR (SEQ ID NO: 29),

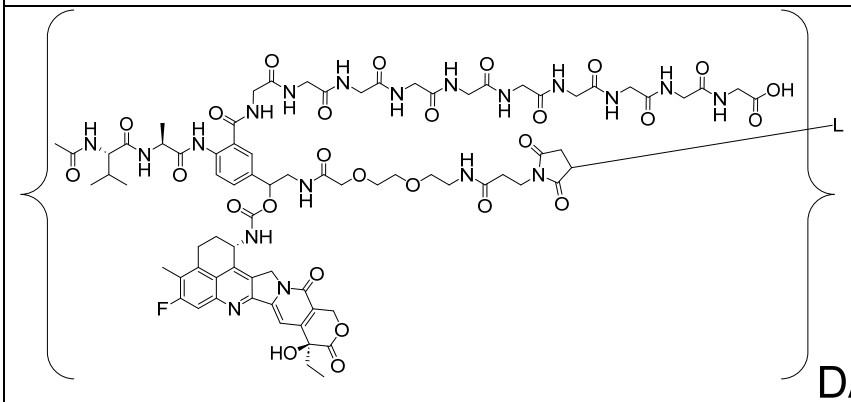
1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or

2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



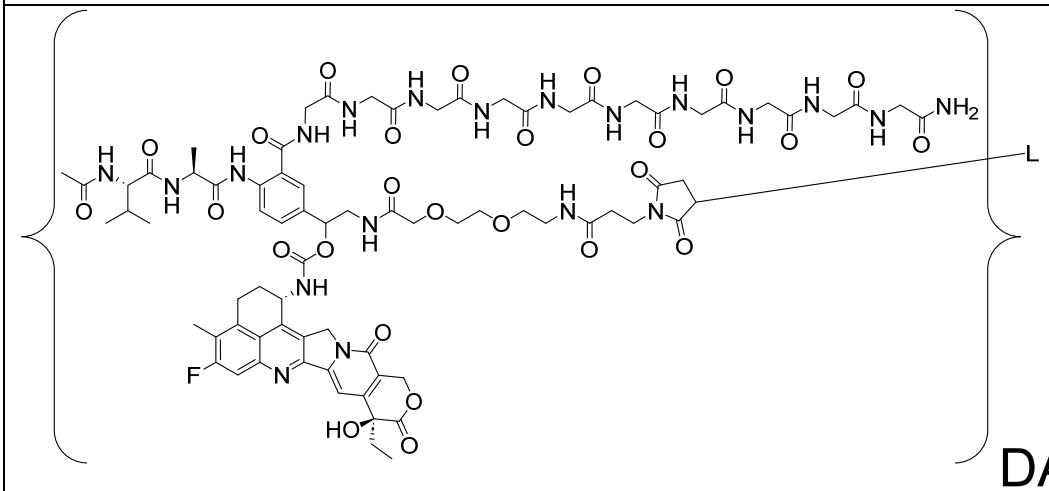
DAR (SEQ ID NO: 29),

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



DAR (SEQ ID NO: 38)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.

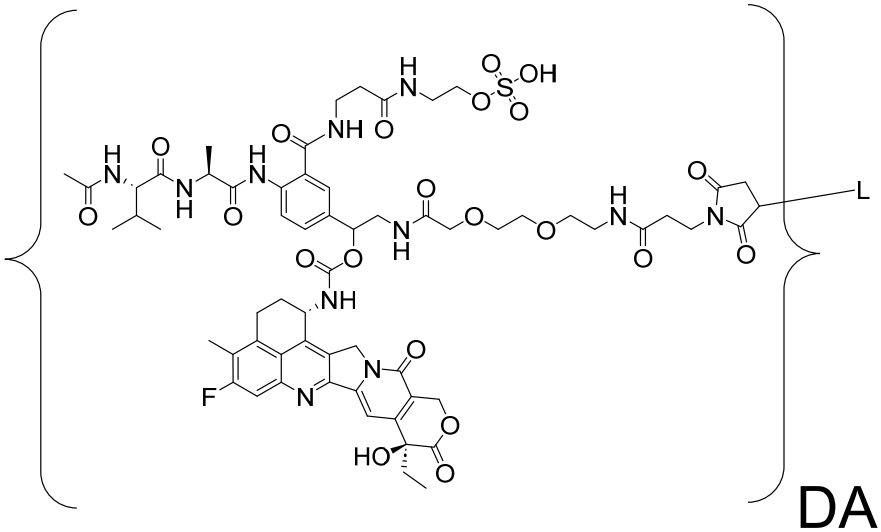


DAR

(SEQ ID NO: 38)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or

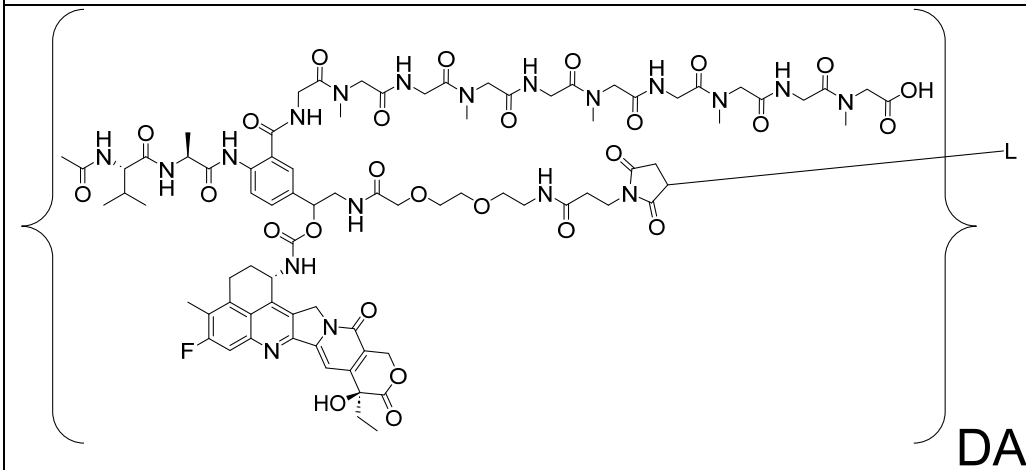
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



DAR

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or

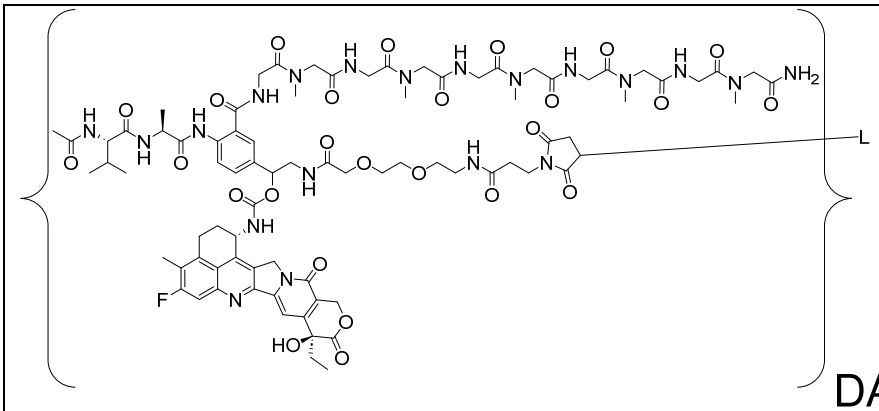
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



DAR (SEQ ID NO: 30)

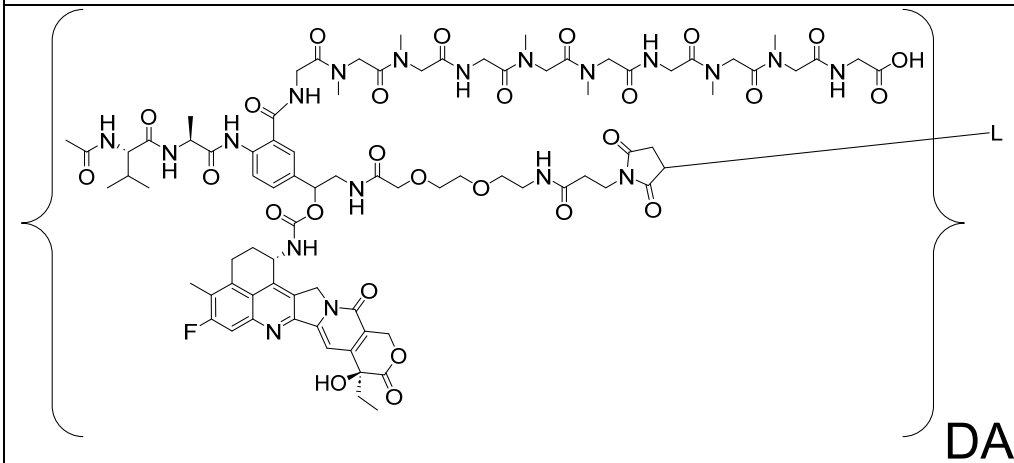
1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or

2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



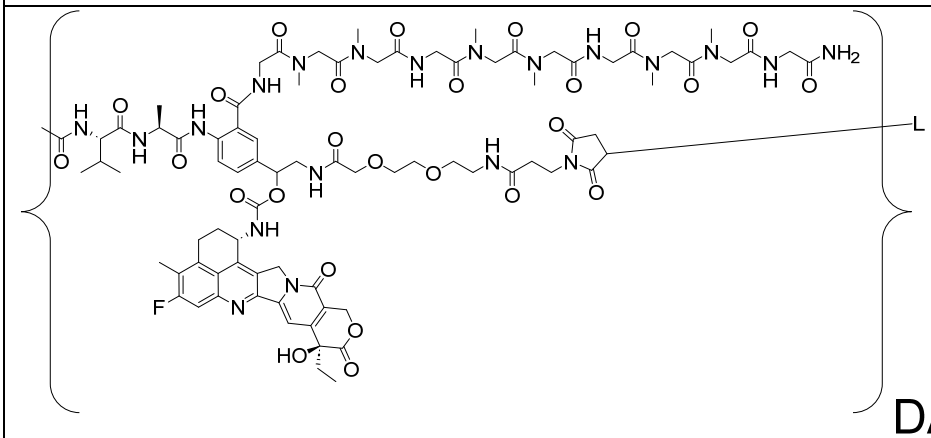
DAR (SEQ ID NO: 30)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



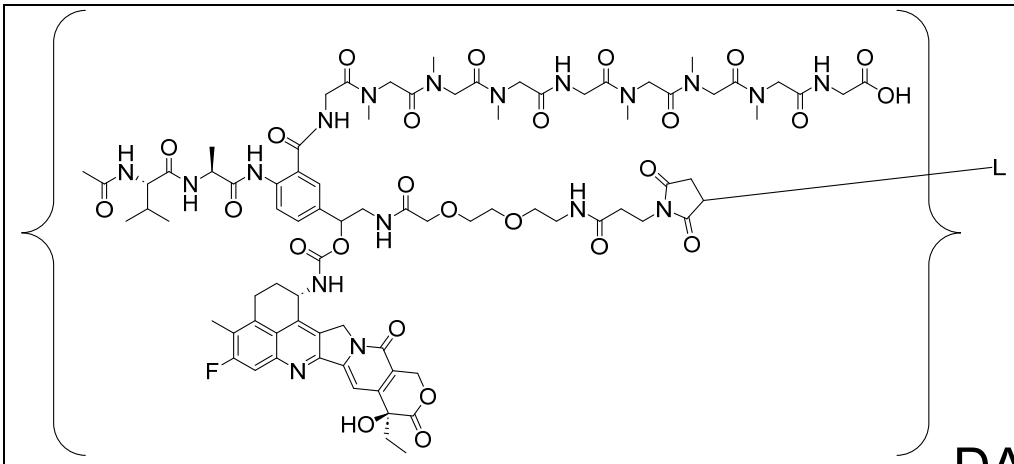
DAR (SEQ ID NO: 33)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



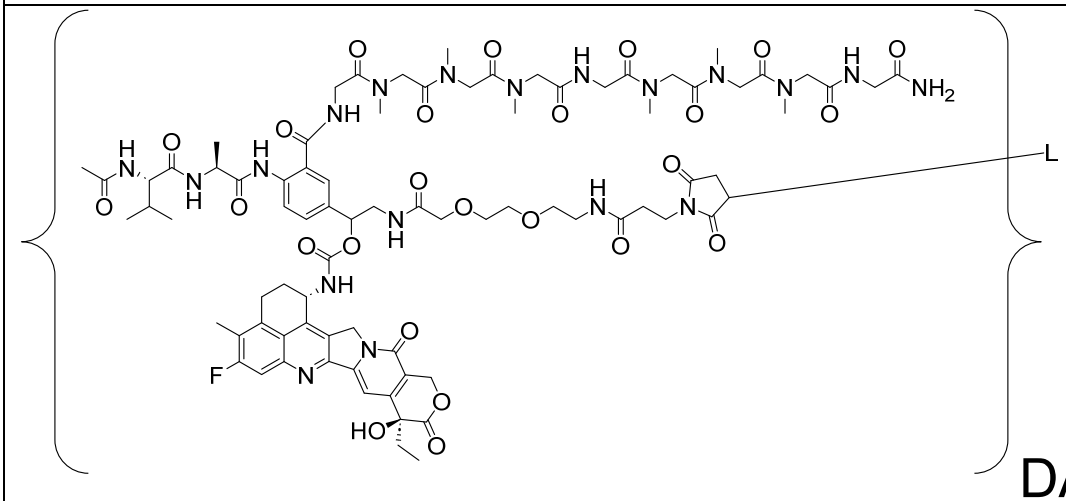
DAR (SEQ ID NO: 33)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



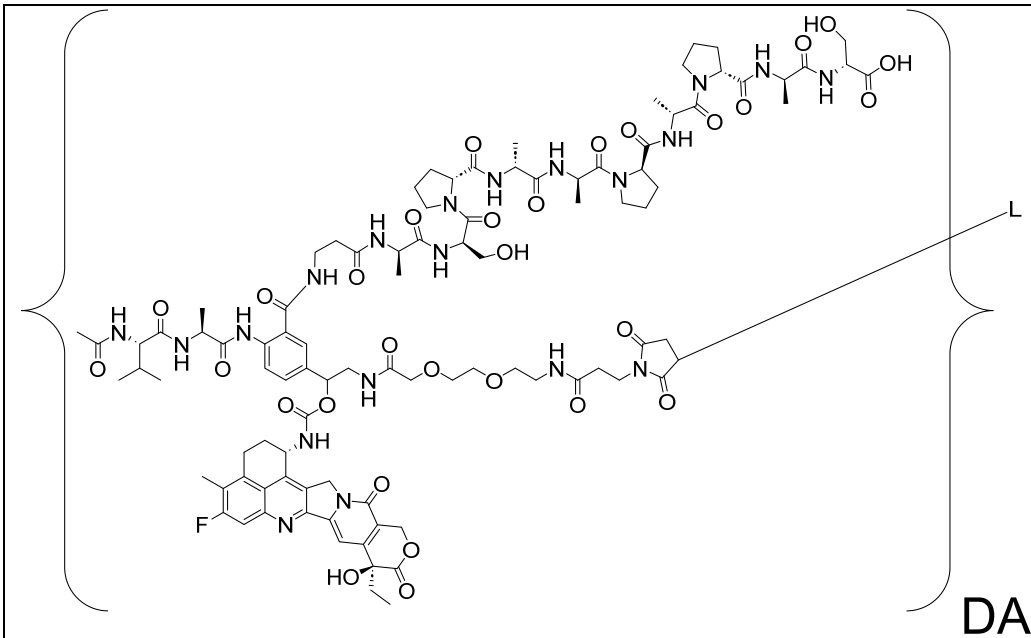
DAR (SEQ ID NO: 34)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



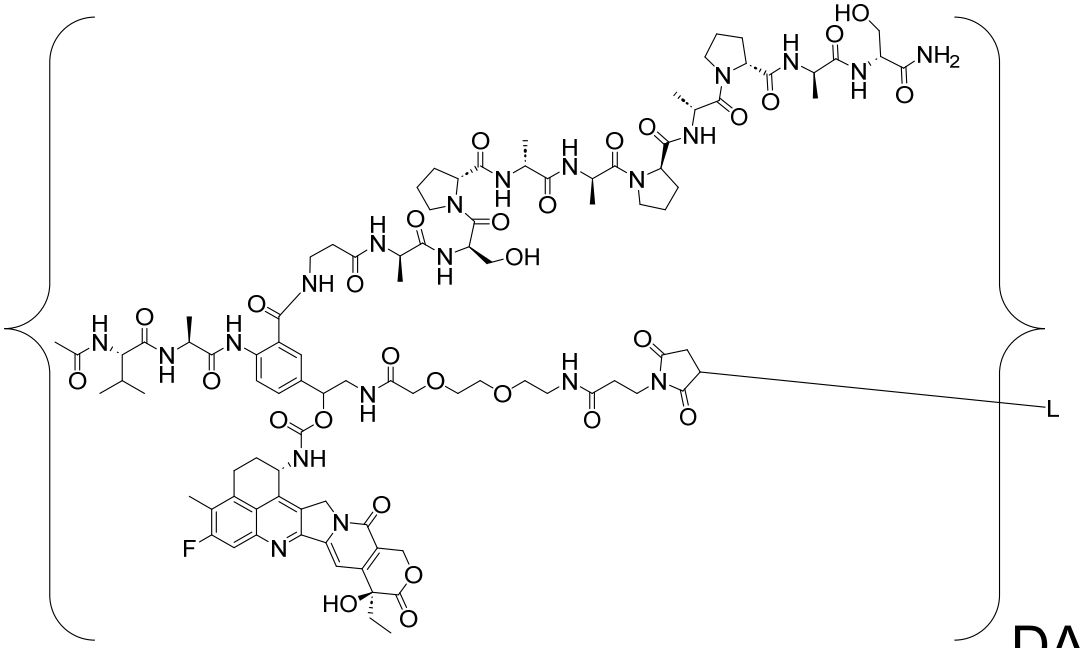
DAR (SEQ ID NO: 34)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



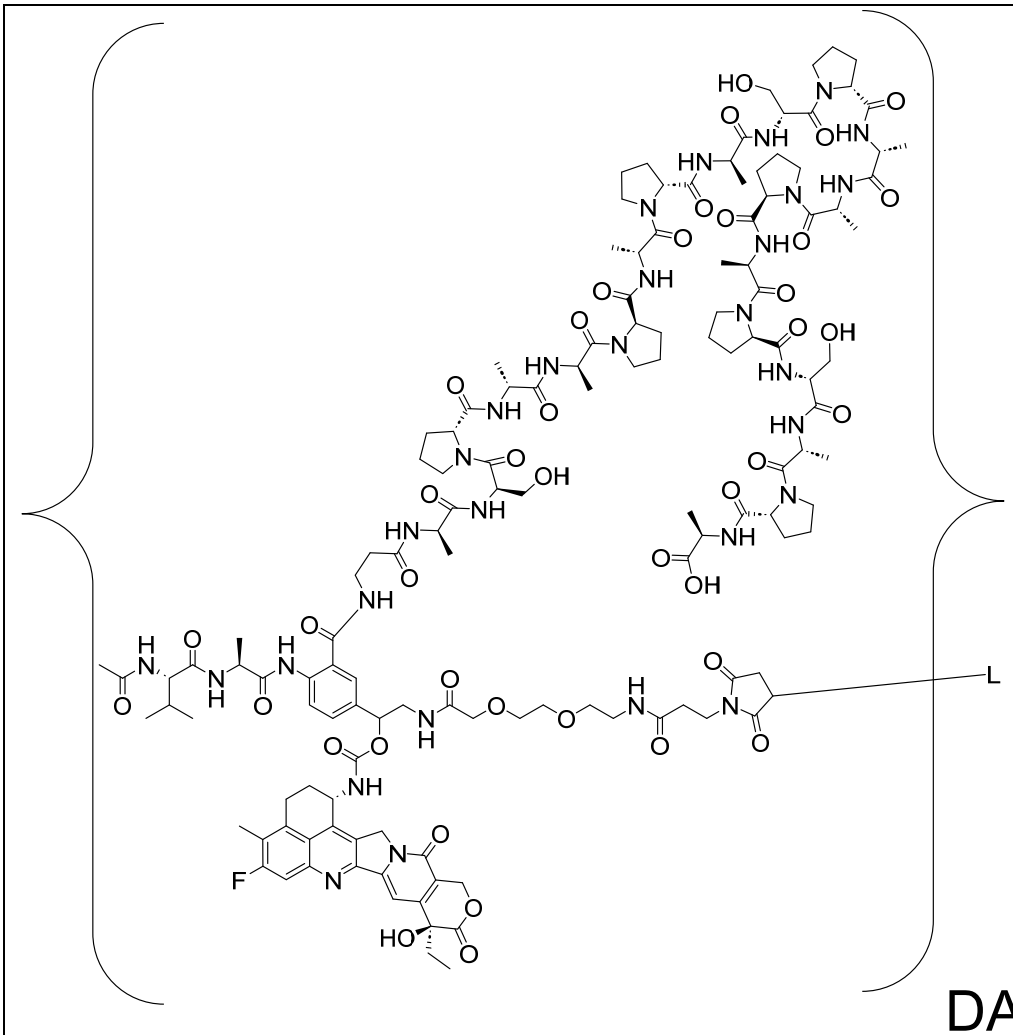
DAR (SEQ ID NO: 35)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



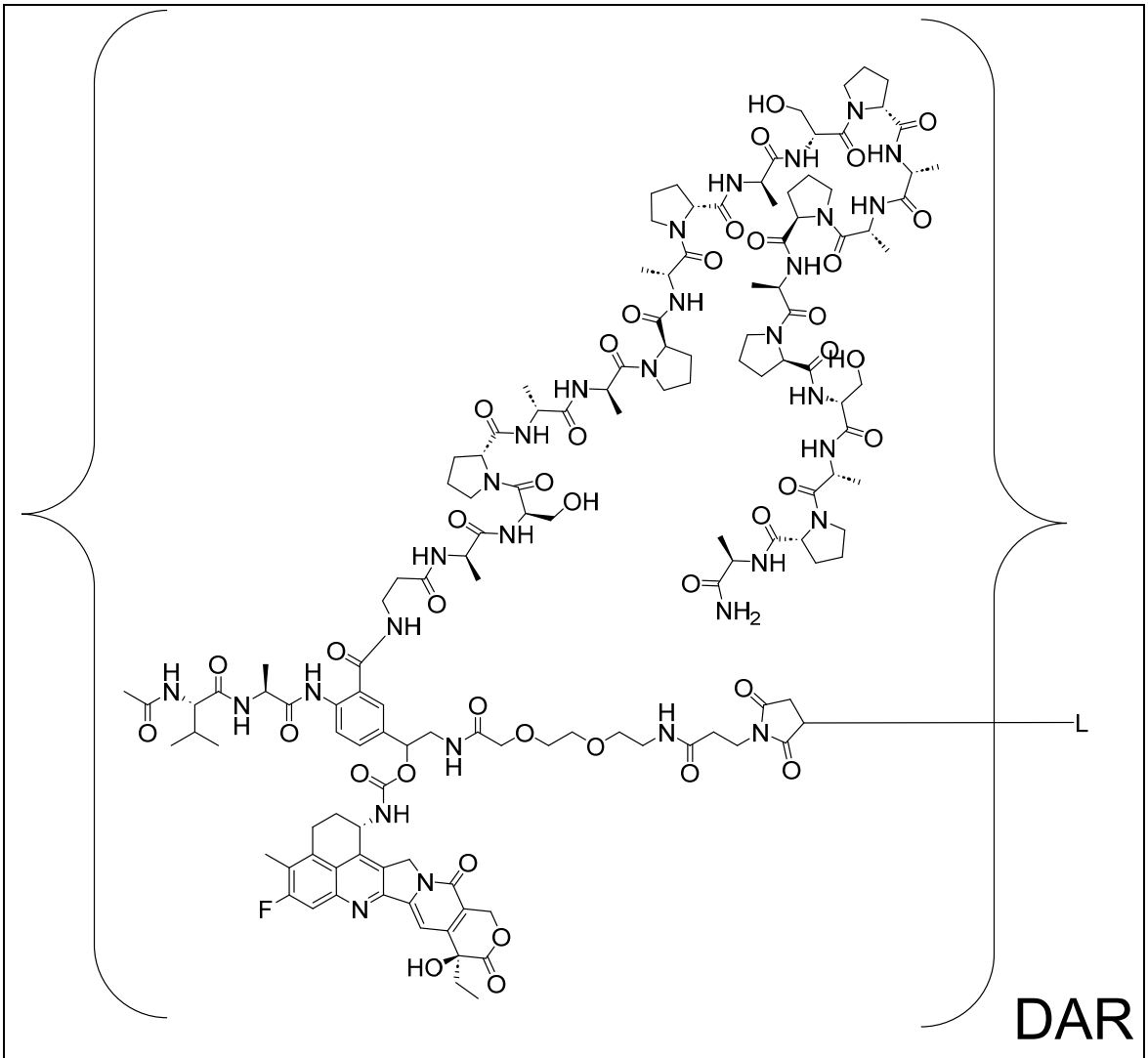
DAR (SEQ ID NO: 35)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



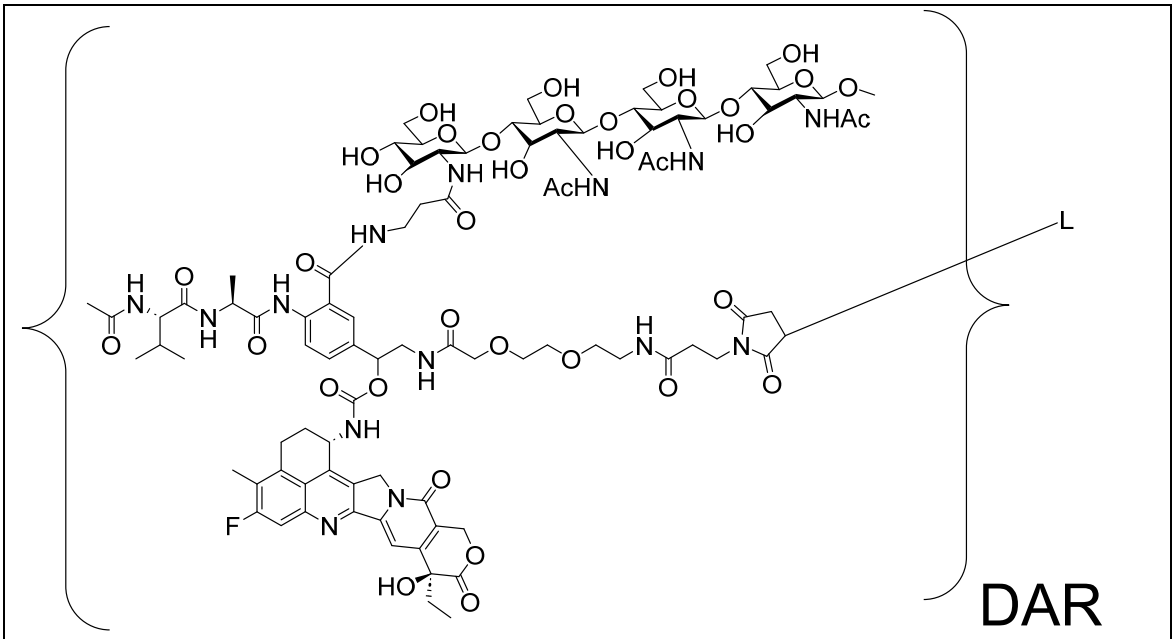
DAR (SEQ ID NO: 36)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.

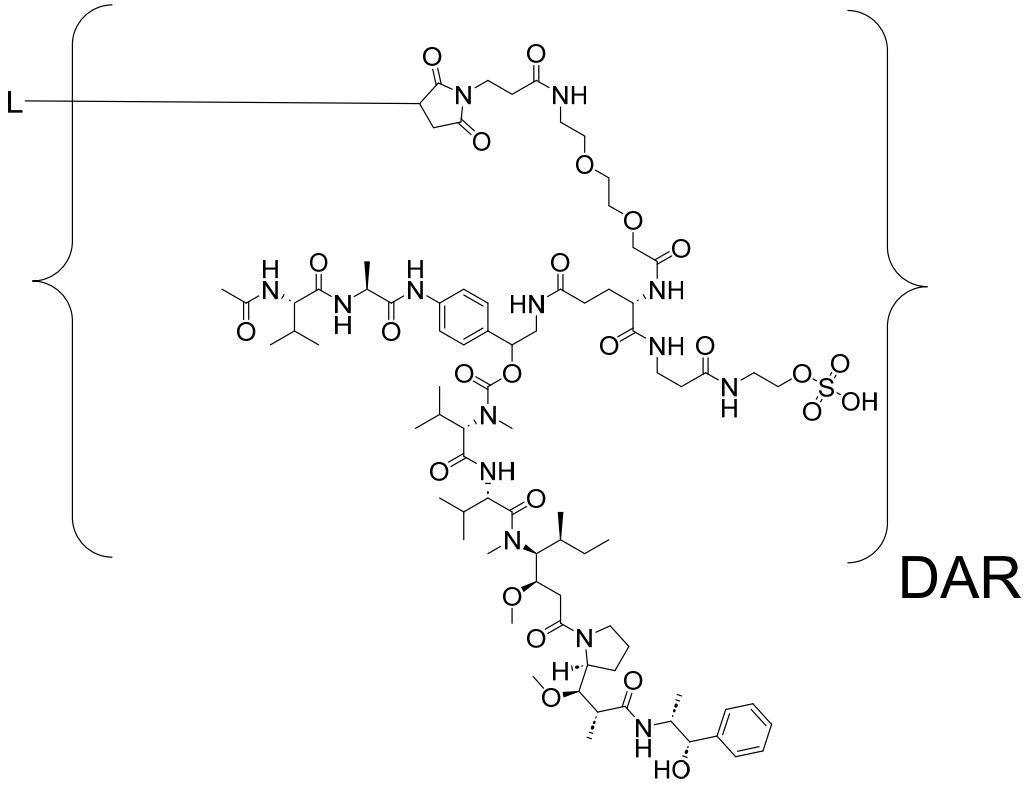


(SEQ ID NO: 36)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.

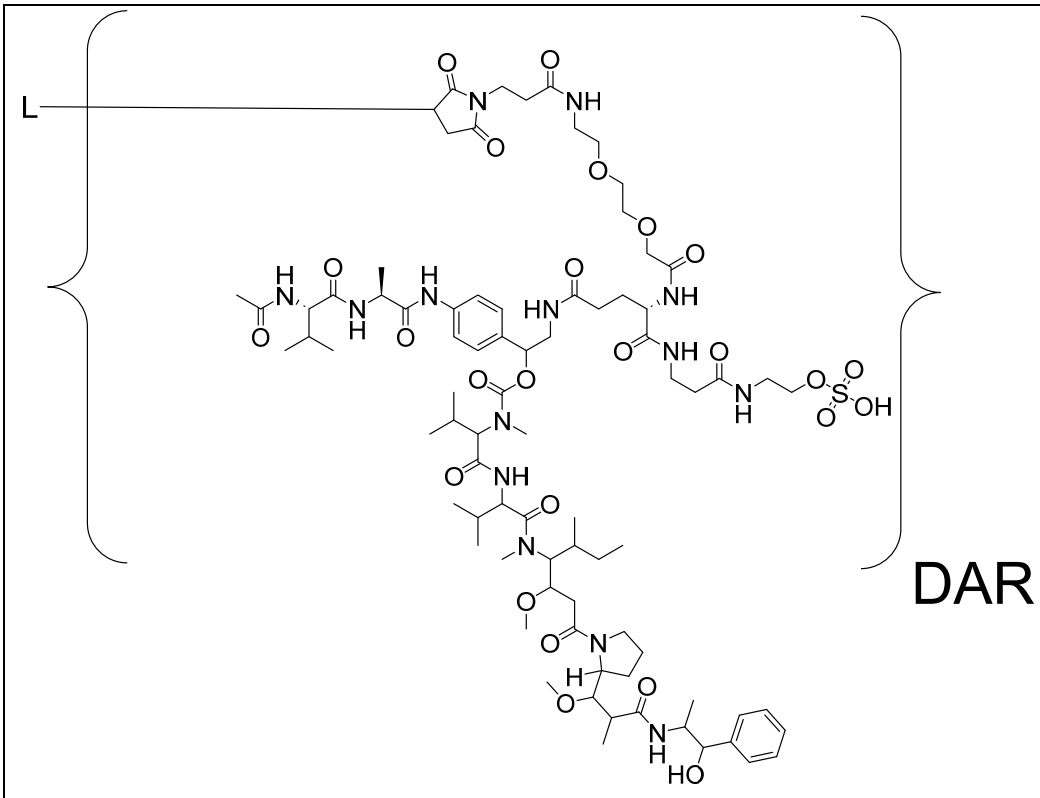


1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



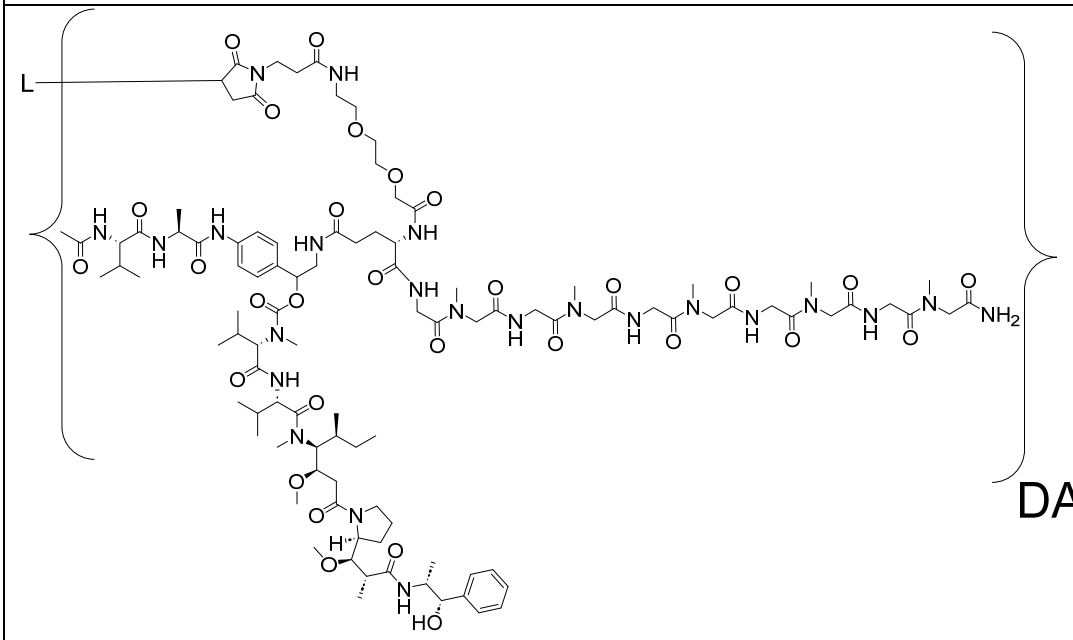
(SEQ ID NO: 22)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



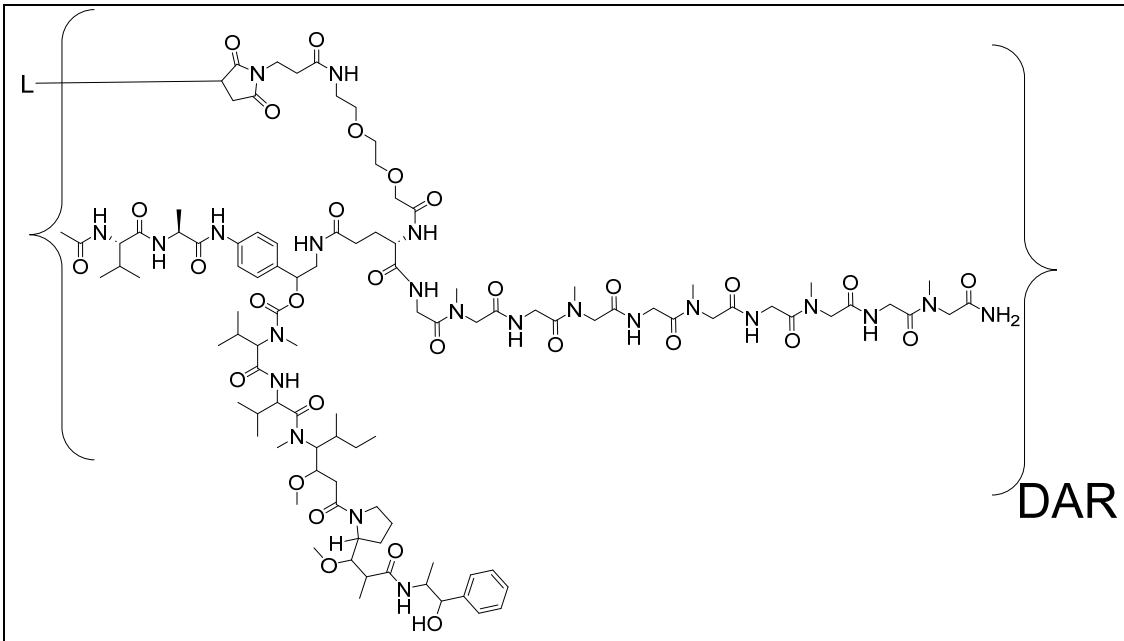
(SEQ ID NO: 22)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



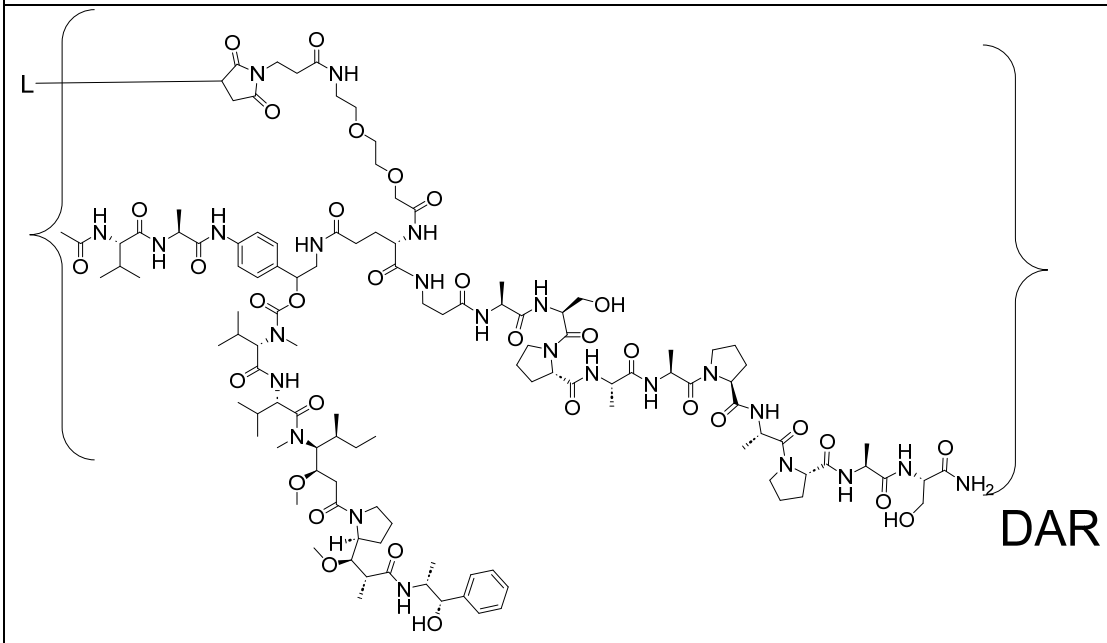
(SEQ ID NOS 26 and 22, respectively, in order of appearance)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



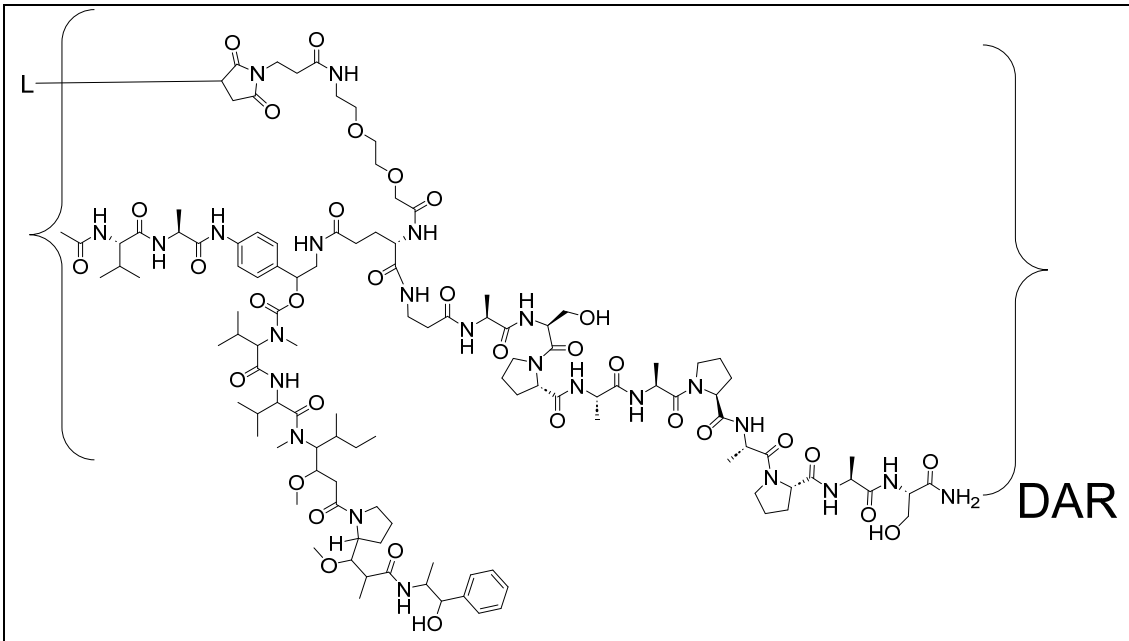
(SEQ ID NOS 26 and 22, respectively, in order of appearance)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



(SEQ ID NOS 27 and 22, respectively, in order of appearance)

1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.



(SEQ ID NOS 27 and 22, respectively, in order of appearance)

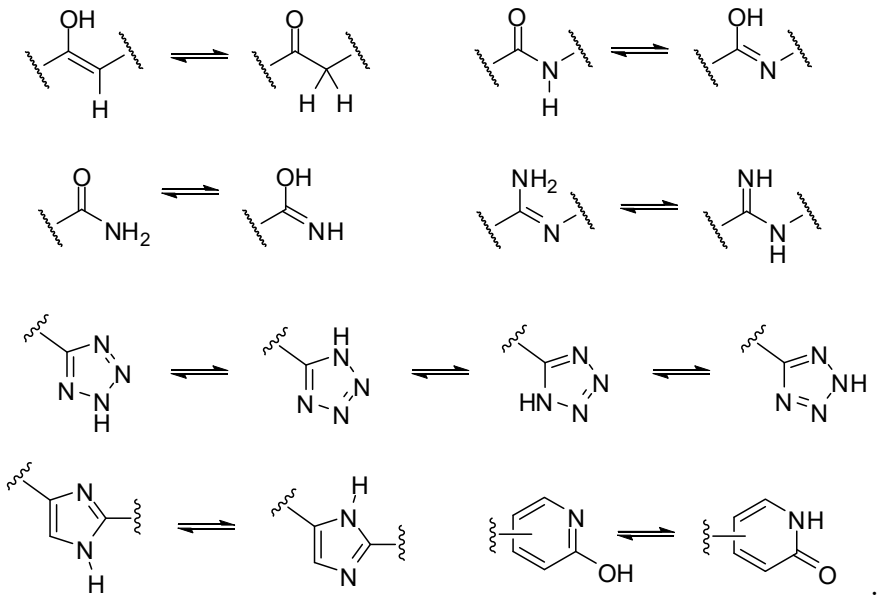
1) L is UC-961 antibody having SEQ ID NO:1 and SEQ ID NO:2; or
2) L is ROR2 antibody having SEQ ID NO:3 and SEQ ID NO:4.

Conjugates of Table A have a DAR of about 1 to about 8. Conjugates of Table A have a DAR of about 2 to about 8. Some of the conjugates have a DAR of about 2. Some of the conjugates have a DAR of about 8.

[00208] Included in the present disclosure are salts, particularly pharmaceutically acceptable salts, of the compounds described herein. The compounds of the present invention that possess a sufficiently acidic, a sufficiently basic, or both functional groups, can react with any of a number of inorganic bases, and inorganic and organic acids, to form a salt. Alternatively, compounds that are inherently charged, such as those with a quaternary nitrogen, can form a salt with an appropriate counterion, e.g., a halide such as bromide, chloride, or fluoride, particularly bromide.

[00209] Chemical entities having carbon-carbon double bonds or carbon-nitrogen double bonds may exist in *Z*- or *E*- form (or *cis*- or *trans*- form). Furthermore, some chemical entities may exist in various tautomeric forms. Unless otherwise specified, compounds described herein are intended to include all *Z*-, *E*- and tautomeric forms as well.

[00210] A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[00211] The compounds disclosed herein, in some embodiments, are used in different enriched isotopic forms, e.g., enriched in the content of ^{2}H, ^{3}H, ^{11}C, ^{13}C and/or ^{14}C. In one particular embodiment, the compound is deuterated in at least one position. Such deuterated forms can be made by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. As described in U.S. Patent Nos. 5,846,514 and 6,334,997, deuteration can improve the metabolic stability and or efficacy, thus increasing the duration of action of drugs.

[00212] Unless otherwise stated, compounds described herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of the present disclosure.

[00213] The compounds of the present disclosure optionally contain unnatural proportions of atomic isotopes at one or more atoms that constitute such compounds. For example, the compounds may be labeled with isotopes, such as for example**,** deuterium (^{2}H), tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). Isotopic substitution with ^{2}H, ^{11}C, ^{13}C, ^{14}C, ^{15}C, ^{12}N, ^{13}N, ^{15}N, ^{16}N, ^{16}O, ^{17}O, ^{14}F, ^{15}F, ^{16}F, ^{17}F, ^{18}F, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{35}Cl, ^{37}Cl, ^{79}Br, ^{81}Br, and ^{125}I are all contemplated. All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[00214] In certain embodiments, the compounds disclosed herein have some or all of the ^{1}H atoms replaced with ^{2}H atoms. The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the following synthetic methods.

[00215] Deuterium substituted compounds are synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] **2000**, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, **1989**, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., **1981**, 64(1-2), 9-32.

[00216] Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

[00217] Compounds of the present invention also include crystalline and amorphous forms of those compounds, pharmaceutically acceptable salts, and active metabolites of these compounds having the same type of activity, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[00218] The compounds described herein may in some cases exist as diastereomers, enantiomers, or other stereoisomeric forms. Where absolute stereochemistry is not specified, the compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Separation of stereoisomers may be performed by chromatography or by forming diastereomers and separating by recrystallization, or chromatography, or any combination thereof. (Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981, herein incorporated by reference for this disclosure). Stereoisomers may also be obtained by stereoselective synthesis.

[00219] The methods and compositions described herein include the use of amorphous forms as well as crystalline forms (also known as polymorphs). The compounds described herein may be in the form of pharmaceutically acceptable salts. As well, in some embodiments, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00220] In certain embodiments, compounds or salts of the compounds may be prodrugs, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate, or carboxylic acid present in the parent compound is presented as an ester. The term "prodrug" is intended to

encompass compounds which, under physiologic conditions, are converted into pharmaceutical agents of the present disclosure. One method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal such as specific target cells in the host animal. For example, esters or carbonates (e.g., esters or carbonates of alcohols or carboxylic acids and esters of phosphonic acids) are preferred prodrugs of the present disclosure.

[00221] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound as set forth herein are included within the scope of the claims. In some cases, some of the herein-described compounds may be a prodrug for another derivative or active compound.

[00222] Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. Prodrugs may help enhance the cell permeability of a compound relative to the parent drug. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues or to increase drug residence inside of a cell.

[00223] In some embodiments, the design of a prodrug increases the lipophilicity of the pharmaceutical agent. In some embodiments, the design of a prodrug increases the effective water solubility. See, e.g., Fedorak *et al*., *Am. J. Physiol.*, 269:G210-218 (1995); McLoed *et al*., *Gastroenterol*, 106:405-413 (1994); Hochhaus *et al*., *Biomed. Chrom.,* 6:283-286 (1992); J. Larsen and H. Bundgaard, *Int. J. Pharmaceutics,* 37, 87 (1987); J. Larsen et al., *Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula *et al*., *J. Pharm. Sci*., 64:181-210 (1975); T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, all incorporated herein for such disclosure). According to another embodiment, the present disclosure provides methods of producing the above-defined compounds. The compounds may be synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

[00224] Synthetic chemistry transformations and methodologies useful in synthesizing the compounds described herein are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations* (1989); T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis,* 2d. Ed. (1991); L. Fieser and M. Fieser, *Fieser*

and Fieser's Reagents for Organic Synthesis (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis* (1995).

Targeting Unit

[00225] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-B), Formula (II-A), Formula (II-B) (each of which further comprises a targeting unit), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), the Targeting Unit is selected from an antibody or an antigen-binding fragment thereof. In some cases, the Targeting Unit is selected from a group consisting of chimeric antibodies, humanized antibodies, and human antibodies. In some cases, the Targeting Unit, performs a targeting function. In some cases, a Targeting unit specifically binds to a target molecule. In some cases, specifically binds refers to the ability of a Targeting unit (e.g., an antibody or portion thereof) described herein to bind to a target with a KD 10^{-5} M (10000 nM) or less, e.g., 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, or less. In some cases, a Targeting unit is said to specifically bind to its target when it preferentially recognizes its target in a complex mixture of proteins and/or macromolecules.

[00226] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-A), Formula (II-B), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), the Targeting unit is an antibody or antigen binding portion thereof is a bispecific or multispecific binding agent. Bispecific and multi-specific antibodies include the following: an scFv1-ScFv2, an ScFv1 2-Fc-scFv2 2, an IgG-scFv, a DVD-Ig, a triomab/quadroma, a two-in-one IgG, a scFv2-Fc, a TandAb, and an scFv-HSA-scFv. In some embodiments, an IgG-scFv is an IgG (H) -scFv, scFv-(H) IgG, IgG (L) -scFv, svFc- (L) IgG, 2scFV-IgG or IgG-2scFv.

[00227] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-A), Formula (II-B), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), the Targeting unit is capable of binding the extracellular domain of ROR1.

[00228] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-A), Formula (II-B), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula

(A-1), Formula (A-2), Formula (A-3), or Formula (A-4), the Targeting unit is UC-961. In some cases, L is UC-961

[00229] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-A), Formula (II-B), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), the Targeting unit is a cancer associated antigen such as CD19, CD20, CD30, CD33, CD38, CA125, MUC-1, prostate-specific membrane antigen (PSMA), CD44 surface adhesion molecule, mesothelin (MLSN), carcinoembryonic antigen (CEA), epidermal growth factor receptor (EGFR), EGFRvIII, vascular endothelial growth factor receptor-2 (VEGFR2) , high molecular weight-melanoma associated antigen (HMW-MAA) , MAGE-A1, IL-13R-a2, GD2, 1p19q, ABL1, AKT1, ALK, APC, AR, ATM, BRAF, BRCA1, BRCA2, cKIT, cMET, CSF1R, CTNNB1, FGFR1, FGFR2, FLT3, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, JAK2, KDR (VEGFR2) , KRAS, MGMT, MGMT-Me, MLH1, MPL, NOTCH1, NRAS, PDGFRA, Pgp, PIK3CA, PR, PTEN, RET, RRM1, SMO, SPARC, TLE3, TOP2A, TOPO1, TP53, TS, TUBB3, VHL, CDH1, ERBB4, FBXW7, HNF1A, JAK3, NPM1, PTPN11, RB1, SMAD4, SMARCB1, STK1, MLH1, MSH2, MSH6, PMS2, ROS1, ERCC1, 5T4 (TPBG) , B7-H3, CCR7, CD105, CD22, CD46, CD47, CD56, CD70, CD71, CD79b, CDH6, CLDN6, CLDN18.2, CLEC12A, DLL3, DR5, ERBB3 (HER3) , EPCAM, FOLR1, IGF1R, IL2RA (CD25) , IL3RA, ITGB6, LIV-1, LRRC15, mesothelin (MSLN) , NaPi2b (SLC34A2) , nectin-4, PTK7, ROR1, SEZ6, SLC44A4, SLITRK6, Tissue Factor (TF) , TROP2 or B7-H4.

[00230] In some embodiments, a Targeting unit specifically binds to a target such as CD19, CD20, CD30, CD33, CD70, LIV-1 or EGFRv3.

[00231] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-B), Formula (II-A), Formula (II-B) (each of which further comprises a targeting unit), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), the Targeting unit includes at least one amino acid. In some cases, the Targeting unit is one or more amino acids. In some cases, the Targeting unit includes one or more natural amino acids. In some cases, the Targeting unit includes one or more unnatural amino acids. In some cases, unnatural amino acids (p-acetylphenylalanine or pAcF and p-azidomethyl-L-phenylalanine or pAMF), or short peptide tags. In some cases, the Targeting unit includes a cysteine. In some cases, the Targeting unit includes a glutamine. In some cases, the Targeting unit is a peptide having less than 50 amino acids. In some cases, the Targeting unit is a peptide having less than 40 amino acids. In some

cases, the Targeting unit is a peptide having less than 30 amino acids. In some cases, the Targeting unit is a peptide having less than 20 amino acids. In some cases, the Targeting unit is a peptide having more than 50 amino acids. In some cases, the Targeting unit is a peptide having more than 40 amino acids. In some cases, the Targeting unit is a peptide having more than 30 amino acids. In some cases, the Targeting unit is a peptide having more than 20 amino acids. In some cases, the Targeting unit is a peptide having more than 10 amino acids. In some cases, the Targeting unit is a peptide having more than 5 amino acids. In some cases, the Targeting unit is a peptide having about 1 to about 50 amino acids. In some cases, the Targeting unit is a peptide having about 2 to about 30 amino acids. In some cases, the Targeting unit is a peptide having about 3 to about 15 amino acids. In some cases, the Targeting unit includes a cyclic peptide.

[00232] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-B), Formula (II-A), Formula (II-B) (each of which further comprises a targeting unit), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), the Targeting unit has at least one sulfur atom. In some cases, the Targeting unit has at least one sulfur atom from a cysteine residue. In some cases, the Targeting unit has at least one sulfur atom from a reduced cysteine residue.

[00233] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-B), Formula (II-A), Formula (II-B) (each of which further comprises a targeting unit), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:1 and the light chain variable region is SEQ ID NO:2. In some cases the Targeting unit has an antibody comprising a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the heavy chain variable region is SEQ ID NO:3 and the light chain variable region is SEQ ID NO:4. In some cases, the heavy chain variable region further comprises a heavy chain constant region. In some cases, the heavy chain constant region is of the IgG isotype. In some cases, the heavy chain constant region is an IgG1 constant region. In some cases, the heavy chain constant region is an IgG4 constant region.

[00234] In some embodiments, for a Drug-Linker or salt of Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-B), Formula (II-A), Formula (II-B) (each of which further comprises a targeting unit), or for a conjugate or salt of Formula (A), Formula (Aa), Formula (Ab), Formula

(A-1), Formula (A-2), Formula (A-3), or Formula (A-4), the Targeting unit, such as an antibody or antigen-binding portion thereof or other Targeting unit, has an antibody constant region(s). In some cases, the constant region is a fully human constant region(s). In some cases, the constant region is a humanized constant region(s). In some cases, the constant region is a non-human constant region(s). In some cases, an immunoglobulin constant region refers to a heavy or light chain constant region. A constant region can be of any suitable type, which can be selected from the classes of immunoglobulins, IgA, IgD, IgE, IgG, and IgM. Several immunoglobulin classes can be further divided into isotypes, e.g., IgG1, IgG2, IgG3, IgG4, or IgAl, and IgA2. The heavy-chain constant regions (Fc) that correspond to the different classes of immunoglobulins can be α, δ, ε, γ, and μ, respectively. The light chains can be one of either kappa (κ) and lambda (λ) .

In some embodiments, a constant region can have an IgG isotype. In some embodiments, a constant region can have an IgG1 isotype. In some embodiments, a constant region can have an IgG2 isotype. In some embodiments, a constant region can have an IgG3 isotype. In some embodiments, a constant region can have an IgG4 isotype. In some embodiments, a constant region can have a hybrid isotype comprising constant regions from two or more isotypes. In some embodiments, an immunoglobulin constant region can be an IgG1 or IgG4 constant region.

Pharmaceutical Formulations

[00235] Provided herein, in certain embodiments, are pharmaceutical compositions comprising a therapeutically effective amount of a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-B), Formula (II-A), Formula (II-B), or for a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), (also referred to herein as “a pharmaceutical agent”).

[00236] Pharmaceutical compositions may be formulated using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the pharmaceutical agent into preparations which are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa., Mack Publishing Company, 1995); Hoover, John E., Remington’s Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L.,

Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins, 1999).

[00237] The compositions and methods of the present disclosure may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the pharmaceutical agent, is preferably administered as a pharmaceutical composition comprising, for example, a pharmaceutical agent and a pharmaceutically acceptable carrier or excipient. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In a preferred embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration, e.g., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier, the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule, granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

[00238] A pharmaceutically acceptable excipient can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a pharmaceutical agent. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable excipient, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a self emulsifying drug delivery system or a self microemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the invention. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

[00239] A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally, for example, drenches as

in aqueous or non-aqueous solutions or suspensions, tablets, capsules, including sprinkle capsules and gelatin capsules, boluses, powders, granules, pastes for application to the tongue; absorption through the oral mucosa, e.g., sublingually; anally, rectally or vaginally, for example, as a pessary, cream or foam; parenterally, including intramuscularly, intravenously, subcutaneously or intrathecally as, for example, a sterile solution or suspension; nasally; intraperitoneally; subcutaneously; transdermally, for example, as a patch applied to the skin; and topically, for example, as a cream, ointment or spray applied to the skin, or as an eye drop. The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water.

[00240] A pharmaceutical composition may be a sterile aqueous or non-aqueous solution, suspension or emulsion, *e.g.,* a microemulsion. The excipients described herein are examples and are in no way limiting. An effective amount or therapeutically effective amount refers to an amount of the one or more pharmaceutical agents administered to a subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[00241] Subjects may generally be monitored for therapeutic effectiveness using assays and methods suitable for the condition being treated, which assays will be familiar to those having ordinary skill in the art and are described herein. Pharmacokinetics of a pharmaceutical agent, or one or more metabolites thereof, that is administered to a subject may be monitored by determining the level of the pharmaceutical agent or metabolite in a biological fluid, for example, in the blood, blood fraction, *e.g.,* serum, and/or in the urine, and/or other biological sample or biological tissue from the subject. Any method practiced in the art and described herein to detect the agent may be used to measure the level of the pharmaceutical agent or metabolite during a treatment course.

[00242] The dose of a pharmaceutical agent described herein for treating a disease or disorder may depend upon the subject's condition, that is, stage of the disease, severity of symptoms caused by the disease, general health status, as well as age, gender, and weight, and other factors apparent to a person skilled in the medical art. Pharmaceutical compositions may be administered in a manner appropriate to the disease to be treated as determined by persons skilled in the medical arts. In addition to the factors described herein and above related to use of pharmaceutical agent for treating a disease or disorder, suitable duration and frequency of administration of the pharmaceutical agent may also be determined or adjusted by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. Optimal doses of an agent may generally be determined using experimental models and/or clinical trials. The optimal dose may depend upon the body mass, weight, or blood volume of the subject. The use of the minimum

dose that is sufficient to provide effective therapy is usually preferred. Design and execution of pre-clinical and clinical studies for a pharmaceutical agent, including when administered for prophylactic benefit, described herein are well within the skill of a person skilled in the relevant art. When two or more pharmaceutical agents are administered to treat a disease or disorder, the optimal dose of each pharmaceutical agent may be different, such as less than when either agent is administered alone as a single agent therapy. In certain particular embodiments, two pharmaceutical agents in combination may act synergistically or additively, and either agent may be used in a lesser amount than if administered alone. An amount of a pharmaceutical agent that may be administered per day may be, for example, between about 0.01 mg/kg and 100 mg/kg, *e.g.*, between about 0.1 to 1 mg/kg, between about 1 to 10 mg/kg, between about 10-50 mg/kg, between about 50-100 mg/kg body weight. In other embodiments, the amount of a pharmaceutical agent that may be administered per day is between about 0.01 mg/kg and 1000 mg/kg, between about 100-500 mg/kg, or between about 500-1000 mg/kg body weight. The optimal dose, per day or per course of treatment, may be different for the disease or disorder to be treated and may also vary with the administrative route and therapeutic regimen.

[00243] Pharmaceutical compositions comprising a pharmaceutical agent can be formulated in a manner appropriate for the delivery method by using techniques routinely practiced in the art. The composition may be in the form of a solid, *e.g.,* tablet, capsule, semi-solid, *e.g.,* gel, liquid, or gas, e.g., aerosol. In other embodiments, the pharmaceutical composition is administered as a bolus infusion.

[00244] Pharmaceutical acceptable excipients are well known in the pharmaceutical art and described, for example, in Rowe et al., Handbook of Pharmaceutical Excipients: A Comprehensive Guide to Uses, Properties, and Safety, 5th Ed., 2006, and in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)). Exemplary pharmaceutically acceptable excipients include sterile saline and phosphate buffered saline at physiological pH. Preservatives, stabilizers, dyes, buffers, and the like may be provided in the pharmaceutical composition. In addition, antioxidants and suspending agents may also be used. In general, the type of excipient is selected based on the mode of administration, as well as the chemical composition of the active ingredient(s). Alternatively, compositions described herein may be formulated as a lyophilizate. A composition described herein may be lyophilized or otherwise formulated as a lyophilized product using one or more appropriate excipient solutions for solubilizing and/or diluting the pharmaceutical agent(s) of the composition upon administration. In other embodiments, the pharmaceutical agent may be encapsulated within liposomes using technology known and practiced in the art. In certain particular embodiments, a pharmaceutical agent is not formulated within liposomes for application to a stent that is used

for treating highly, though not totally, occluded arteries. Pharmaceutical compositions may be formulated for any appropriate manner of administration described herein and in the art.

[00245] A pharmaceutical composition, *e.g.,* for oral administration or for injection, infusion, subcutaneous delivery, intramuscular delivery, intraperitoneal delivery or other method, may be in the form of a liquid. A liquid pharmaceutical composition may include, for example, one or more of the following: a sterile diluent such as water, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils that may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents; antioxidants; chelating agents; buffers and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral composition can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. The use of physiological saline is preferred, and an injectable pharmaceutical composition is preferably sterile. In another embodiment, for treatment of an ophthalmological condition or disease, a liquid pharmaceutical composition may be applied to the eye in the form of eye drops. A liquid pharmaceutical composition may be delivered orally.

[00246] For oral formulations, at least one of the pharmaceutical agents described herein can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, and if desired, with diluents, buffering agents, moistening agents, preservatives, coloring agents, and flavoring agents. The pharmaceutical agents may be formulated with a buffering agent to provide for protection of the compound from low pH of the gastric environment and/or an enteric coating. A pharmaceutical agent included in a pharmaceutical composition may be formulated for oral delivery with a flavoring agent, *e.g.*, in a liquid, solid or semi-solid formulation and/or with an enteric coating.

[00247] A pharmaceutical composition comprising any one of the pharmaceutical agents described herein may be formulated for sustained or slow release, also called timed release or controlled release. Such compositions may generally be prepared using well known technology and administered by, for example, oral, rectal, intradermal, or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain the compound dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Excipients for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of pharmaceutical agent contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release, and the nature of the condition, disease or disorder to be treated or prevented.

[00248] In certain embodiments, the pharmaceutical compositions comprising a pharmaceutical agent are formulated for transdermal, intradermal, or topical administration. The compositions can be administered using a syringe, bandage, transdermal patch, insert, or syringe-like applicator, as a powder/talc or other solid, liquid, spray, aerosol, ointment, foam, cream, gel, paste. This preferably is in the form of a controlled release formulation or sustained release formulation administered topically or injected directly into the skin adjacent to or within the area to be treated, e.g., intradermally or subcutaneously. The active compositions can also be delivered via iontophoresis. Preservatives can be used to prevent the growth of fungi and other microorganisms. Suitable preservatives include, but are not limited to, benzoic acid, butylparaben, ethyl paraben, methyl paraben, propylparaben, sodium benzoate, sodium propionate, benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, thimerosal, and combinations thereof.

[00249] Pharmaceutical compositions comprising a pharmaceutical agent can be formulated as emulsions for topical application. An emulsion contains one liquid distributed in the body of a second liquid. The emulsion may be an oil-in-water emulsion or a water-in-oil emulsion. Either or both of the oil phase and the aqueous phase may contain one or more surfactants, emulsifiers, emulsion stabilizers, buffers, and other excipients. The oil phase may contain other oily pharmaceutically approved excipients. Suitable surfactants include, but are not limited to, anionic surfactants, non-ionic surfactants, cationic surfactants, and amphoteric surfactants. Compositions for topical application may also include at least one suitable suspending agent, antioxidant, chelating agent, emollient, or humectant.

[00250] Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Liquid sprays may be delivered from pressurized packs, for example, via a specially shaped closure. Oil-in-water emulsions can also be used in the compositions, patches, bandages and articles. These systems are semisolid emulsions, micro-emulsions, or foam emulsion systems.

[00251] In some embodiments, the pharmaceutical agent described herein can be formulated as in inhalant. Inhaled methods can deliver medication directly to the airway. The pharmaceutical agent can be formulated as aerosols, microspheres, liposomes, or nanoparticles. The pharmaceutical agent can be formulated with solvents, gases, nitrates, or any combinations thereof. Compositions described herein are optionally formulated for delivery as a liquid aerosol or inhalable dry powder. Liquid aerosol formulations are optionally nebulized predominantly into particle sizes that can be delivered to the terminal and respiratory bronchioles. Liquid

aerosol and inhalable dry powder formulations are preferably delivered throughout the endobronchial tree to the terminal bronchioles and eventually to the parenchymal tissue.

[00252] Aerosolized formulations described herein are optionally delivered using an aerosol forming device, such as a jet, vibrating porous plate or ultrasonic nebulizer, preferably selected to allow the formation of aerosol particles having with a mass medium average diameter predominantly between 1 to 5 μ. Further, the formulation preferably has balanced osmolarity ionic strength and chloride concentration, and the smallest aerosolizable volume able to deliver effective dose of the pharmaceutical agent. Additionally, the aerosolized formulation preferably does not impair negatively the functionality of the airways and does not cause undesirable side effects.

[00253] Aerosolization devices suitable for administration of aerosol formulations described herein include, for example, jet, vibrating porous plate, ultrasonic nebulizers and energized dry powder inhalers, that are able to nebulize the formulation into aerosol particle size predominantly in the size range from 1-5 μ. Predominantly in this application means that at least 70% but preferably more than 90% of all generated aerosol particles are within 1-5 μ range. A jet nebulizer works by air pressure to break a liquid solution into aerosol droplets. Vibrating porous plate nebulizers work by using a sonic vacuum produced by a rapidly vibrating porous plate to extrude a solvent droplet through a porous plate. An ultrasonic nebulizer works by a piezoelectric crystal that shears a liquid into small aerosol droplets. A variety of suitable devices are available, including, for example, AeroNebTM and AeroDoseTM vibrating porous plate nebulizers (AeroGen, Inc., Sunnyvale, California), Sidestream® nebulizers (Medic-Aid Ltd., West Sussex, England), Pari LC® and Pari LC Star® jet nebulizers (Pari Respiratory Equipment, Inc., Richmond, Virginia), and AerosonicTM (DeVilbiss Medizinische Produkte (Deutschland) GmbH, Heiden, Germany) and UltraAire® (Omron Healthcare, Inc., Vernon Hills, Illinois) ultrasonic nebulizers.

[00254] In some embodiments, the pharmaceutical agent(s) can be formulated with oleaginous bases or ointments to form a semisolid composition with a desired shape. In addition to the pharmaceutical agent, these semisolid compositions can contain dissolved and/or suspended bactericidal agents, preservatives and/or a buffer system. A petrolatum component that may be included may be any paraffin ranging in viscosity from mineral oil that incorporates isobutylene, colloidal silica, or stearate salts to paraffin waxes. Absorption bases can be used with an oleaginous system. Additives may include cholesterol, lanolin (lanolin derivatives, beeswax, fatty alcohols, wool wax alcohols, low HLB (hydrophobellipophobe balance) emulsifiers, and assorted ionic and nonionic surfactants, singularly or in combination.

[00255] Controlled or sustained release transdermal or topical formulations can be achieved by the addition of time-release additives, such as polymeric structures, matrices, that are available in the art. For example, the compositions may be administered through use of hot-melt extrusion articles, such as bioadhesive hot-melt extruded film. The formulation can comprise a cross-linked polycarboxylic acid polymer formulation. A cross-linking agent may be present in an amount that provides adequate adhesion to allow the system to remain attached to target epithelial or endothelial cell surfaces for a sufficient time to allow the desired release of the compound.

[00256] An insert, transdermal patch, bandage or article can comprise a mixture or coating of polymers that provide release of the pharmaceutical agents at a constant rate over a prolonged period of time. In some embodiments, the article, transdermal patch or insert comprises water-soluble pore forming agents, such as polyethylene glycol (PEG) that can be mixed with water insoluble polymers to increase the durability of the insert and to prolong the release of the active ingredients.

[00257] Transdermal devices (inserts, patches, bandages) may also comprise a water insoluble polymer. Rate controlling polymers may be useful for administration to sites where pH change can be used to effect release. These rate controlling polymers can be applied using a continuous coating film during the process of spraying and drying with the active compound. In one embodiment, the coating formulation is used to coat pellets comprising the active ingredients that are compressed to form a solid, biodegradable insert.

[00258] A polymer formulation can also be utilized to provide controlled or sustained release. Bioadhesive polymers described in the art may be used. By way of example, a sustained-release gel and the compound may be incorporated in a polymeric matrix, such as a hydrophobic polymer matrix. Examples of a polymeric matrix include a microparticle. The microparticles can be microspheres, and the core may be of a different material than the polymeric shell. Alternatively, the polymer may be cast as a thin slab or film, a powder produced by grinding or other standard techniques, or a gel such as a hydrogel. The polymer can also be in the form of a coating or part of a bandage, stent, catheter, vascular graft, or other device to facilitate delivery of the pharmaceutical agent. The matrices can be formed by solvent evaporation, spray drying, solvent extraction and other methods known to those skilled in the art.

[00259] Kits with unit doses of one or more of the agents described herein, usually in oral or injectable doses, are provided. Such kits may include a container containing the unit dose, an informational package insert describing the use and attendant benefits of the drugs in treating disease, and optionally an appliance or device for delivery of the composition.

Methods of Treatment

[00260] In an aspect, the present disclosure provides a method of treating a subject with a tumor. In some cases, the treatment of a subject with the tumor includes administering to a subject in need thereof a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-A), Formula (II-B) (which further comprises a targeting unit), or a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), or a pharmaceutical composition of any one thereof. In some cases, the tumor is associated with a cancer. In some cases, the cancer is selected from the group consisting of lung cancer, kidney cancer, urethral cancer, colorectal cancer, prostate cancer, glioblastoma multiforme, ovarian cancer, pancreatic, breast, melanoma, liver, bladder, stomach, and esophageal cancers. In some cases, the cancer is small cell lung cancer. In some cases, the cancer is large cell lung cancer.

[00261] In an aspect, the present disclosure provides a method of treating a subject with a cancer. In some cases, the treatment of a subject with the cancer includes administering to a subject in need thereof a Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-A), Formula (II-B) (which further comprises a targeting unit), or a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), or Formula (A-4), or a pharmaceutical composition of any one thereof. In some cases, the tumor is associated with a cancer. In some cases, the cancer is selected from the group consisting of lung cancer, kidney cancer, urethral cancer, colorectal cancer, prostate cancer, glioblastoma multiforme, ovarian cancer, pancreatic, breast, melanoma, liver, bladder, stomach, and esophageal cancers. In some cases, the cancer is small cell lung cancer. In some cases, the cancer is large cell lung cancer.

[00262] In some embodiments, compounds described herein can be used for treating diseases such as, but not limited to, hyperproliferative diseases, including: cancers of the head and neck which include tumors of the head, neck, nasal cavity, paranasal sinuses, nasopharynx, oral cavity, oropharynx, larynx, hypopharynx, salivary glands, and paragangliomas; cancers of the liver and biliary tree, particularly hepatocellular carcinoma; intestinal cancers, particularly colorectal cancer; ovarian cancer; small cell and non-small cell lung cancer (SCLC and NSCLC); breast cancer sarcomas, such as fibrosarcoma, malignant fibrous histiocytoma, embryonal rhabdomyosarcoma, leiomysosarcoma, neurofibrosarcoma, osteosarcoma, synovial

sarcoma, liposarcoma, and alveolar soft part sarcoma; leukemias such as acute promyelocytic leukemia (APL), acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelogenous leukemia (CML); neoplasms of the central nervous systems, particularly brain cancer; multiple myeloma (MM), lymphomas such as Hodgkin's lymphoma, lymphoplasmacytoid lymphoma, follicular lymphoma, mucosa-associated lymphoid tissue lymphoma, mantle cell lymphoma, B-lineage large cell lymphoma, Burkitt's lymphoma, and T-cell anaplastic large cell lymphoma. Clinically, practice of the methods and use of compositions described herein will result in a reduction in the size or number of the cancerous growth and/or a reduction in associated symptoms (where applicable). Pathologically, practice of the method and use of compositions described herein will produce a pathologically relevant response, such as: inhibition of cancer cell proliferation, reduction in the size of the cancer or tumor, prevention of further metastasis, and inhibition of tumor angiogenesis. The method of treating such diseases comprises administering a therapeutically effective amount of an inventive combination to a subject. The method may be repeated as necessary. The cancer can be renal, lung, gastric, or ovarian cancer.

[00263] In some embodiments, the treatment of tumor-bearing subjects inhibits tumor growth by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects. A therapeutically effective amount of a therapeutic compound can decrease tumor size, or otherwise ameliorate symptoms in a subject, which is typically a human but can be another mammal.

[00264] In some embodiments, compositions described herein can be administered in combination with other therapeutic agents, including antibodies, alkylating agents, angiogenesis inhibitors, antimetabolites, DNA cleavers, DNA crosslinkers, DNA intercalators, DNA minor groove binders, enediynes, heat shock protein 90 inhibitors, histone deacetylase inhibitors, immunomodulators, microtubule stabilizers, nucleoside (purine or pyrimidine) analogs, nuclear export inhibitors, proteasome inhibitors, topoisomerase (I or II) inhibitors, tyrosine kinase inhibitors, and serine/threonine kinase inhibitors. Specific therapeutic agents include adalimumab, ansamitocin P3, auristatin, bendamustine, bevacizumab, bicalutamide, bleomycin, bortezomib, busulfan, callistatin A, camptothecin, capecitabine, carboplatin, carmustine, cetuximab, cisplatin, cladribin, cytarabin, cryptophycins, dacarbazine, dasatinib, daunorubicin, docetaxel, doxorubicin, duocarmycin, dynemycin A, epothilones, etoposide, floxuridine, fludarabine, 5-fluorouracil, gefitinib, gemcitabine, ipilimumab, hydroxyurea, imatinib, infliximab, interferons, interleukins, β-lapachone, lenalidomide, irinotecan, maytansine, mechlorethamine, melphalan, 6-mercaptopurine, methotrexate, mitomycin C, nilotinib,

oxaliplatin, paclitaxel, procarbazine, suberoylanilide hydroxamic acid (SAHA), 6-thioguanidine, thiotepa, teniposide, topotecan, trastuzumab, trichostatin A, vinblastine, vincristine, and vindesine.

[00265] The Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-D), Formula (II-E), Formula (II-F), or a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), can be used in the preparation of medicaments for the prevention or treatment of diseases or conditions. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing at least one compound described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

[00266] The Drug-Linker or salt of Formula (X), Formula (XI), Formula (XII), Formula (XIII), Formula (I), Formula (I-A), Formula (Ia), Formula (I-AAa), Formula (Ib), Formula (I-AAb), Formula (I-AA), Formula (I-AB), Formula (I-B), Formula (II-A), Formula (II-B), Formula (II-C), Formula (II-CA), Formula (II-D), Formula (II-E), Formula (II-F), Formula (II-G), or a conjugate or salt of Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (A), Formula (Aa), Formula (Ab), Formula (A-1), Formula (A-2), Formula (A-3), Formula (A-4), Formula (A-5), or Formula (A-6), described herein can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. Amounts effective for this use will depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician.

[00267] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

[00268] In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds may be administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00269] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00270] The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease or condition and its severity, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be determined in a manner recognized in the field according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. In general, however, doses employed for adult human treatment will typically be in the range of about 0.02 - about 5000 mg per day, in some embodiments, about 1 – about 1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00271] The pharmaceutical composition described herein may be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. The unit dosage may be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers can be used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection may be presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative.

[00272] Toxicity and therapeutic efficacy of such therapeutic regimens can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50}

and ED_{50}. Compounds exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

[00273] In certain embodiments, the invention provides a method of treating or preventing a disease, state, or condition in a patient in need thereof comprising administering to the patient an effective amount of a compound of any one of embodiments of the invention or a pharmaceutically acceptable salt thereof. The disease, state or condition may be selected from a group as described elsewhere herein.

Preparation of Drug-Linkers and Conjugates of the Disclosure

[00274] The Linkers, Drug-Linkers and conjugates of the present disclosure can generally be prepared in a number of ways well known to those skilled in the art of organic synthesis.

[00275] In some embodiments, Linkers, Drug-Linkers and conjugates of the present disclosure can be synthesized using the methods described herein, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. In some embodiments, a conjugate may be prepared by several routes employing organic chemistry reactions, conditions, and reagents known to those skilled in the art, including: (1) reaction of a nucleophilic group of a Targeting unit (e.g., an antibody or antigen binding portion thereof or non-antibody protein scaffold) with a bivalent Linker to form a Targeting unit-Linker intermediate via a covalent bond, followed by reaction with a Drug; and (2) reaction of a nucleophilic group of a Drug with a bivalent Linker, to form Drug-Linker, via a covalent bond, followed by reaction with a nucleophilic group of a Targeting unit.

[00276] In some embodiments, techniques for attaching a drug to Targeting units (such as antibodies or antigen binding portions thereof or non-antibody scaffolds) via linkers may be used. In some cases, a Linker is first attached to a Drug (e.g., a cytotoxic agent (s), immune modulatory agent or other agent) and then the Drug-Linker (s) is attached to the Targeting unit (e.g., an antibody or antigen binding portion thereof or non-antibody protein scaffold). In some cases, a Linker is first attached to a Targeting unit (e.g., an antibody or antigen binding portion thereof or non-antibody protein scaffold), and then a Drug is attached to a Linker.

[00277] In some embodiments, a Drug is attached to a Targeting unit via a Linker in a manner that reduces the activity of the Drug until it is released from the conjugate (e.g., by hydrolysis, by proteolytic degradation or by a cleaving agent.

[00278] In some embodiments, nucleophilic groups on Targeting units such as antibodies, antigen binding portions and other binding agents (including non-antibody scaffolds) include, but are not limited to: (i) N-terminal amine groups, (ii) side chain amine groups, e.g. lysine, (iii) side chain thiol groups, e.g. cysteine, and (iv) sugar hydroxyl or amino groups where the antibody is glycosylated. Amine, thiol, and hydroxyl groups are nucleophilic and capable of reacting to form covalent bonds with electrophilic groups on Linkers including: (i) active esters such as NHS esters, HOBt esters, haloformates, and acid halides; (ii) alkyl and benzyl halides such as haloacetamides; and (iii) aldehydes, ketones, carboxyl, and maleimide groups. In some cases, targeting units, such as antibodies (and antigen binding portions and other binding agents (including non-antibody scaffolds)) have reducible interchain disulfides, i.e., cysteine bridges. In some cases, antibodies (and antigen binding portions and other binding agents (including non-antibody scaffolds)) may be made reactive for conjugation with Linkers or Drug-Linkers by treatment with a reducing agent such as DTT (dithiothreitol) or tricarbonylethylphosphine (TCEP), such that the antibody is fully or partially reduced. In some cases, each cysteine bridge will thus form, theoretically, two reactive thiol nucleophiles. In some cases, additional nucleophilic groups can be introduced into Targeting units such as antibodies (and antigen binding portions and other binding agents (including non-antibody scaffolds)) through modification of lysine residues, e.g., by reacting lysine residues with 2-iminothiolane (Traut's reagent), resulting in conversion of an amine into a thiol. In some cases, reactive thiol groups may also be introduced into a Targeting unit (such as an antibody and antigen binding portions and other binding agents (including non-antibody scaffolds)) by introducing one, two, three, four, or more cysteine residues (e.g., by preparing antibodies, antigen binding portions and other binding agents (including non-antibody scaffolds) comprising one or more non-native cysteine amino acid residues).

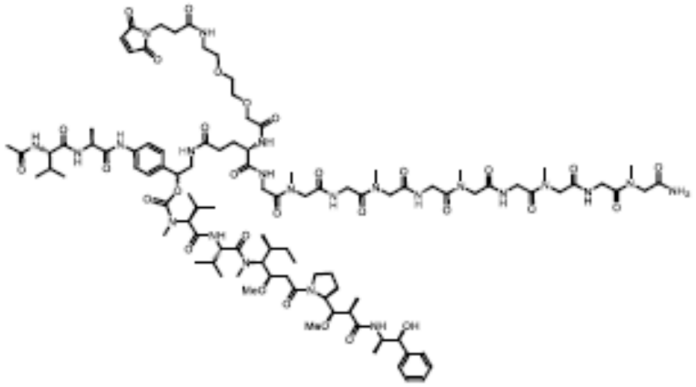
[00279] In some embodiments, conjugates may also be produced by reaction between an electrophilic group on a Targeting unit, such as an aldehyde or ketone carbonyl group, with a nucleophilic group on a Linker or Drug-Linker. In some cases, useful nucleophilic groups on a linker reagent include, but are not limited to, hydrazide, oxime, amino, hydrazine, thiosemicarbazone, hydrazine carboxyl, and arylhydrazide. In some cases, an antibody (or antigen binding portion thereof or other binding agent (including non-antibody scaffolds)) is modified to introduce electrophilic moieties that are capable of reacting with nucleophilic substituents on a Linker or Drug-Linker. In some cases, the sugars of glycosylated antibodies may be oxidized, e.g. with periodate oxidizing reagents, to form aldehyde or ketone groups which may react with the amine group of a Linker or Drug-Linker. In some cases, the resulting imine Schiff base groups may form a stable linkage, or may be reduced, e.g., by borohydride

reagents to form stable amine linkages. In some cases, reaction of the carbohydrate portion of a glycosylated antibody with either galactose oxidase or sodium meta-periodate may yield carbonyl (aldehyde and ketone) groups in the antibody (or antigen binding portion thereof or other binding agent (including non-antibody scaffolds)) that can react with appropriate groups on the Linker or Drug-Linker (see, e.g., Hermanson, Bioconjugate Techniques).

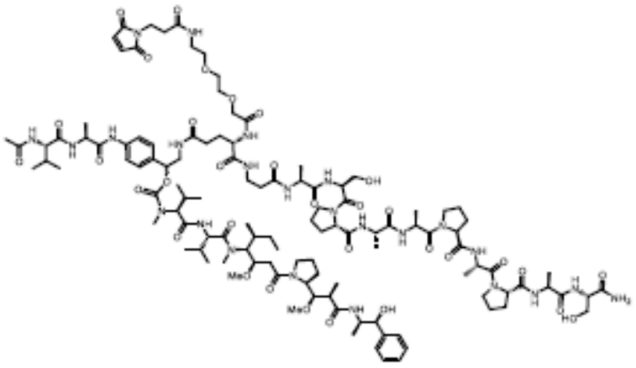
[00280] In some embodiments, exemplary nucleophilic groups on a Drug, such as a cytotoxic agent, include, but are not limited to: amine, thiol, hydroxyl, hydrazide, oxime, hydrazine, thiosemicarbazone, hydrazine carboxyl, and arylhydrazide groups capable of reacting to form covalent bonds with electrophilic groups on a Linker including: (i) active esters such as NHS esters, HOBt esters, haloformates, and acid halides; (ii) alkyl and benzyl halides such as haloacetamides; (iii) aldehydes, ketones, carboxyl, and maleimide groups, ultimately forming a Drug-Linker or a conjugate.

[00281] In some embodiments, a Linker or Drug-Linker is attached to an interchain cysteine residue(s) of an antibody (or antigen binding portion thereof or other binding agent (including non-antibody scaffolds)). In some cases, the Linker or Drug-Linker typically comprises a maleimide group for attachment to the cysteine residues of an interchain disulfide. In some cases, a Linker or Drug-Linker is attached to a cysteine residue(s) of an antibody or antigen binding portion thereof.

[00282] In some cases, the drug linker is selected from

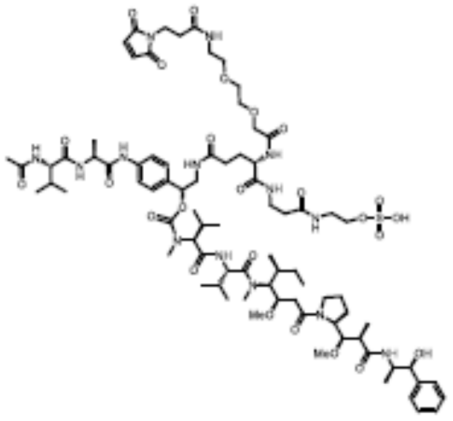


(SEQ ID NOS 26 and 22,



respectively, in order of appearance),

(SEQ ID NOS 27 and 22, respectively, in order of appearance), and


(SEQ ID NO: 22). Each drug linker may be conjugated to UC-961 antibody or ROR2 antibody using the appropriate conditions.

[00283] The compounds of the present disclosure may be prepared as described in the schemes and examples described elsewhere herein.

[00284] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLES

[00285] The following synthetic schemes are provided for purposes of illustration, not limitation. The following examples illustrate the various methods of making compounds described herein. It is understood that one skilled in the art may be able to make these compounds by similar methods or by combining other methods known to one skilled in the art. It is also understood that one skilled in the art would be able to make, in a similar manner as described below by using the appropriate starting materials and modifying the synthetic route as needed. In general, starting materials and reagents can be obtained from commercial vendors or synthesized according to sources known to those skilled in the art or prepared as described herein. As used below, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN	acetonitrile
^{o}C	degrees Celsius
δ_H	chemical shift in parts per million downfield from tetramethylsilane
DCM	dichloromethane (CH_2Cl_2)
DIAD	diisopropyl azodicarboxylate
DIEA	diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide

EA	ethyl acetate
EtOAc	ethyl acetate
ESI	electrospray ionization
Et	ethyl
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
Hz	hertz
J	coupling constant (in NMR spectrometry)
LCMS	liquid chromatography mass spectrometry
μ	micro
m	multiplet (spectral); meter(s); milli
M	molar
M^+	parent molecular ion
Me	methyl
MsCl	methanesulfonyl chloride
MHz	megahertz
min	minute(s)
mol	mole(s); molecular (as in mol wt)
mL	milliliter
MS	mass spectrometry
nm	nanometer(s)
NMR	nuclear magnetic resonance
pH	potential of hydrogen; a measure of the acidity or basicity of an aqueous
	solution
PE	petroleum ether
RT	room temperature
s	singlet (spectral)
d	doublet (spectral)
t	triplet (spectral)
m	multiplet (spectral)

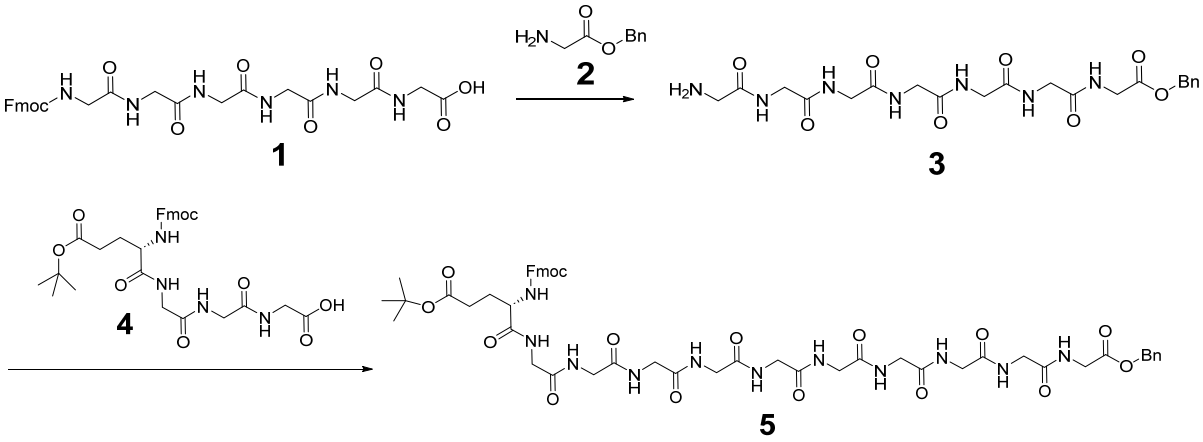
SFC	Supercritical fluid chromatography
T	temperature
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TPP	Triphenylphosphine
EDC	N-(Dimethylaminopropyl)-N'-ethyl-carbodiimide
HOAt	1-Hydroxy-7-azabenzotriazole
TSTU	N'-Tetramethyl-O-(N-succinimidyl)uronium tetrafluoroborate
AOP	(7-Azabenzotriazol-1-yl)oxytris(dimethylamino) phosphonium
	Hexafluorophosphate
PyAOP hexafluorophosphate	(7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium
EEDQ	2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
Pfp	Pentafluorophenyl
NAC	N-Acetyl Cysteine
NIS	N-Iodosuccinimide
NMM	N-Methylmorpholine

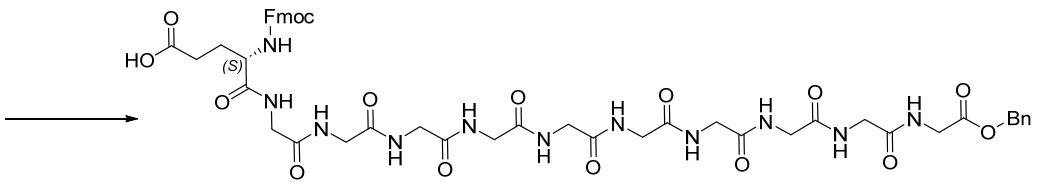
Preparation of Drug Linkers

Example 1: Synthesis of Drug-Linker compound 18

[00286] Compounds **6** and **14** were prepared as shown in schemes 1 and 2 and coupled to provide Drug-Linker **18** as shown in scheme 3.

Scheme 1 (SEQ ID NOS 40-44, respectively, in order of appearance)





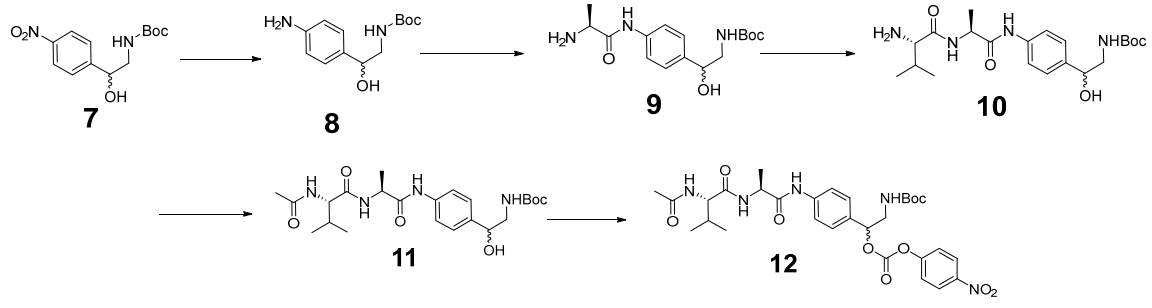
6

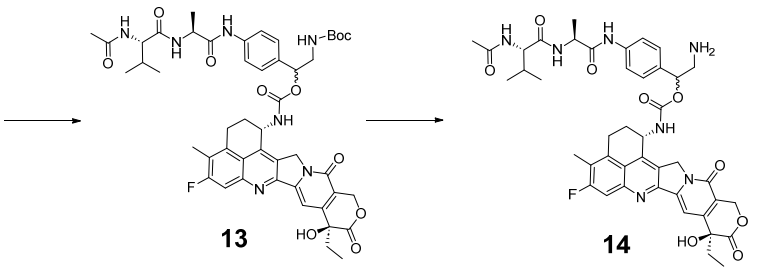
[00287] To a solution of Fmoc-Gly6-COOH (SEQ ID NO: 40) (**1**, synthesized on Cl-Trt resin using standard Fmoc SPPS protocol, 116 mg, 0.2 mmol) and compound **2** (HCl salt, 40 mg, 0.2 mmol) in anhydrous DMSO (4 mL) was added HOAt (28 mg, 0.2 mmol) and EDC.HCl (115 mg, 0.6 mmol), followed by DIEA (0.07 mL). The mixture was stirred at room temperature for 4 h. Water (30 mL) was added, and the precipitate was collected by filtration. The white solid obtained was washed with water (10 mL x 2) and dried in vacuo to give the crude Fmoc-Gly7-OBn (SEQ ID NO: 41), which was dissolved in DMF (4 mL). Piperidine (0.2 mL) was added, and the reaction was stirred at room temperature for 2 h. The mixture was poured into ether (100 mL) under stirring. The solid precipitated was collected, washed with ether (2 x 10 mL), and dried in vacuo to give the crude compound **3** as a white solid, which was used in the next step with no further purification.

[00288] Fmoc-Glu(tBu)-Gly3-COOH (SEQ ID NO: 42) (**4**, synthesized on Cl-Trt resin using standard Fmoc SPPS protocol, 32 mg) and compound **3** (25 mg) were dissolved in anhydrous DMSO (3 mL). HOAt (8 mg) and EDC.HCl (33 mg) were added, and the reaction was stirred at room temperature. After 2h, the mixture was purified directly by RP-HPLC to give compound **5** as a white solid (19 mg).

[00289] The compound **5** (19 mg) was treated with TFA/DCM (2/3, v/v, 2 mL) at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to give compound **6** as a white solid (18 mg).

Scheme 2





[00290] To a solution of compound **7** (1.0 g, 3.62 mmol) in methanol (30 mL) was added Pd/C (10% Pd, 0.5 g). The mixture was purged with argon gas, then filled with hydrogen, and hydrogenated for a period of 1 h. The catalyst was removed by filtration, and the solvent was evaporated to give compound **8** as a clear solid (0.6 g).

[00291] To a solution of compound **8** (600 mg, 2.38 mmol) in DCM (15 mL) was added Fmoc-L-Ala-OH (740 mg, 2.38 mmol) and EEDQ (588 mg, 2.38 mmol). The mixture was stirred at RT over a period of 20 h. The solvent was evaporated under vacuum and the resulting residue was dissolved in 3 mL of DMF. Then piperidine (0.3 mL) was added, and the mixture was stirred for 20 min. Then the mixture was purified by RP-HPLC to give compound **9** as a TFA salt (470 mg).

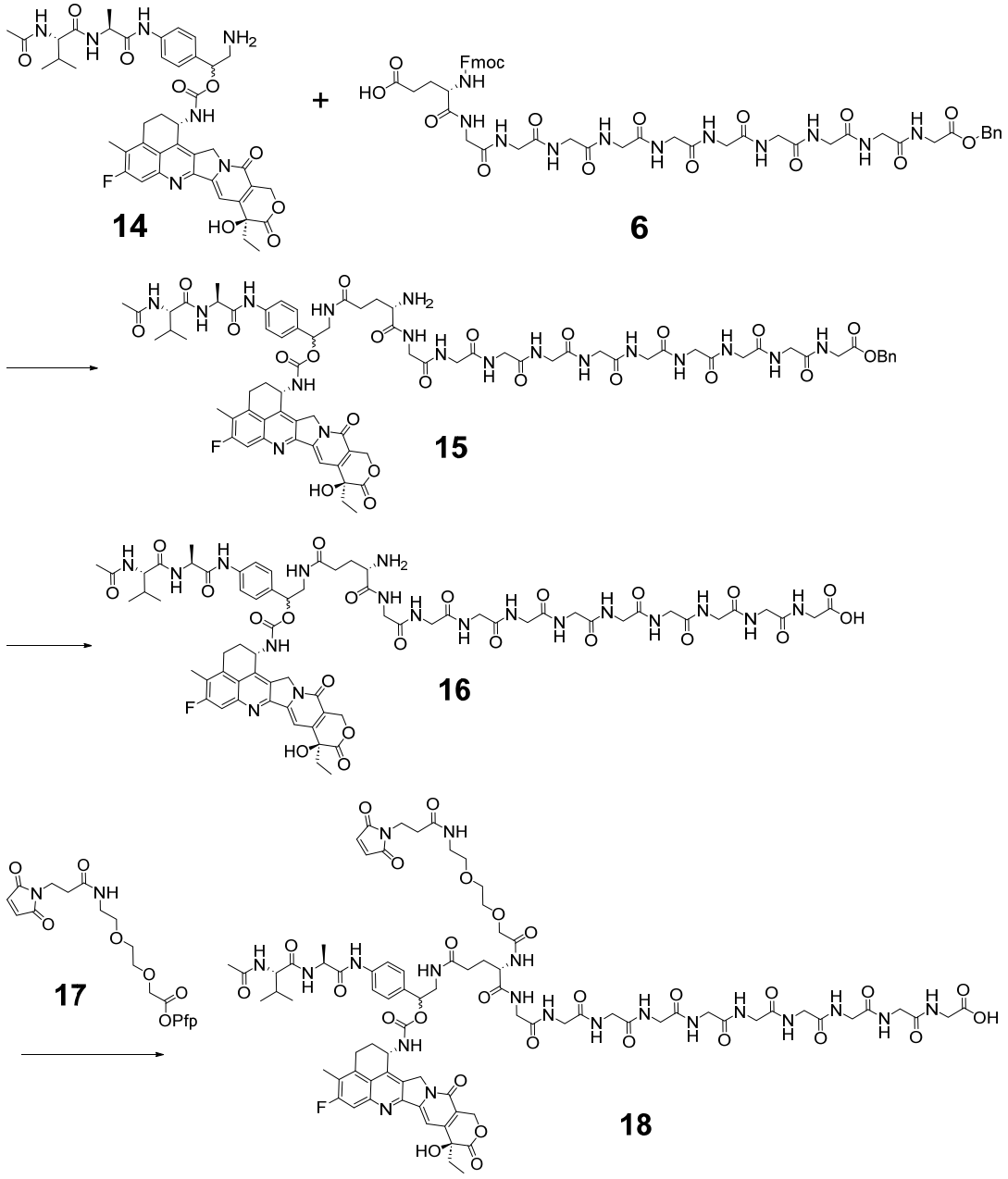
[00292] To a solution of compound **9** (TFA salt, 237 mg, 0.54 mmol) in anhydrous DMF (2 mL) was added Fmoc-L-Val-OH (184 mg, 0.54 mmol), PyAOP (283 mg, 0.54 mmol), and DIEA (0.4 mL). The mixture was stirred at RT over a period of 20 min. Then piperidine (0.2 mL) was added, and the mixture was stirred for 10 min. Then the mixture was purified by RP-HPLC to give compound **10** as a TFA salt (230 mg).

[00293] To a solution of compound **10** (TFA salt, 230 mg, 0.43 mmol) in anhydrous DMF (2 mL) was added acetic acid (53 mg, 0.51 mol), PyAOP (224 mg, 0.43 mmol) and DIEA (0.3 mL). The mixture was stirred at room temperature for a period of 20 min. Then the mixture was purified directly by RP-HPLC to give compound **11** as a tan solid (117 mg).

[00294] To a solution of compound **11** (50 mg, 0.11 mmol) in anhydrous DMF (2 mL) was added bis(4-nitrophenyl) carbonate (66 mg, 0.22 mol) and DIEA (18 μL). The mixture was stirred at room temperature for a period of 24 h to give a solution of compound **12**. Then a solution of exatecan mesylate (85 mg, 0.16 mmol) and DIEA (30 μL) in 1 mL of anhydrous DMF was added, and the stirring continued for 2 d. Then the mixture was purified by RP-HPLC to give compound **13** as a pale-yellow solid (70 mg).

[00295] Compound **13** (70 mg, 75.7 μmol) was dissolved in a mixture of DCM (3 mL) and TFA (1 mL). The mixture was stirred at room temperature for a period of 15 min, then the solvent was removed under vacuum, and the residue was purified by RP-HPLC to give compound **14** as a TFA salt (66 mg).

Scheme 3 (SEQ ID NOS 44-46 and 24, respectively, in order of appearance)

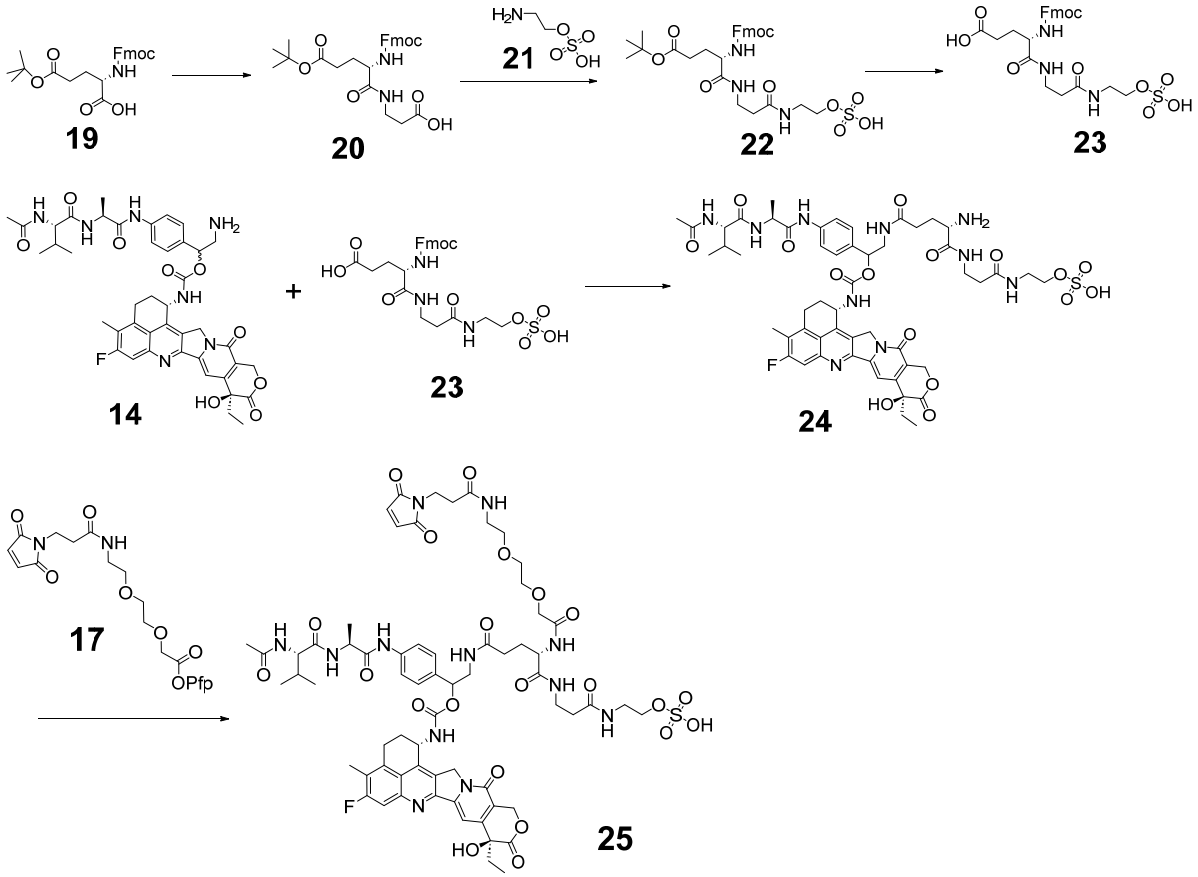


[00296] To a stirred solution of compound **6** (18 mg) and compound **14** (TFA salt, 18 mg) in anhydrous DMSO (4 mL) was added HOAt (3 mg), followed by EDC.HCl (10 mg) and DIEA (0.01 mL). The mixture was stirred at room temperature for 1 h. Water (20 mL) was added, and the precipitated solid was collected, washed with water (5 mL) and acetonitrile (5 mL x 2). The solid obtained was suspended in DMF/DMSO (1/1, v/v, 4 mL). Piperidine (0.2 mL) was added, and the mixture was stirred at room temperature for 2 h. Ether (20 mL) was added, and the solid precipitated was washed with ether (10 mL x 2) and suspended in acetonitrile/water (6/4, v/v, 4 mL). NaOH (1N, aq., 0.4 mL) was added and the solution was stirred at room temperature. After

1h, TFA (0.3 mL) was added, followed by DMSO (3 mL). The mixture was purified directly by RP-HPLC to give compound **16** as a yellow solid after lyophilization (9 mg).

[00297] Compound **16** (9 mg) and the Pfp ester (**17**, 6 mg) were dissolved in DMSO (2 mL), and DIEA (0.004 mL) was added. After stirring at room temperature for 1 h. the mixture was purified by RP-HPLC to give compound **18** as a yellow solid (6 mg) after lyophilization. MS: m/z 1822.4 $[M+H]^+$.

Example 2: Synthesis of Drug-Linker compound 25



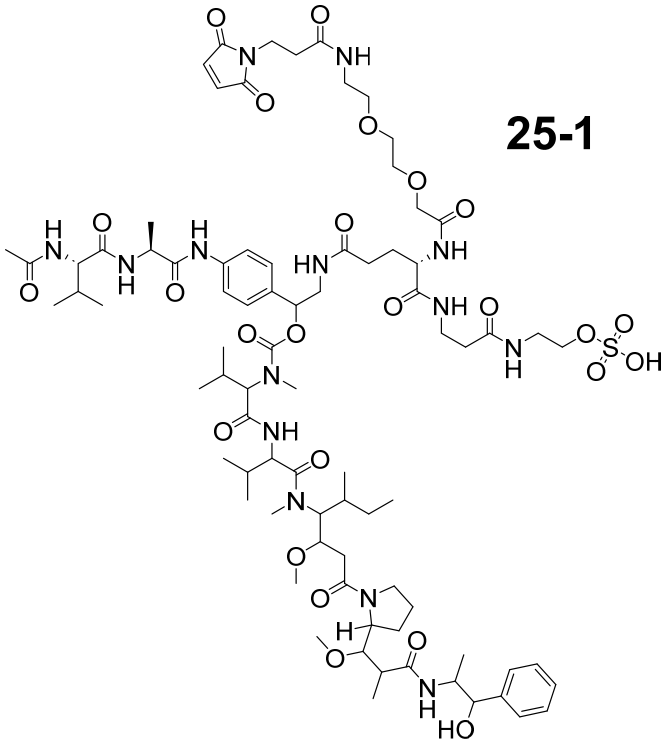
[00298] To a solution of Fmoc-Glu(tBu)-COOH.H_2O (44 mg, 0.1 mmol) in DMF (2 mL) was added TSTU (32 mg), followed by DIEA (0.035 mL). The mixture was stirred at room temperature. After 10 min, beta-Alanine (10 mg) in water (0.5 mL) was added, followed by DIEA (0.02 mL). After stirring at room temperature for 30 min, the crude product was purified by RP-HPLC to give compound **20** as a white solid (48 mg), which was dissolved in DMF (2 mL). TSTU (32 mg) was added, followed by DIEA (0.04 mL). After 10 min, the sulfate (**21**, 28 mg) in water (0.5 mL) was added, followed by DIEA (0.06 mL). After stirring at room temperature for 1 h, the crude product was purified by RP-HPLC to give compound **22** as a white solid (TEA salt, 61 mg).

[00299] The compound **22** (61 mg) was treated with TFA/DCM (2/3, v/v, 3 mL) at room temperature for 1 h. The mixture was concentrated to dryness under reduced pressure to give compound **23** as a white solid which was used directly in the next step.

[00300] Compound **23** (TEA salt, 20 mg) and compound **14** (TFA salt, 19 mg) were dissolved in anhydrous DMF (2 mL). AOP (12 mg) was added, followed by DIEA (0.02 mL), and the mixture was stirred at room temperature. After 30 mins, piperidine (0.1 mL) was added, and the mixture was stirred at room temperature for 15 min. The crude product was purified by RP-HPLC to give compound **24** as a yellow solid (TFA salt, 18 mg).

[00301] Compound **24** (18 mg) and the Pfp ester (**17**, 9 mg) were dissolved in DMF (2 mL), and DIEA (0.01 mL) was added. After stirring at room temperature for 4 h, the mixture was purified by RP-HPLC to give compound **25** as an off-white solid (16 mg, NH_4^+ salt) after lyophilization. MS: m/z 1443.4 $[M-H]^-$.

[00302] Compound **25-1** was prepared in a similar manner as compound **25**, using the appropriate reagents**.**

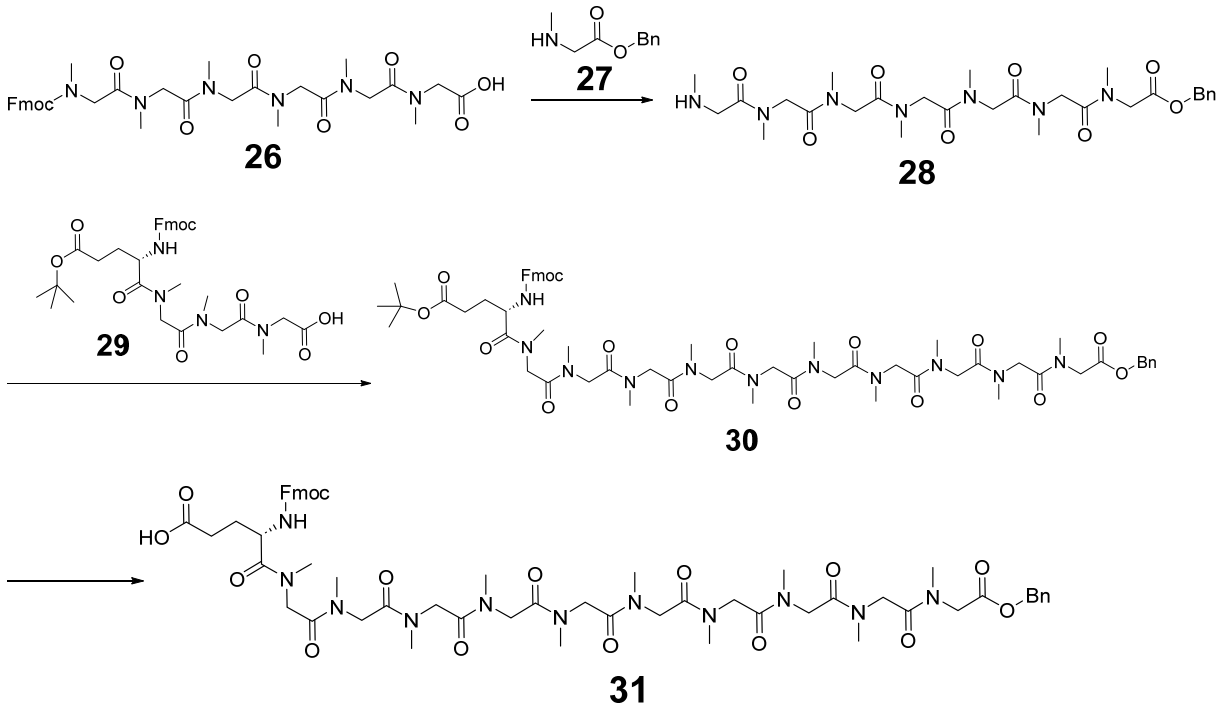


(SEQ ID NO: 22)

Example 3: Synthesis of Drug-Linker compound 34

[00303] Compound **31** was prepared as shown in scheme 4 and coupled with compound **14** to provide Drug-Linker **34** as shown in scheme 5.

Scheme 4 (SEQ ID NOS 47-51, respectively, in order of appearance)

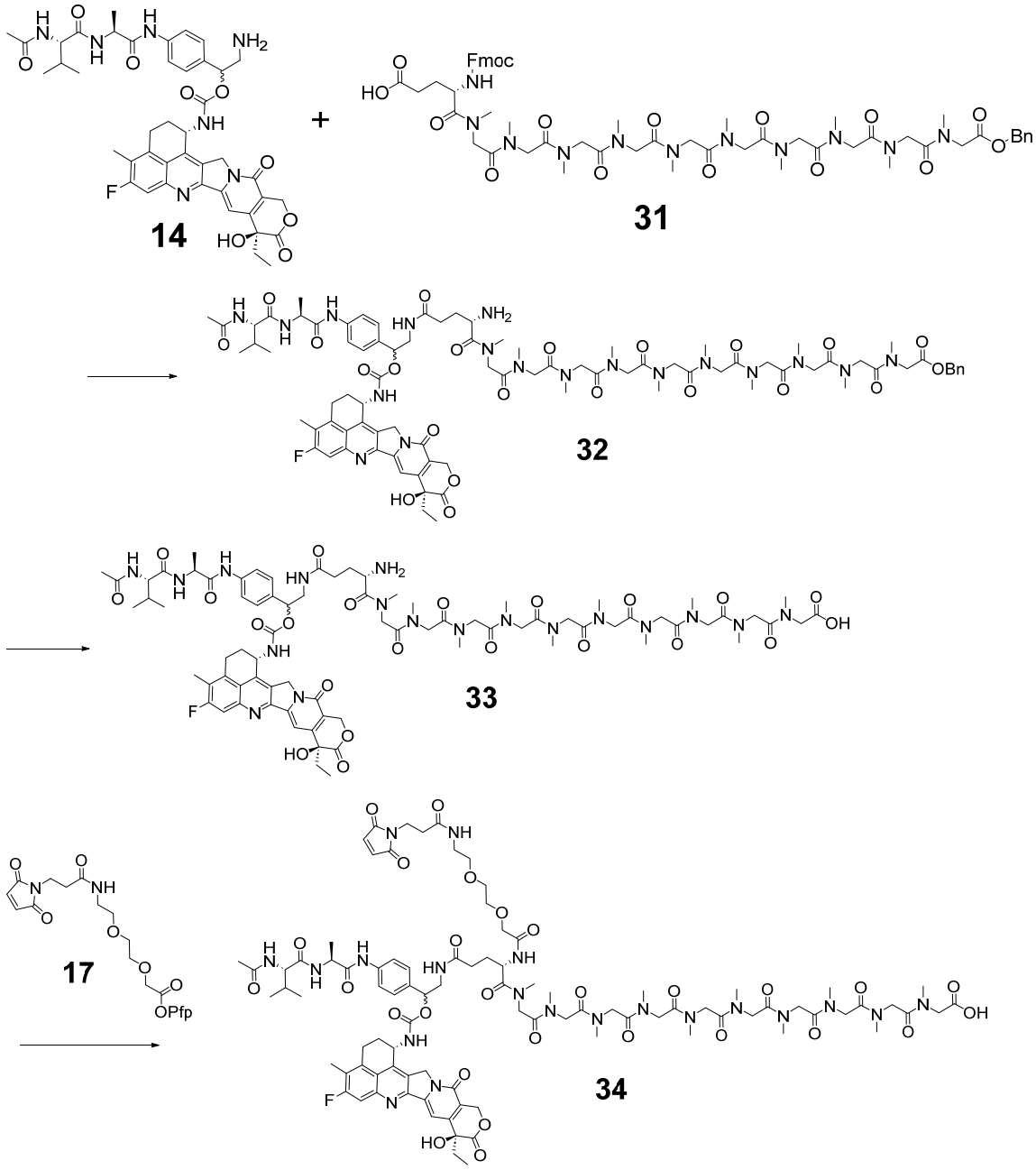


[00304] To a solution of Fmoc-Sar6-COOH (SEQ ID NO: 47) (**26**, synthesized on Cl-Trt resin using standard Fmoc SPPS protocol, 66 mg, 0.1 mmol) and compound **27** (HCl salt, 22 mg, 0.1 mmol) in anhydrous DMF (2 mL) was added PyAOP (52 mg, 0.1 mmol), followed by DIEA (0.07 mL). The mixture was stirred at room temperature for 10 mins. Piperidine (0.1 mL) was added, and the reaction was stirred at room temperature for 20 mins. The crude reaction mixture was purified directly by RP-HPLC to give compound **28** as a white solid (TFA salt, 66 mg).

[00305] Fmoc-Glu(tBu)-Sar3-COOH (SEQ ID NO: 49) (**29**, synthesized on Cl-Trt resin using standard Fmoc SPPS protocol, 60 mg) and compound **28** (66 mg) were dissolved in anhydrous DMF (2 mL). AOP (44 mg) and DIEA (0.05 mL) were added, and the reaction was stirred at room temperature. After 15 mins, the mixture was purified directly by RP-HPLC to give compound **30** as a white solid (110 mg).

[00306] The compound **30** (110 mg) was treated with TFA/DCM (1/1, v/v, 3 mL) at room temperature for 20 mins. The mixture was concentrated to dryness under reduced pressure to give compound **31** as a white solid.

Scheme 5 (SEQ ID NOS 51-53 and 25, respectively, in order of appearance)

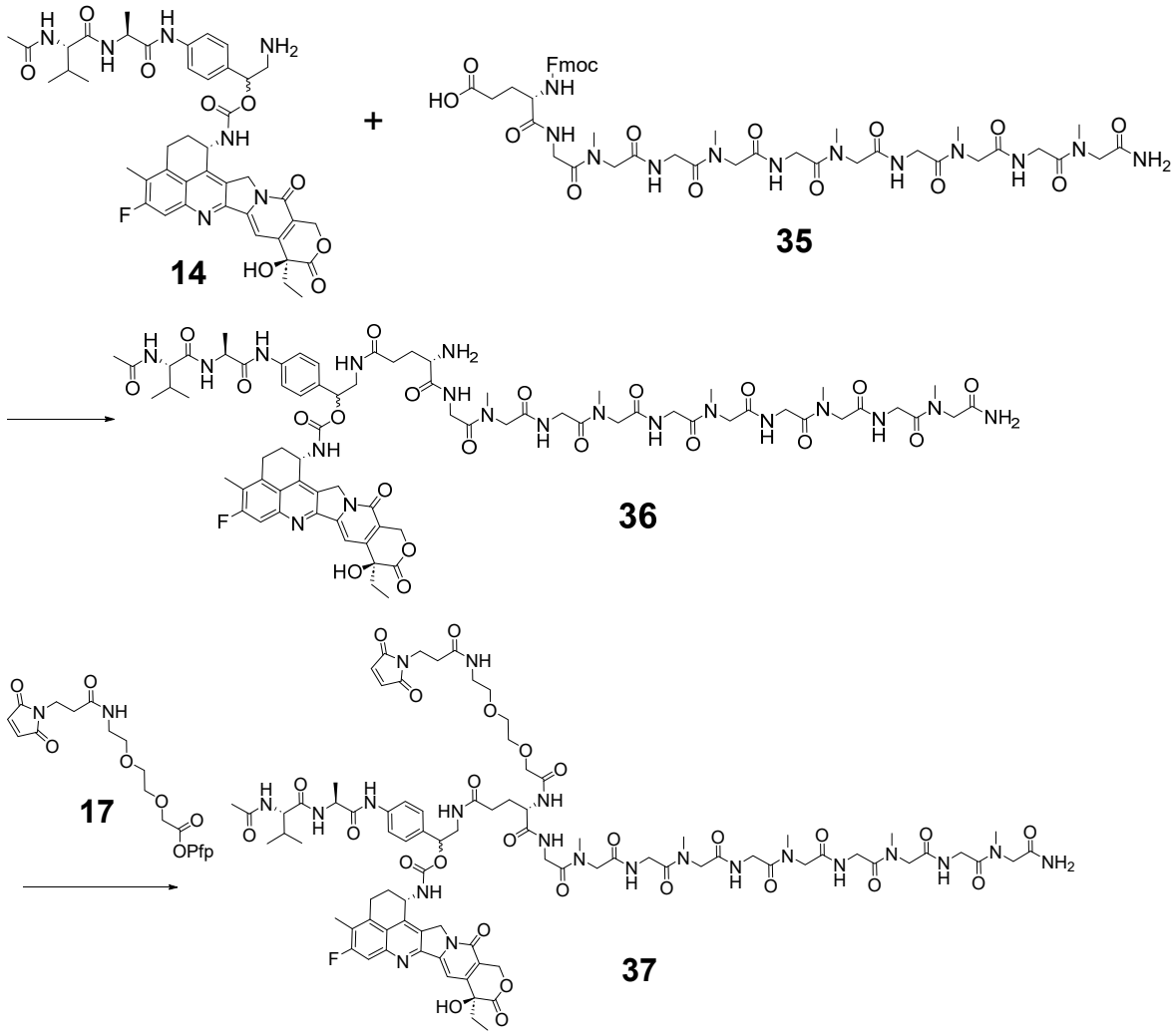


[00307] Compound **31** (13 mg) and compound **14** (TFA salt, 9 mg) were dissolved in anhydrous DMF (1 mL). PyAOP (7 mg) was added, followed by DIEA (0.01 mL), and the mixture was stirred at room temperature. After 1 hour, piperidine (0.05 mL) was added, and the mixture was stirred at room temperature for 10 min. The crude product was purified by RP-HPLC to give compound **32** as a yellow solid (TFA salt, 15 mg), which was dissolved in acetonitrile/water (6/4, v/v, 2 mL). NaOH (1N, aq., 0.1 mL) was added and the solution was stirred at room temperature. After 1h, TFA (0.1 mL) was added, and the mixture was purified directly by RP-HPLC to give compound **33** as a yellow solid after lyophilization (11 mg).

[00308] Compound **33** (10 mg) and the Pfp ester (**17**, 4 mg) were dissolved in DMF (1 mL), and DIEA (0.005 mL) was added. After stirring at room temperature for 2 h, the mixture was

purified by RP-HPLC to give compound **34** as a yellow solid (10 mg) after lyophilization. MS: m/z 1963.0 $[M+H]^+$.

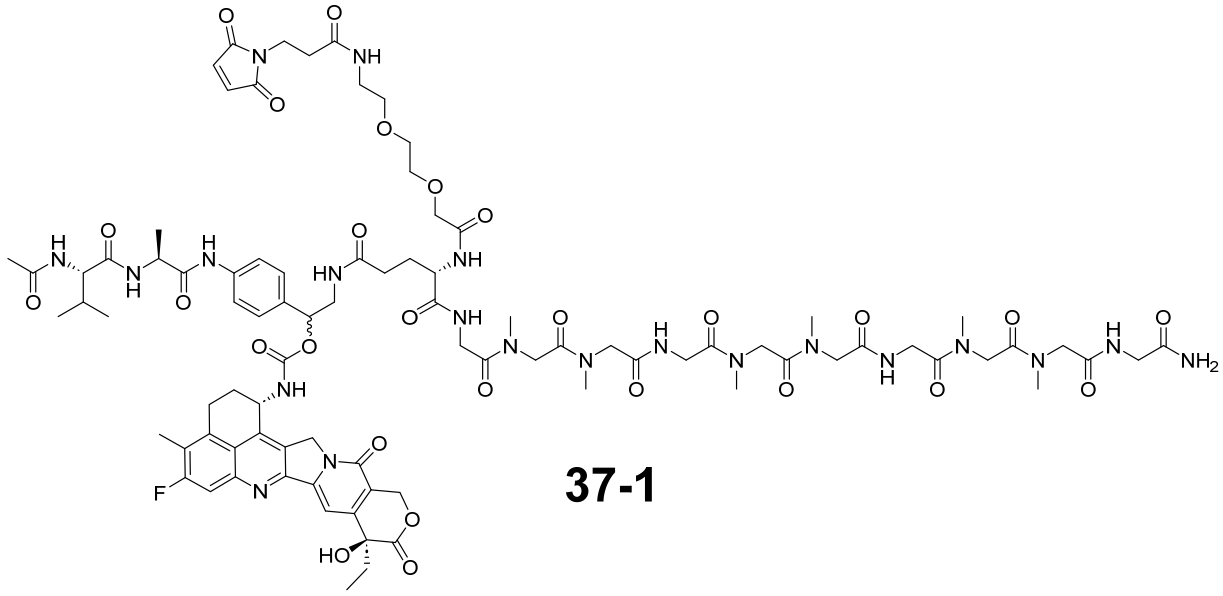
Example 4: Synthesis of Drug-Linker compound 37 (SEQ ID NOS 54-55 and 26, respectively, in order of appearance)



[00309] Compound **35** (11 mg, purchased from InnoPep, San Diego, CA) and compound **14** (TFA salt, 9 mg) were dissolved in anhydrous DMF (1 mL). PyAOP (6 mg) was added, followed by DIEA (0.007 mL), and the mixture was stirred at room temperature. After 2 hour, piperidine (0.05 mL) was added, and the mixture was stirred at room temperature for 10 min. The crude product was purified by RP-HPLC to give compound **36** as a yellow solid (TFA salt, 13 mg).

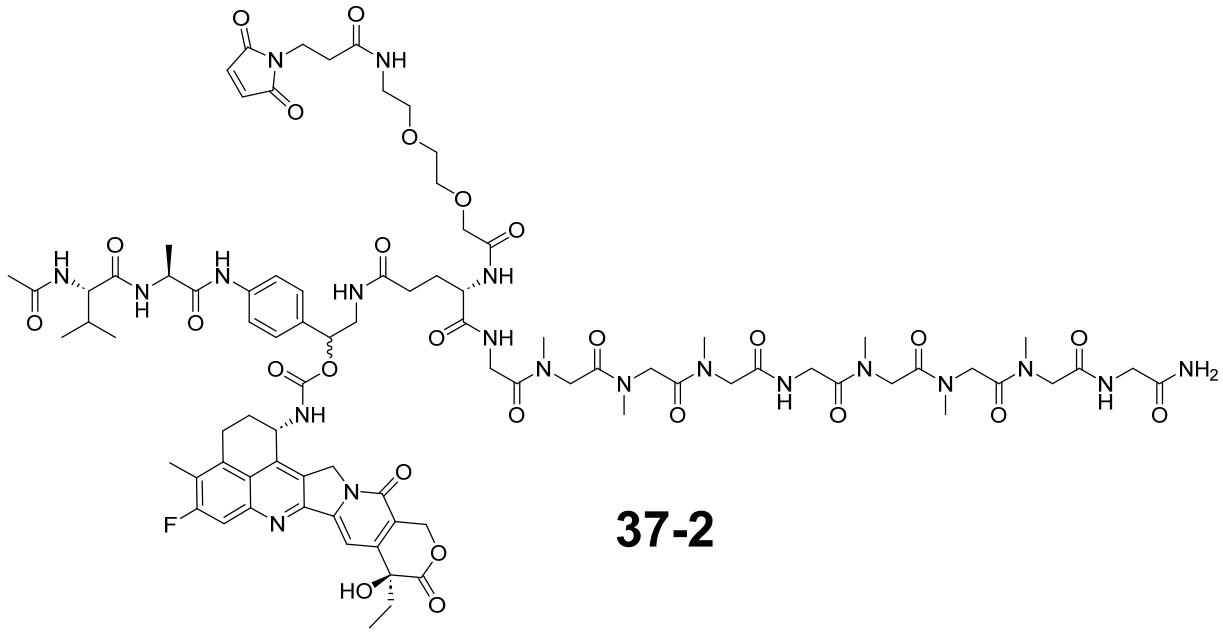
[00310] Compound **36** (13 mg) and the Pfp ester (**17**, 4 mg) were dissolved in DMF (1 mL), and DIEA (0.005 mL) was added. After stirring at room temperature for 1 h, the mixture was purified by RP-HPLC to give compound **37** as a yellow solid (11 mg) after lyophilization. MS: m/z 1891.9 $[M+H]^+$.

[00311] Compound **37-1** and compound **37-2**, were prepared in a similar manner as compound **37.**



37-1

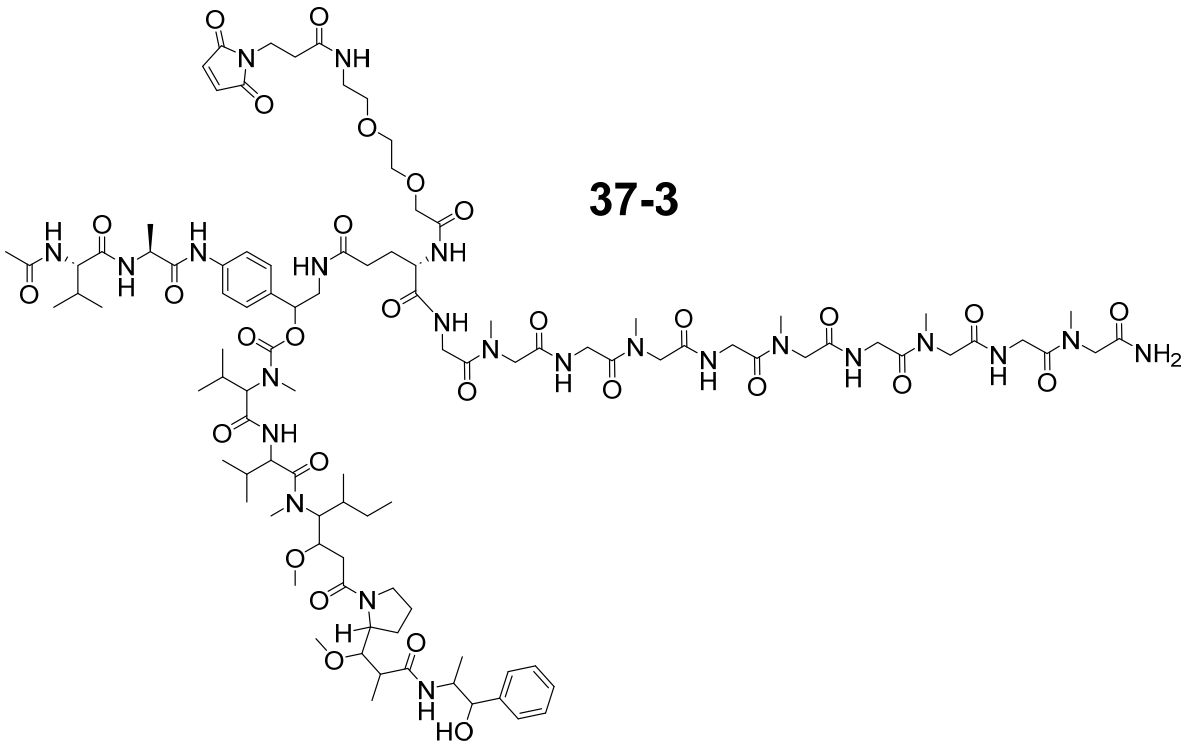
(SEQ ID NO: 31)



37-2

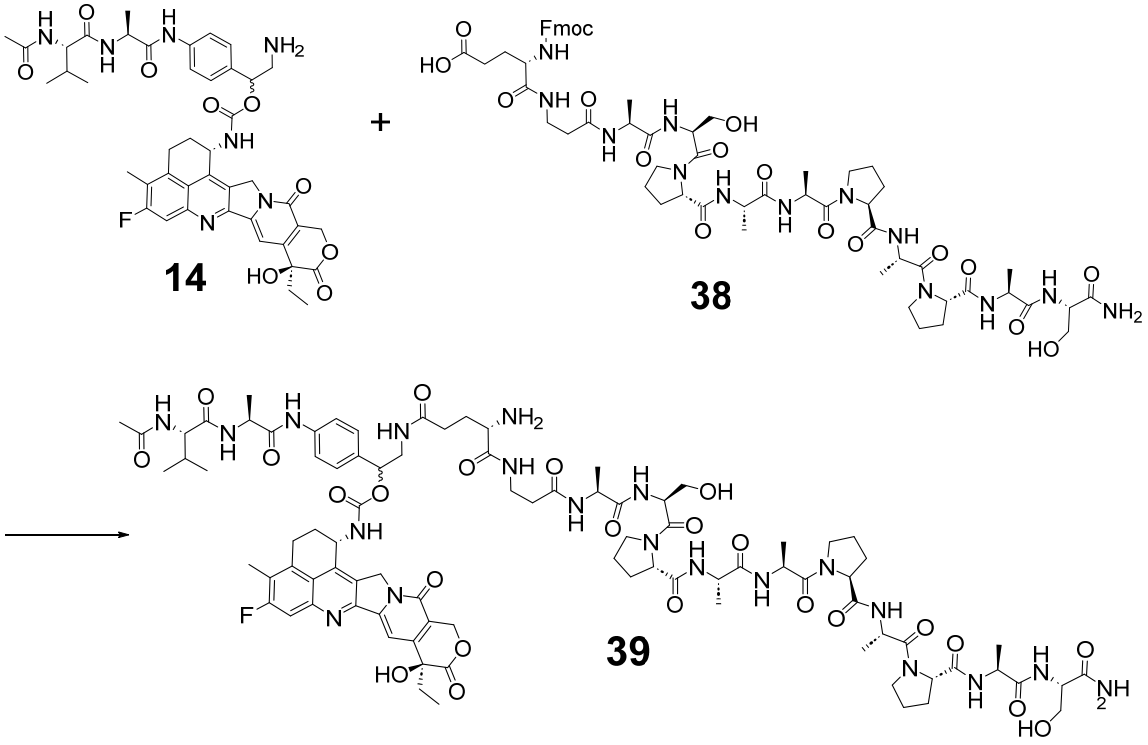
(SEQ ID NO: 32)

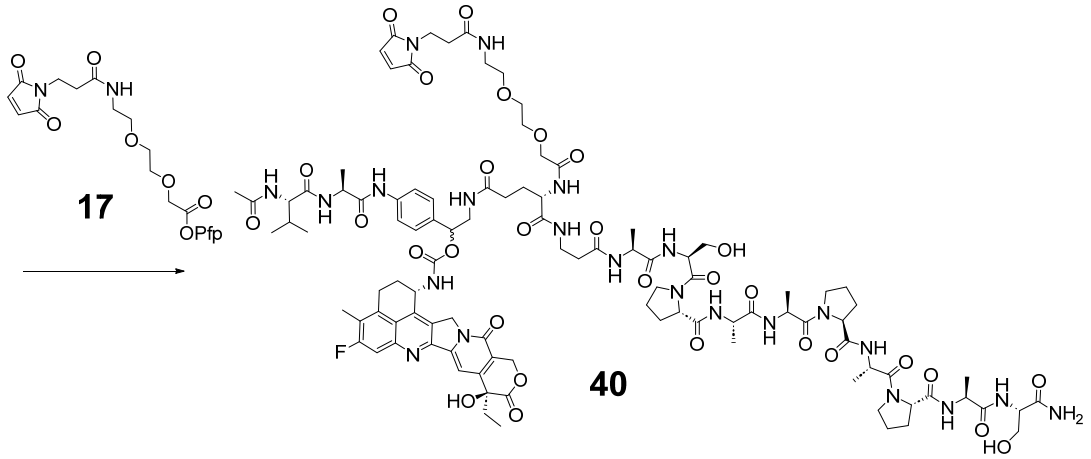
[00312] Compound **37-3** was prepared in a similar manner as compound **37**, using the appropriate reagents.



(SEQ ID NOS 26 and 22, respectively, in order of appearance)

Example 5: Synthesis of Drug-Linker compound 40 (SEQ ID NOS 56-57 and 27, respectively, in order of appearance)

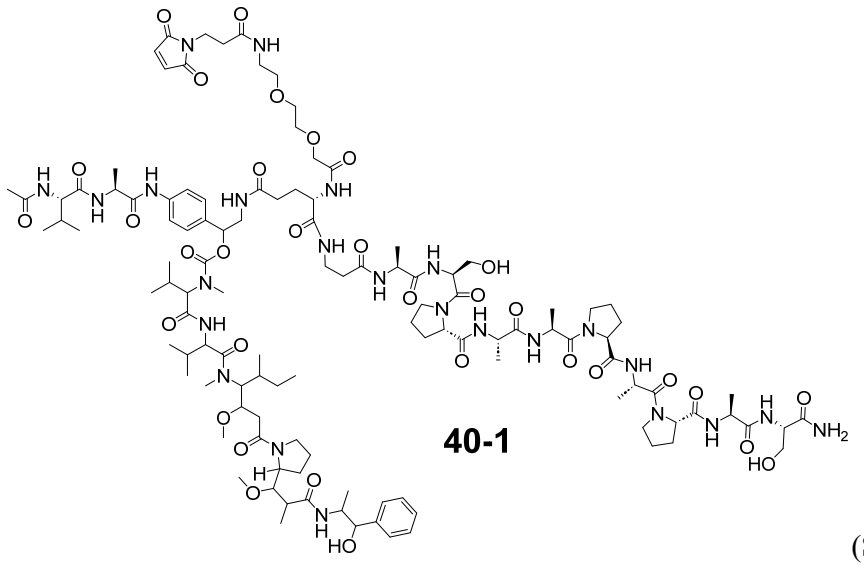




[00313] Compound **38** (14 mg, purchased from InnoPep, San Diego, CA) and compound **14** (TFA salt, 9 mg) were dissolved in anhydrous DMF (1 mL). PyAOP (6 mg) was added, followed by DIEA (0.007 mL), and the mixture was stirred at room temperature. After 2 hour, piperidine (0.05 mL) was added, and the mixture was stirred at room temperature for 10 min. The crude product was purified by RP-HPLC to give compound **39** as a yellow solid (TFA salt, 17 mg).

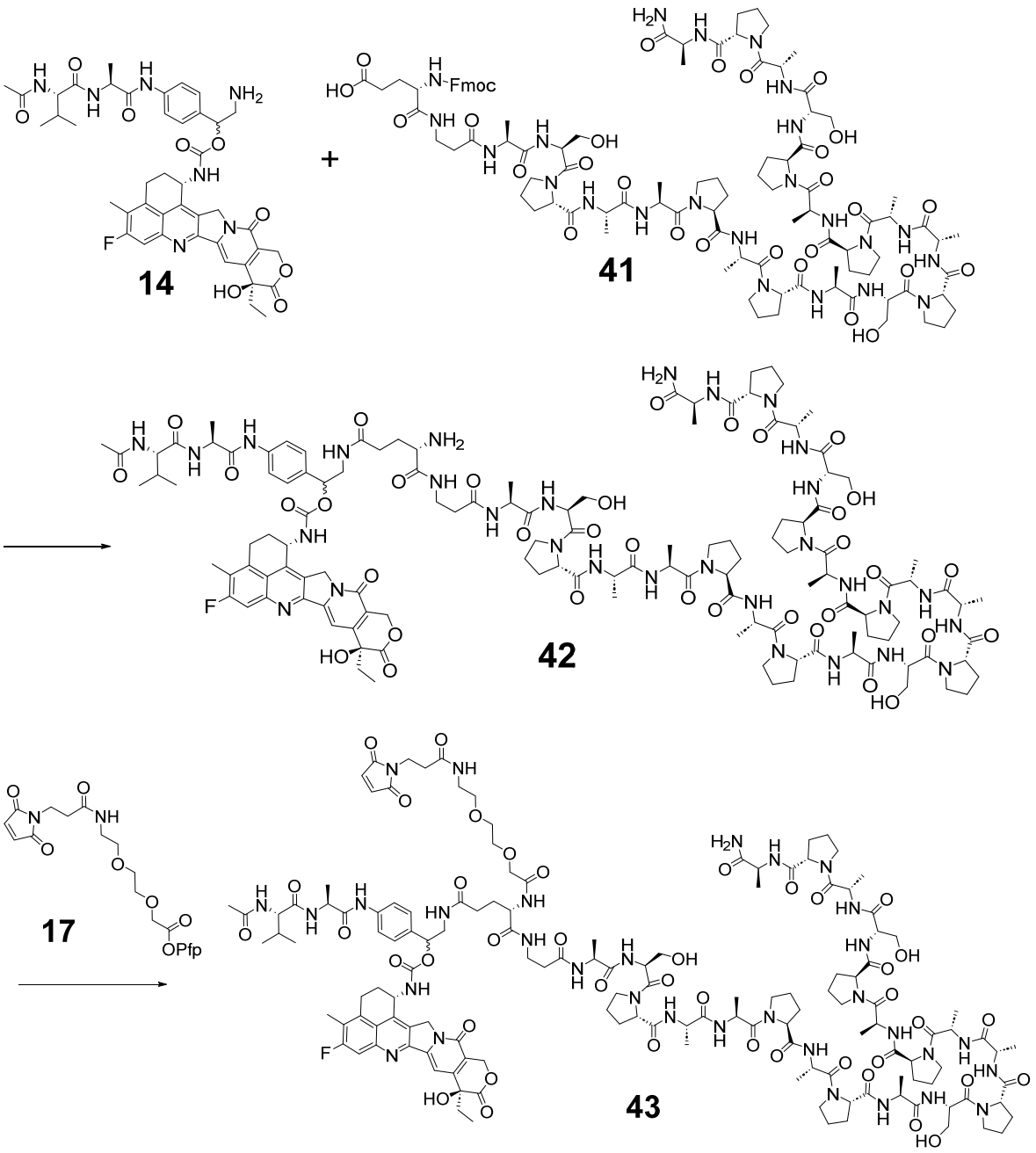
[00314] Compound **39** (17 mg) and the Pfp ester (**17**, 5 mg) were dissolved in DMF (1 mL), and DIEA (0.007 mL) was added. After stirring at room temperature for 1 h, the mixture was purified by RP-HPLC to give compound **40** as a yellow solid (17 mg) after lyophilization. MS: m/z 1071.7 $[M+2H^+]/2$.

[00315] Compound **40-1** was prepared in a similar manner as compound **40**, using the appropriate reagents**.**



(SEQ ID NOS 27 and 22, respectively, in order of appearance)

Example 6: Synthesis of Drug-Linker compound 43 (SEQ ID NOS 58-59 and 28, respectively, in order of appearance)



[00316] Compound **41** (21 mg, purchased from InnoPep, San Diego, CA) and compound **14** (TFA salt, 9 mg) were dissolved in anhydrous DMF (1 mL). PyAOP (6 mg) was added, followed by DIEA (0.007 mL), and the mixture was stirred at room temperature. After 2 hour, piperidine (0.05 mL) was added, and the mixture was stirred at room temperature for 10 min. The crude product was purified by RP-HPLC to give compound **42** as a yellow solid (TFA salt, 24 mg).

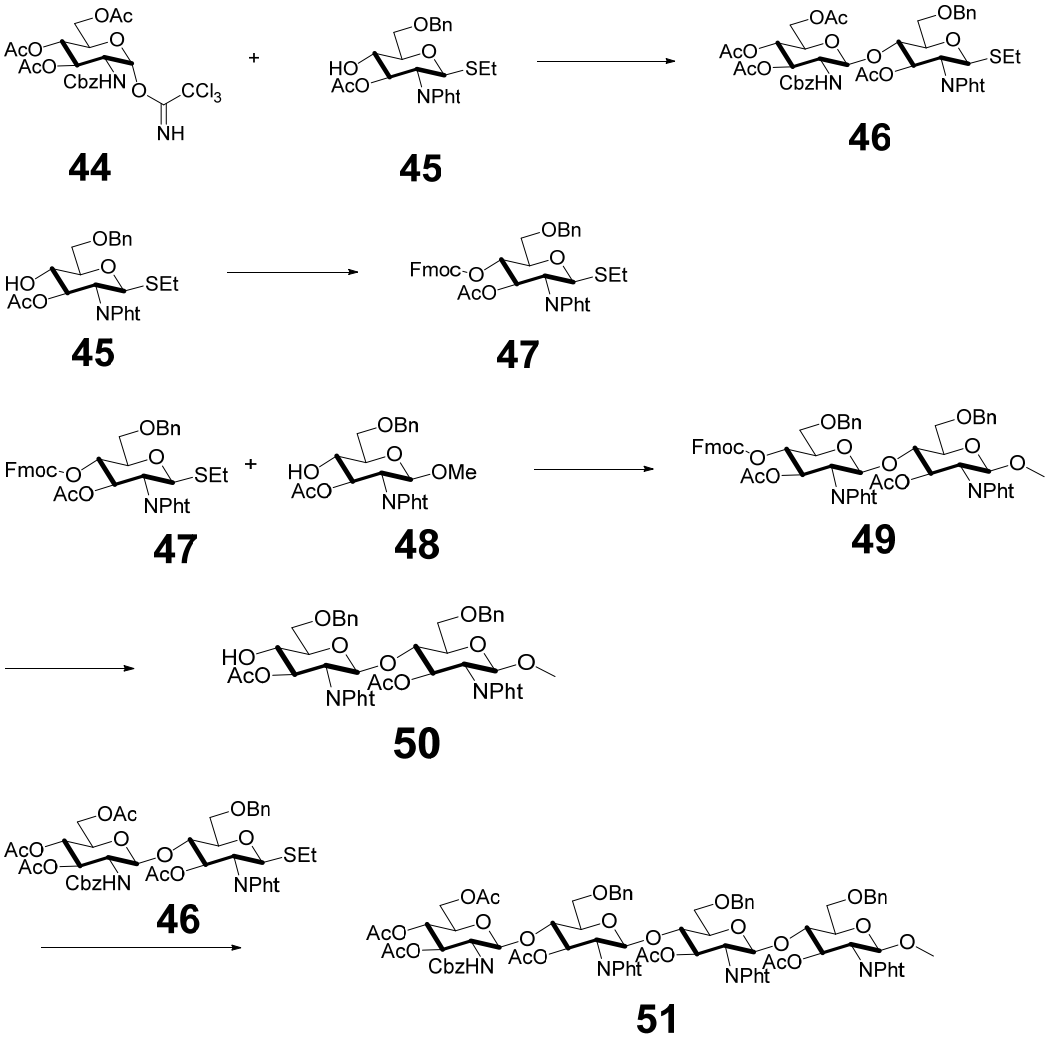
[00317] Compound **42** (14 mg) and the Pfp ester (**17**, 3 mg) were dissolved in DMF (1 mL), and DIEA (0.005 mL) was added. After stirring at room temperature for 2 h, the mixture was

purified by RP-HPLC to give compound **43** as a yellow solid (14 mg) after lyophilization. MS: m/z 1487.5 [M+2H$^+$]/2

Example 7: Synthesis of Drug-Linker compound 58

[00318] Compound **58** was prepared as shown in schemes 6-8.

Scheme 6



[00319] Compound **44** (2.9 g, 5 mmol, *Eur. J. Org. Chem*., 2013, 7382-7390) and compound **45** (1.2 g, 2.5 mmol, *Eur. J. Org. Chem*., 2006, 5158-5166) were dissolved in anhydrous toluene (30 mL) and cooled to -78 °C. $BF_3.Et_2O$ (0.16 mL) was added dropwise. The reaction mixture was stirred at this temperature for 2 h, then it was warmed slowly to room temperature over a period of 3 h. Triethylamine (1 mL) was added, and the reaction was concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, EtOAc/hexanes, 1/3 to 1/1) to give disaccharide **46** (1.3 g) as an amorphous white solid.

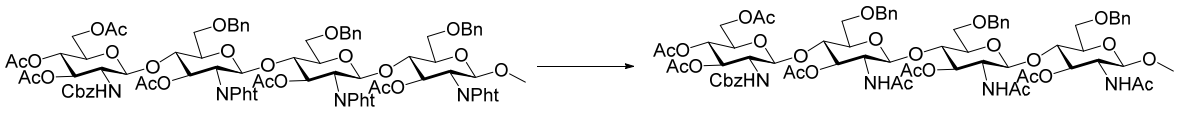
[00320] Compound **45** (2.4 g, 5 mmol) was dissolved in anhydrous DCM (50 mL). To this solution, pyridine (1.6 mL) was added, followed by FmocCl (10 mmol, 2.6 g), and the reaction was stirred at room temperature for 2 h. The mixture was diluted with DCM (50 mL) and washed with 1 N hydrochloric acid (40 mL) and water (50 mL). The organic layer was evaporated to dryness under reduced pressure and the residue was purified by column chromatography (silica gel, EtOAc/hexanes, 1/10 to 1/3) to give compound **47** (2.9 g) as an amorphous white solid.

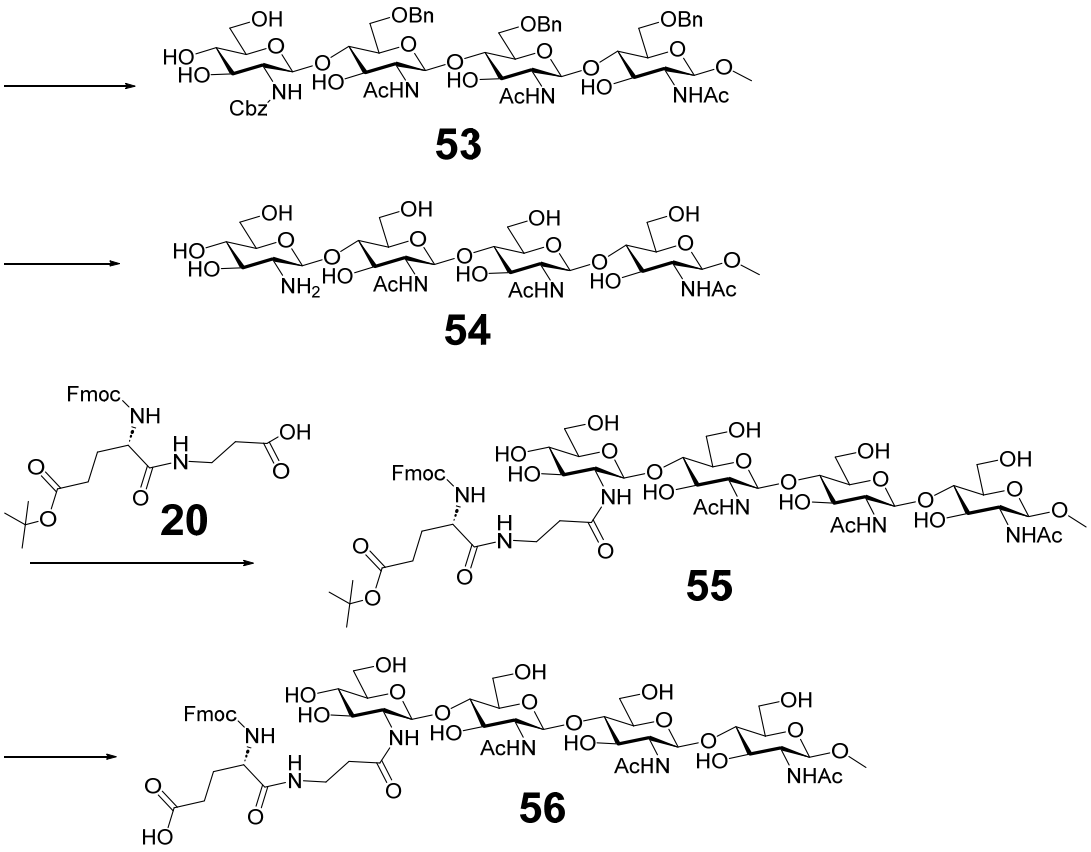
[00321] A solution of compound **47** (2.3 g) and compound **48** (1 g) in anhydrous DCM (30 mL) was stirred at room temperature in the presence of molecular sieves 4Å under argon atmosphere for 30 min. The mixture was cooled in an ice bath, and NIS (0.95 g) and TfOH (0.084 mL) were added. The reaction was stirred at this temperature, and after 30 mins, molecular sieves were removed by filtration and the filtrate was washed successively with $Na_2S_2O_3$ (10% in water, 40 mL) and water (50 mL). The organic layer was evaporated to dryness under reduced pressure and the residue was purified by column chromatography (silica gel, EtOAc/hexanes, 1/3 to 1/1) to give compound **49** (1.8 g) as an amorphous white solid.

[00322] Compound **49** (1.8 g) was dissolved in DCM (20 mL). To this solution, TEA (2 mL) was added, and the mixture was stirred at room temperature for 2 h. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (silica gel, EtOAc/hexanes, 1/2 to 2/1) to give compound **50** (1.3 g) as an amorphous white solid.

[00323] A solution of compound **46** (0.33 g) and compound **50** (0.27 g) in anhydrous DCM (6 mL) was stirred at room temperature in the presence of molecular sieves 4Å under argon atmosphere for 30 min. The mixture was cooled in an ice bath, and NIS (0.1 g) and TfOH (0.006 mL) were added. The reaction was stirred at this temperature, and after 30 mins, the reaction was diluted with DCM (30 mL) and molecular sieves were removed by filtration and the filtrate was washed successively with $Na_2S_2O_3$ (10% in water, 20 mL) and water (20 mL). The organic layer was evaporated to dryness under reduced pressure and the residue was purified by column chromatography (silica gel, EtOAc/hexanes, 1/3 to 2/1) to give compound **51** (0.35 g) as an amorphous white solid.

Scheme 7





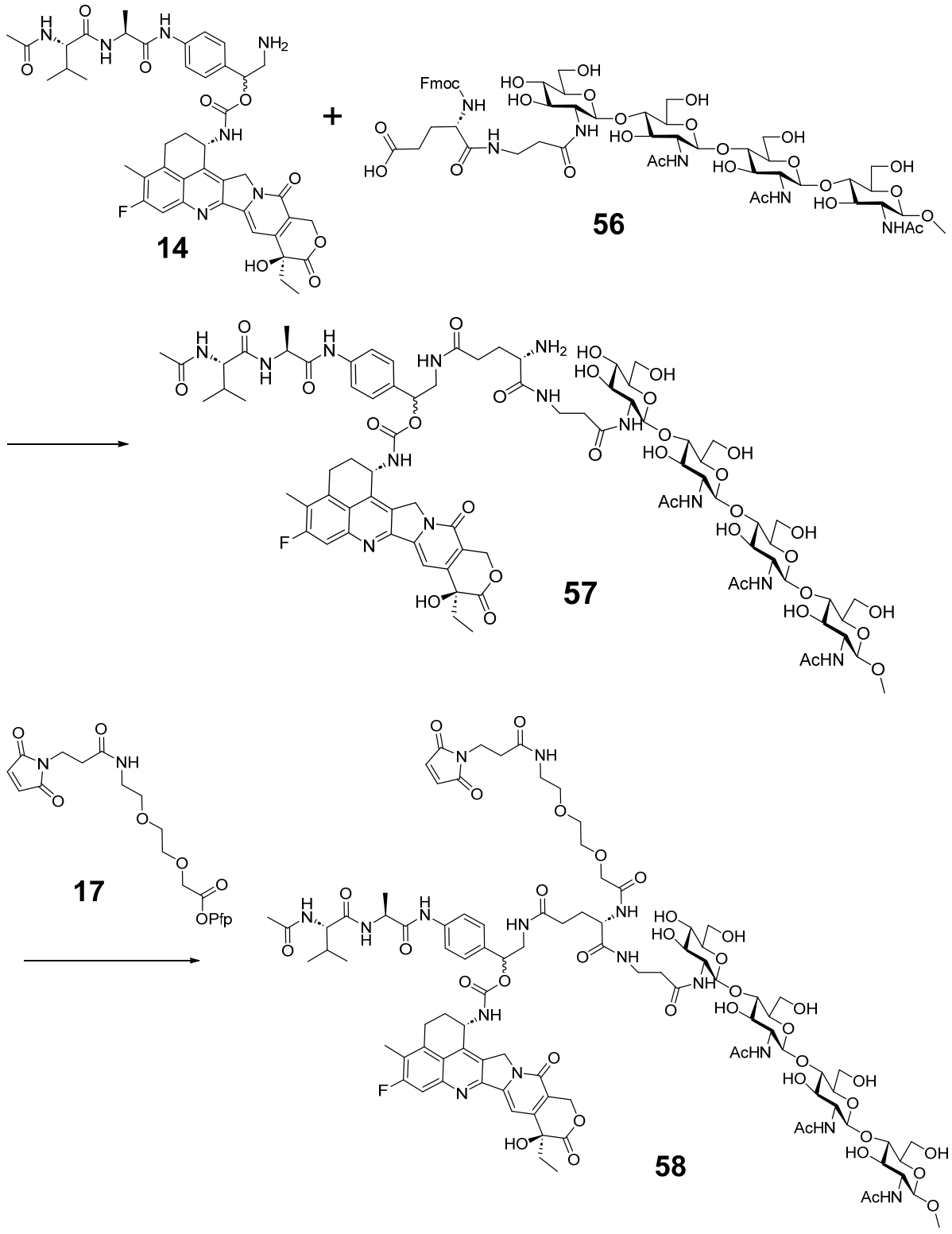
[00324] Tetrasaccharide **51** (60 mg) and ethylenediamine (0.4 mL) were suspended in anhydrous EtOH (6 mL) and the mixture was stirred at 60 °C for 18 h. The volatiles were then evaporated under reduced pressure, and the residue was dissolved in pyridine (3 mL). Acetic anhydride (2 mL) was added, and the mixture was stirred at room temperature for 18 h. MeOH (3 mL) was added, and the volatiles were removed under reduced pressure. The residue was purified directly by RP-HPLC to give compound **52** as a white solid (41 mg).

[00325] Compound **52** (40 mg) was dissolved in MeOH (10 mL). MeONa (4.4 M in MeOH, 0.16 mL) was added, and the mixture was stirred at room temperature. After 18 h, HCl (4M in dioxane, 0.2 mL) was added to neutralize the reaction. The reaction mixture was evaporated to dryness under reduced pressure. The residue was suspended in EtOH/water (1/1, v/v, 10 mL). Pd/C (40 mg) was added, and the mixture was stirred under hydrogen atmosphere for 3 h. The reaction was then filtered, and the filtrate was concentrated to dryness under reduced pressure to give compound **54** (20 mg) which was used in the next step without further purification.

[00326] To a suspension of compound **54** (20 mg) and compound **20** (27 mg) in DMF (4 mL) was added AOP (24 mg), followed by NMM (0.012 mL). The mixture was stirred at room temperature for 3 h, and the crude product was purified by RP-HPLC to give compound **55** as a white solid (21 mg), which was treated with TFA/DCM (1/2, v/v, 2 mL) for 1 h. The reaction

was then concentrated to dryness under reduced pressure to give compound **56** (18 mg) as an amorphous solid.

Scheme 8



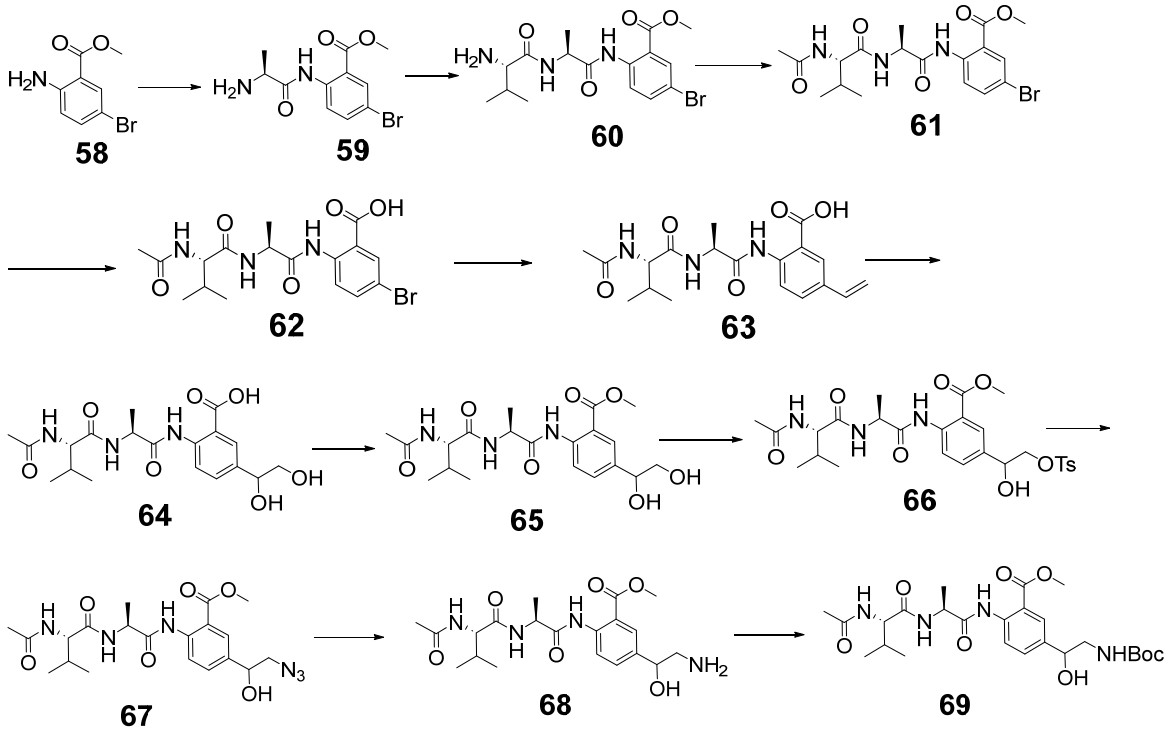
[00327] Compound **56** (18 mg) and compound **14** (TFA salt, 17 mg) were dissolved in anhydrous DMF (2 mL). PyAOP (15 mg) was added, followed by DIEA (0.011 mL), and the mixture was stirred at room temperature. After 5 hour, piperidine (0.1 mL) was added, and the mixture was stirred at room temperature for 30 min. The crude product was purified by RP-HPLC to give compound **57** as a yellow solid (TFA salt, 14 mg).

[00328] Compound **57** (14 mg) and the Pfp ester (**17**, 6 mg) were dissolved in DMF (2 mL), and DIEA (0.006 mL) was added. After stirring at room temperature for 5 h, the mixture was purified by RP-HPLC to give compound **58** as a yellow solid (8 mg) after lyophilization. MS: m/z 1054.4 $[M+2H^+]/2$.

Example 8: Synthesis of Drug-Linker compound 78

[00329] Compounds **69** was prepared as shown in scheme 9 and coupled with exatecan to provide Drug-Linker **78** as shown in scheme 10.

Scheme 9



[00330] To a solution of compound **58** (807 mg, 3.51 mmol) in anhydrous DCM (3 mL) and pyridine (4 mL) was added Fmoc-L-Ala-Cl (1.43 g, 4.4 mmol) in 3 mL of DCM. The mixture was stirred at room temperature over a period of 30 min. Then ether (10 mL) was added, and the precipitate was filtered, washed with 10 mL of water and dried. This precipitate was dissolved in

anhydrous DMF (6 mL) and piperidine (1 mL) was added. The mixture was stirred for 20 min, then it was purified by RP-HPLC to give compound **59** as a tan solid (630 mg).

[00331] To a solution of compound **59** (TFA salt, 630 mg, 1.52 mmol) in anhydrous DMF (4 mL) was added Fmoc-L-Val-OH (518 mg, 1.52 mmol), PyAOP (797 mg, 1.52 mmol), and DIEA (1 mL). The mixture was stirred at room temperature over a period of 20 min. Then piperidine (0.6 mL) was added, and the stirring continued for another 20 min. Then the mixture was purified by RP-HPLC to give compound **60** as a tan solid (730 mg).

[00332] To a solution of compound **60** (TFA salt, 730 mg, 1.42 mmol) in anhydrous DMF (3 mL) was added DIEA (1 mL), and acetic anhydride (290 mg, 2.84 mmol). The mixture was stirred at room temperature over a period of 20 min. Then the mixture was purified by RP-HPLC to give compound **61** as a white solid (353 mg).

[00333] To a solution of compound **61** (350 mg, 0.79 mmol) in a mixture of DMF (2 mL) and water (1 mL) was added 1N NaOH (2 mL). The mixture was stirred at room temperature over a period of 2 h. Then the mixture was purified by RP-HPLC to give compound **62** as a white solid (253 mg).

[00334] To a solution of compound **62** (184 mg, 0.43 mmol) in a mixture of DME (10 mL) and water (10 mL) was added sodium bicarbonate (144 mg, 1.72 mmol), pinacol vinylboronate (132 mg, 0.86 mmol) and Pd(PPh3)4 (25 mg, 0.02 mmol). The mixture was stirred at 80 °C over a period of 20 h. Then the mixture was cooled to room temperature and purified by RP-HPLC to give compound **63** as a white solid (145 mg).

[00335] To a solution of compound **63** (145 mg, 0.39 mmol) in a mixture of acetone (5 mL) and water (3 mL) was added NMO (68 mg, 0.58 mmol), and osmium tetroxide (4% in water, 25 µL, 0.01 eq). The mixture was stirred at room temperature over a period of 3 h. Then the mixture was purified by RP-HPLC to give compound **64** as a white solid (100 mg).

[00336] To a solution of compound **64** (100 mg, 0.24 mmol) in DCM (4 mL) was added trimethylsilyldiazomethane (0.6 M in hexane, 0.41 mL, 0.24 mmol). The mixture was stirred at room temperature over a period of 20 min. Then the mixture was purified by RP-HPLC to give compound **65** as a white solid (80 mg).

[00337] To a solution of compound **65** (80 mg, 0.188 mmol) in pyridine (2 mL) was added p-toluenesulfonyl chloride (72 mg, 0.376 mmol). The mixture was stirred at room temperature over a period of 2 h. Then the mixture was purified by RP-HPLC to give compound **66** as a tan solid (77 mg).

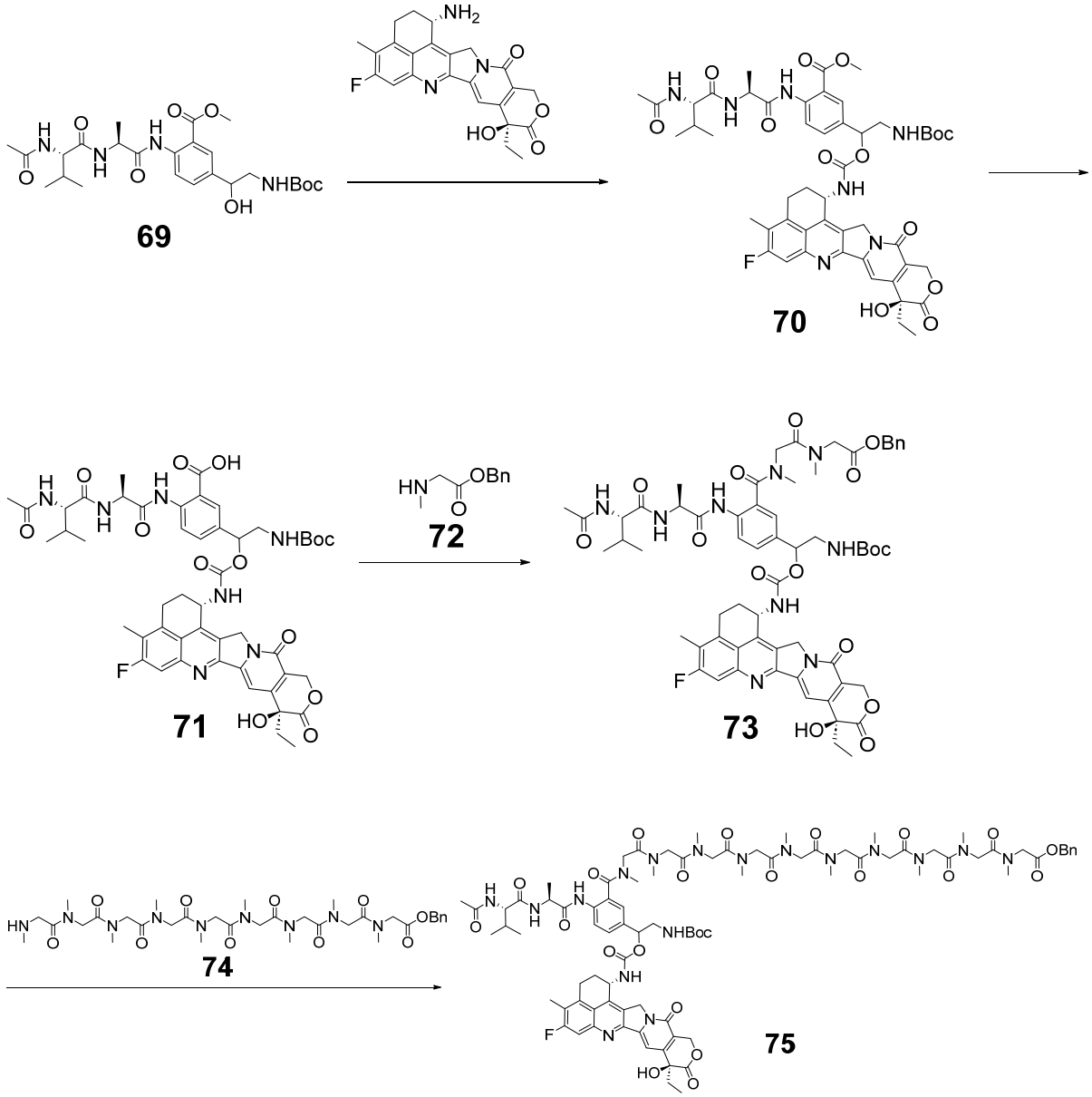
[00338] To a solution of compound **66** (77 mg, 0.133 mmol) in DMF (2 mL) was added sodium azide (86 mg, 1.33 mmol). The mixture was stirred at 80 °C over a period of 2 h. Then

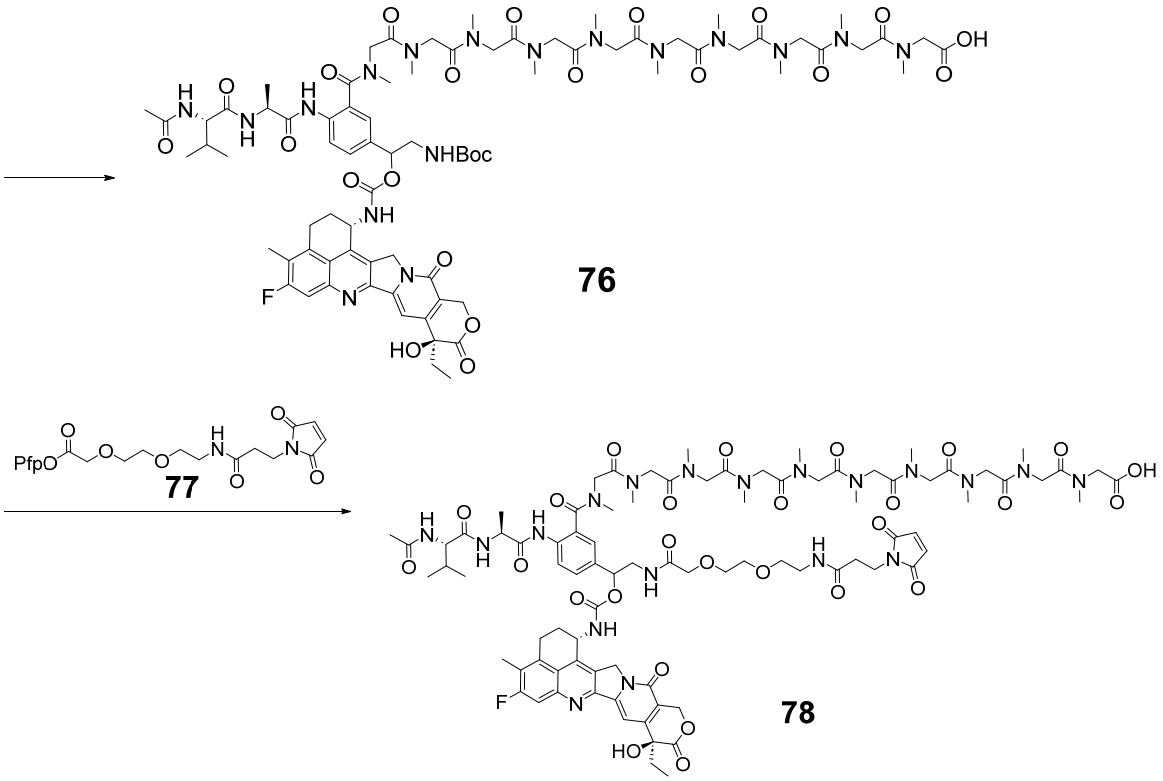
the mixture was cooled to room temperature and purified by RP-HPLC to give compound **67** as a white solid (50 mg).

[00339] To a solution of compound **67** (36 mg, 80 μmol) in THF (5 mL) was added PPh3 (31 mg, 120 μmol). The mixture was stirred at room temperature over a period of 20 h. Then the mixture was purified by RP-HPLC to give compound **68** as a white solid (30 mg).

[00340] To a solution of compound **68** (TFA salt, 17 mg, 32 μmol) in DMF (2 mL) was added di-tert-butyl dicarbonate (14 mg, 63 μmol), and DIEA (11 μL). The mixture was stirred at room temperature over a period of 20 min. Then the mixture was purified by RP-HPLC to give compound **69** as a white solid (15 mg).

Scheme 10 (SEQ ID NOS 60-61, 29 and 29, respectively, in order of appearance)





[00341] To a solution of compound **69** (15 mg, 28 μmol) in anhydrous DMF (1 mL) was added bis (4-nitrophenyl) carbonate (8.6 mg, 28 μmol) and DIEA (5.0 μL). The mixture was stirred at room temperature over 2 d. Then exatecan mesylate (15 mg, 28 μmol) and DIEA (10 μL) was added to the reaction. The mixture was stirred at 60 °C over a period of 5 h. Then the mixture was cooled to room temperature and purified by RP-HPLC to give compound **70** as a yellow solid (24 mg).

[00342] To a solution of compound **70** (24 mg, 24 μmol) in a mixture of ACN (2 mL) and water (1 mL) was added 1N NaOH in water (1 mL). The mixture was stirred at room temperature over a period of 20 min. Then the mixture was purified by RP-HPLC to give compound **71** as a yellow solid (14 mg).

[00343] To a solution of compound **71** (10 mg, 11 μmol) in anhydrous DMF (1 mL) was added compound **72** (HCl salt, 4.6 mg, 22 mmol), PyAOP (11 mg, 20 μmol), and DIEA (18 μL). The mixture was stirred at 60 °C over a period of 5 h. Then the mixture was cooled to room temperature and purified by RP-HPLC to give compound **73** as a yellow solid (4 mg).

[00344] To a solution of compound **73** (4 mg, 3.5 μmol) in a mixture of ACN (0.6 mL) and water (0.4 mL) was added 1N NaOH in water (0.1 mL). The mixture was stirred at room temperature over a period of 20 min. Then 1N HCl (0.1 mL) was added, and the mixture was evaporated to dryness under vacuum. The remaining residue was dissolved in anhydrous DMF

(1 mL) and compound **74** (3.0 mg, 3.5 µmol), PyAOP (1.8 mg, 3.5 µmol), and DIEA (3 µL) was added. The mixture was stirred at room temperature over a period of 20 min. Then the mixture was purified by RP-HPLC to give compound **75** as a yellow solid (5 mg).

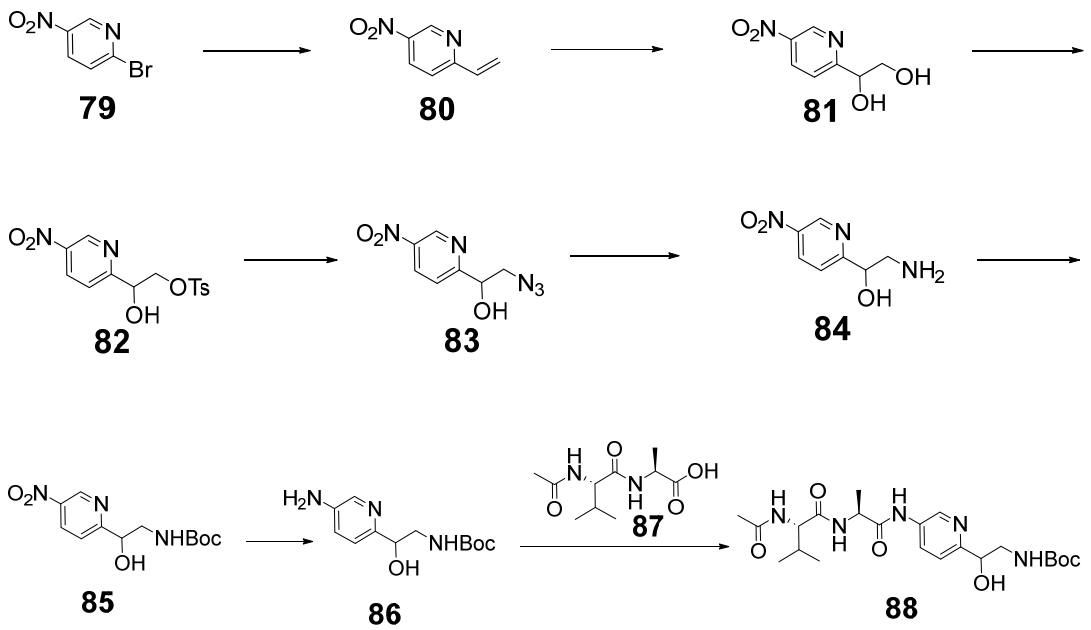
[00345] To a solution of compound **75** (5 mg, 2.8 µmol) in a mixture of ACN (0.6 mL) and water (0.4 mL) was added 1N NaOH in water (0.1 mL). The mixture was stirred at room temperature over a period of 20 min. Then the mixture was purified by RP-HPLC to give compound **76** as a yellow solid (3.3 mg).

[00346] To a solution of compound **76** (3.3 mg, 2.0 µmol) in DCM (1 mL) was added TFA (0.3 mL). The mixture was stirred at room temperature over a period of 20 min. Then the mixture was evaporated to dryness under vacuum. The remaining residue was dissolved in anhydrous DMF (1 mL) and compound **77** (1.0 mg, 2.0 µmol), and DIEA (3 µL) was added. The mixture was stirred at room temperature over a period of 20 min. Then the mixture was purified by RP-HPLC to give compound **78** as a yellowish solid (3.0 mg). MS: m/z 1878.5 $[M+H]^+$.

Example 9: Synthesis of Drug-Linker compound 95

[00347] Compounds **88** was prepared as shown in scheme 11 and coupled with exatecan to provide Drug-Linker **95** as shown in scheme 12.

Scheme 11



[00348] To a solution of compound **79** (3.9 g, 19 mmol) in a mixture of DME (80 mL) and water (40 mL) was added sodium bicarbonate (6.4 g, 76 mmol), pinacol vinylboronate (5.92 g,

38 mmol) and Pd(PPh3)4 (1.1 g, 0.95 mmol). The mixture was stirred at 80 °C over a period of 20 h. Then the mixture was cooled to room temperature, extracted with EtOAc (150 mL), evaporated, and purified by silica gel column (Hexane/EtOAc 10%) to give compound **80** as a brown solid (2.4 g).

[00349] To a solution of AD-mix beta (22.5 g) in a mixture of tBuOH (80 mL) and water (80 mL) was added compound **80** (2.4 g, 16 mmol). The mixture was stirred at room temperature over a period of 20 h. Then the mixture was extracted with EtOAc (200 mL), evaporated, and purified by silicagel column (Hexane/EtOAc 40%) to give compound **81** as a brown solid (2.1 g).

[00350] To a solution of compound **81** (735 mg, 4.0 mmol) in pyridine (10 mL) was added p-toluenesulfonyl chloride (759 mg, 4.0 mmol). The mixture was stirred at room temperature over a period of 3 h. Then the mixture was purified by RP-HPLC to give compound **82** as a tan solid (890 mg).

[00351] To a solution of compound **82** (759 mg, 2.2 mmol) in DMF (7 mL) was added sodium azide (876 mg, 13 mmol). The mixture was stirred at 80 °C over a period of 5 h. Then the mixture was cooled to room temperature and purified by RP-HPLC to give compound **83** as a tan solid (114 mg).

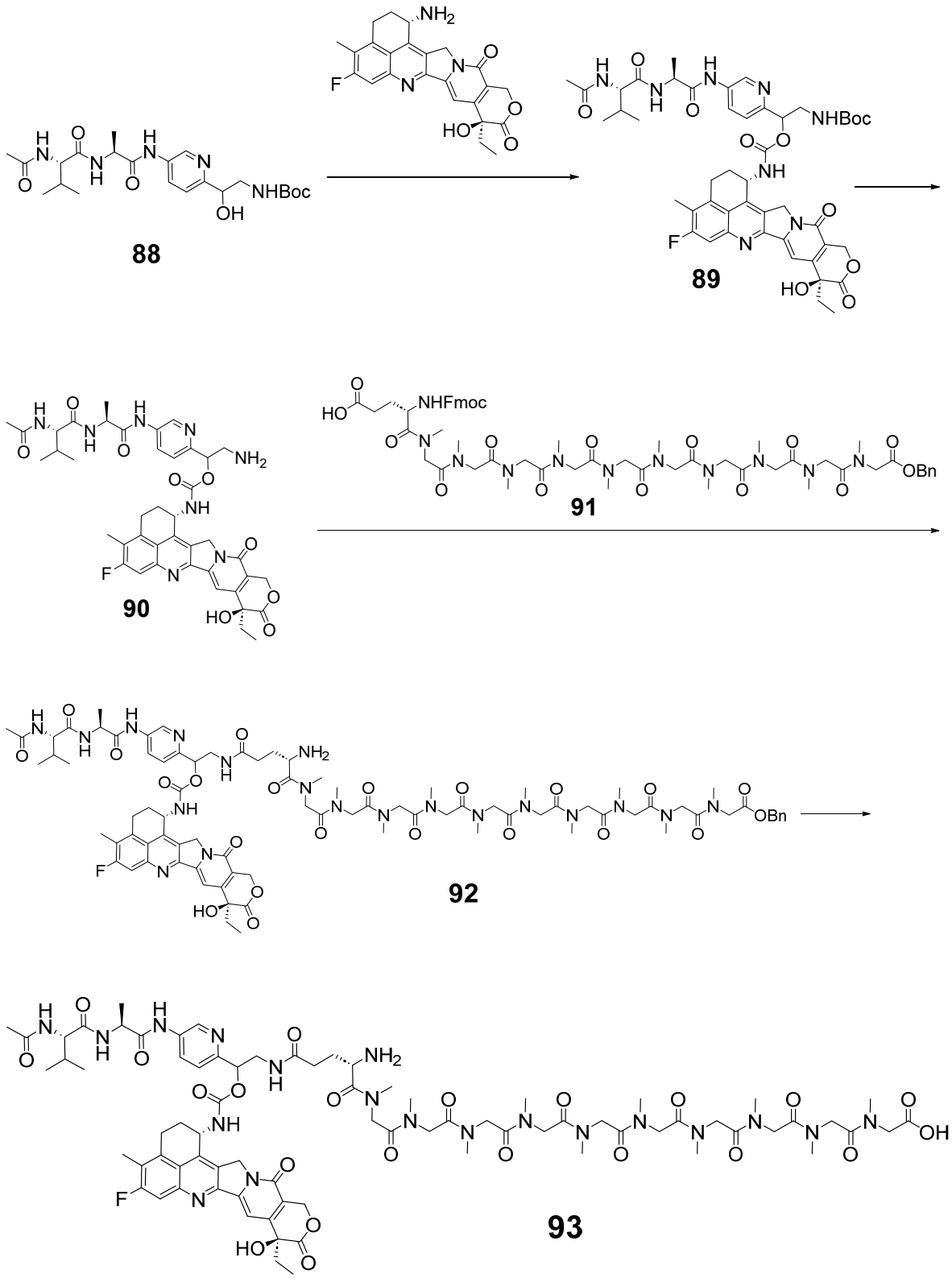
[00352] To a solution of compound **83** (88 mg, 0.42 mmol) in THF (5 mL) was added PPh3 (131 mg, 0.50 mmol). The mixture was stirred at room temperature over a period of 20 h. Then the mixture was purified by RP-HPLC to give compound **84** as a TFA salt (114 mg).

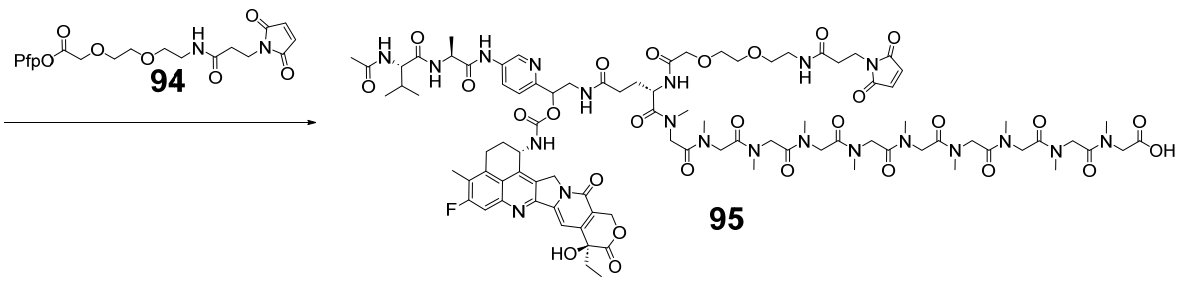
[00353] To a solution of compound **84** (TFA salt, 114 mg, 0.38 mmol) in DMF (2 mL) was added di-tert-butyl dicarbonate (84 mg, 0.38 mol), and DIEA (134 μL). The mixture was stirred at room temperature over a period of 20 min. Then the mixture was purified by RP-HPLC to give compound **85** as a tan solid (100 mg).

[00354] To a solution of compound **85** (89 mg, 0.31 mmol) in methanol (1 mL) and water (0.5 mL) was added formic acid (0.1 mL), and Zn metal powder (0.3 g). The mixture was stirred at room temperature over a period of 20 min. Then saturated $NaHCO_3$ (10 mL) was added, and the mixture was extracted with EtOAc (90 mL) and evaporated to give crude compound **86** as a clear solid (50 mg).

[00355] To a solution of compound **86** (50 mg, 0.20 mmol) in anhydrous DCM (5 mL) was added compound **87** (46 mg, 0.20 mmol), and EEDQ (49 mg, 0.20 mmol). The mixture was stirred at room temperature over a period of 20 h. Then the solvent was evaporated under vacuum and the mixture was purified by RP-HPLC to give compound **88** as a tan solid (35 mg).

Scheme 12 (SEQ ID NOS 51-53 and 25, respectively, in order of appearance)





[00356] To a solution of compound **88** (15.8 mg, 34 μmol) in anhydrous DCM (1 mL) was added carbonyl diimidazole (11 mg, 68 μmol). The mixture was stirred at room temperature over 2 h. Then the mixture was evaporated under vacuum and a solution of exatecan mesylate (54 mg, 102 μmol) and DIEA (40 μL) in anhydrous DMF (2 mL) was added to the reaction. The mixture was stirred at 100 °C over a period of 1 h. Then the mixture was cooled to room temperature and purified by RP-HPLC to give compound **89** as a yellow solid (16 mg).

[00357] To a solution of compound **89** (16 mg, 17.3 μmol) in DCM (1 mL) was added TFA (0.3 mL). The mixture was stirred at room temperature over a period of 20 min. Then the mixture was evaporated to dryness under vacuum to give compound **90** as a TFA salt (16 mg).

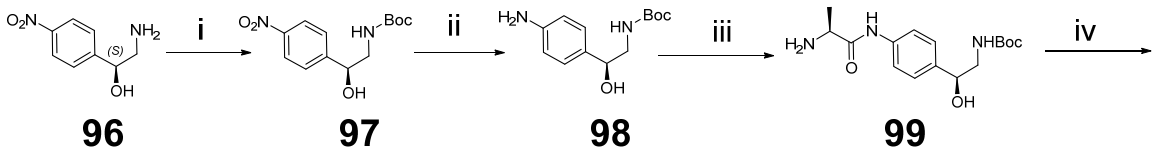
[00358] To a solution of compound **90** (TFA salt, 16 mg, 17.0 μmol) in anhydrous DMF (2 mL) was added compound **91** (20 mg, 17.0 μmol), PyAOP (8.9 mg, 17.0 mmol), and DIEA (4 μL). The mixture was stirred at room temperature over a period of 20 min. Then piperidine (0.2 mL) was added and the stirring continued for another 20 min. Then the mixture was purified by RP-HPLC to give compound **92** as a yellow solid (21 mg).

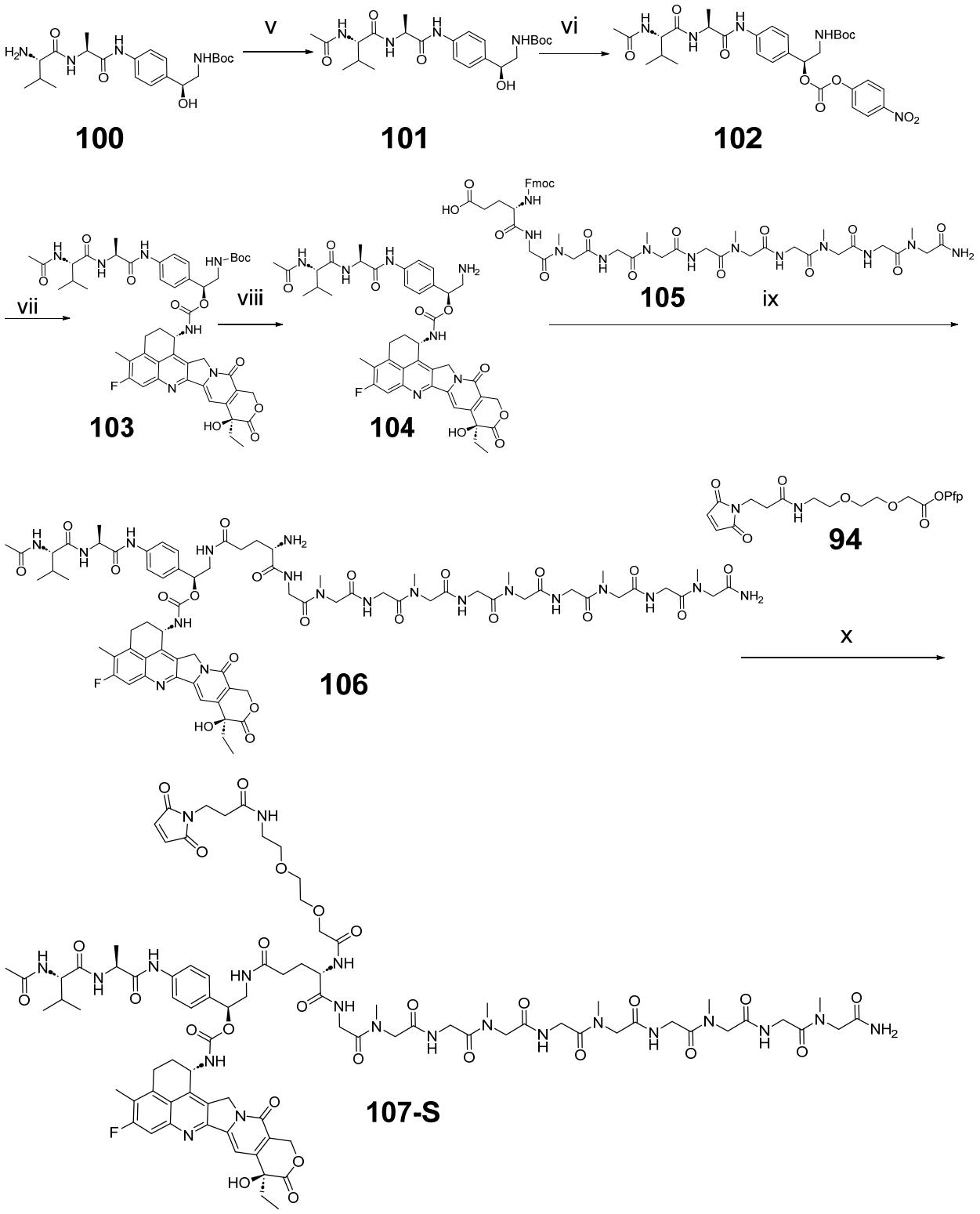
[00359] To a solution of compound **92** (21 mg, 11.2 μmol) in a mixture of ACN (1 mL) and water (1 mL) was added 1N NaOH in water (0.2 mL). The mixture was stirred at room temperature over a period of 20 min. Then the mixture was purified by RP-HPLC to give compound **93** as a yellow solid (12.3 mg).

[00360] To a solution of compound **93** (TFA salt, 5.2 mg, 2.9 μmol) in anhydrous DMF (1 mL) was added compound **94** (1.4 mg, 2.9 μmol), and DIEA (3 μL). The mixture was stirred at room temperature over a period of 20 min. Then the mixture was purified by RP-HPLC to give compound **95** as a yellowish solid (3.0 mg). MS: m/z 1963.5 $[M+H]^+$.

Example 10: Synthesis of Drug-Linker Compound 107-S

Scheme 13 (SEQ ID NOS 54-55 and 26, respectively, in order of appearance)





[00361] Reagents and conditions: i. Boc_2O, DIEA, DCM; ii. Pd/C, H_2, MeOH, rt, 1 h; iii. Fmoc-Ala-OH, EEDQ, DCM, rt, 20 h. then piperidine/DMF; iv. Fmoc-Val-OH, PyAOP, DIEA, DMF, rt., 20 min, then piperidine, rt., 10 min.; v. HOAc, PyAOP, DIEA, DMF; vi. BisPNP carbonate, DIEA, DMF, rt., 24 h; vii. exatecan mesylate, DIEA, DMF, rt., 48 h; viii. TFA/DCM,

1/3, rt., 15 min; ix. EDC/HOAt, DIEA, DMSO, rt., 1 h, then piperidine, rt., 2 h; x. DIEA, DMSO.

Step i: tert-butyl (S)-(2-hydroxy-2-(4-nitrophenyl)ethyl)carbamate (Compound 97)

[00362] To a solution of (S)-2-amino-1-(4-nitrophenyl)ethan-1-ol (Compound **96**) (318 mg, 1.75 mmol) in anhydrous DMF (3 mL) was added DIEA (0.3 mL, 1.75 mmol), and tert-butoxycarbonyl anhydride (381 mg, 1.75 mmol). The mixture was stirred at RT for a period of 1 h. The solvent was evaporated under vacuum and the residue was purified by silica gel column (DCM 99% / MeOH 1%) to give Compound **97** as a tan solid (466 mg, 94%).

Step ii: tert-butyl (S)-(2-(4-aminophenyl)-2-hydroxyethyl)carbamate (Compound 98)

[00363] To a solution of Compound **97** (238 mg, 0.84 mmol) in methanol (6 mL) was added Pd/C (10% Pd, 50 mg). The mixture was purged with argon gas, then filled with hydrogen, and hydrogenated for a period of 1 h. The catalyst was removed by filtration, and the solvent was evaporated to give Compound **98** as a clear solid (197 mg, 92%).

Step iii: tert-butyl ((S)-2-(4-((S)-2-aminopropanamido)phenyl)-2-hydroxyethyl)carbamate (Compound 99)

[00364] To a solution of Compound **98** (197 mg, 0.78 mmol) in DCM (5 mL)/MeOH (1 mL) mixture was added Fmoc-L-Ala-OH (243 mg, 0.78 mmol) and EEDQ (232 mg, 0.94 mmol). The mixture was stirred at RT over a period of 20 h. The solvent was evaporated under vacuum and the resulting residue was dissolved in 2 mL of DMF. Then piperidine (0.3 mL) was added, and the mixture was stirred for 10 min. Then the mixture was purified by RP-HPLC to give Compound **99** as a TFA salt (258 mg, 76%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile Gradient: 2-30% B over 20 min, flow 50 mL/min. The desired compound eluted at 17 min.

Step iv: tert-butyl ((S)-2-(4-((S)-2-((S)-2-amino-3-methylbutanamido)propanamido)phenyl)-2-hydroxyethyl)carbamate (Compound 100)

[00365] To a solution of Compound **99** (TFA salt, 237 mg, 0.54 mmol) in anhydrous DMF (2 mL) was added Fmoc-L-Val-OH (184 mg, 0.54 mmol), PyAOP (283 mg, 0.54 mmol), and DIEA (0.4 mL). The mixture was stirred at RT over a period of 20 min. Then piperidine (0.2 mL) was added, and the mixture was stirred for 10 min. Then the mixture was purified by RP-HPLC to give compound **100** as a TFA salt (230 mg, 79%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 2-35% B over 20 min, flow 50 mL/min. The desired compound eluted at 20 min.

Step v: tert-butyl ((S)-2-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido)phenyl) -2-hydroxyethyl)carbamate (Compound 101)

[00366] To a solution of Compound **100** (TFA salt, 230 mg, 0.43 mmol) in anhydrous DMF (2 mL) was added acetic acid (32 mg, 0.53 mol), PyAOP (224 mg, 0.43 mmol) and DIEA (0.3 mL). The mixture was stirred at room temperature for a period of 20 min. Then the mixture was purified directly by RP-HPLC to give Compound **101** as a tan solid (167 mg, 85%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 5-60% B over 20 min, flow 50 mL/min. The desired compound eluted at 18 min.

Step vi and Step vii: (S)-1-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido) phenyl)-2-((tert-butoxycarbonyl)amino)ethyl ((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 (Compound 103)

[00367] To a solution of Compound **101** (104 mg, 0.22 mmol) in anhydrous DMF (2 mL) was added bis(4-nitrophenyl) carbonate (77 mg, 0.25 mol) and DIEA (38 µL). The mixture was stirred at room temperature for a period of 24 h to give a solution of tert-butyl ((S)-2-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido)phenyl)-2-(((4-nitrophenoxy)carbonyl)oxy)ethyl)carbamate (compound **102**). Then a solution of exatecan mesylate (133 mg, 0.25 mmol) and DIEA (80 µL) in 1 mL of anhydrous DMF was added, and the stirring continued for 2 d. Then the mixture was purified by RP-HPLC to give Compound **103** as a pale-yellow solid (111 mg, 60%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 15-75% B over 20 min, flow 50 mL/min. The desired compound eluted at 20 min.

Step viii: (S)-1-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido)phenyl)-2-aminoethyl ((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 (Compound 104)

[00368] Compound **103** (70 mg, 75.7 µmol) was dissolved in a mixture of DCM (3 mL) and TFA (1 mL). The mixture was stirred at room temperature for a period of 15 min, then the solvent was removed under vacuum, and the residue was purified by RP-HPLC to give Compound **104** as a TFA salt (58 mg, 81%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 5-50% B over 20 min, flow 50 mL/min. The desired compound eluted at 17 min.

Step ix: (32S,38S)-38-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido)phenyl)-1,32-diamino-3,9,15,21,27-pentamethyl-1,4,7,10,13,16,19,22,25,28,31,35-dodecaoxo-3,6,9,12,15,18,21,24,27,30,36-undecaazaoctatriacontan-38-yl ((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 (Compound 106)

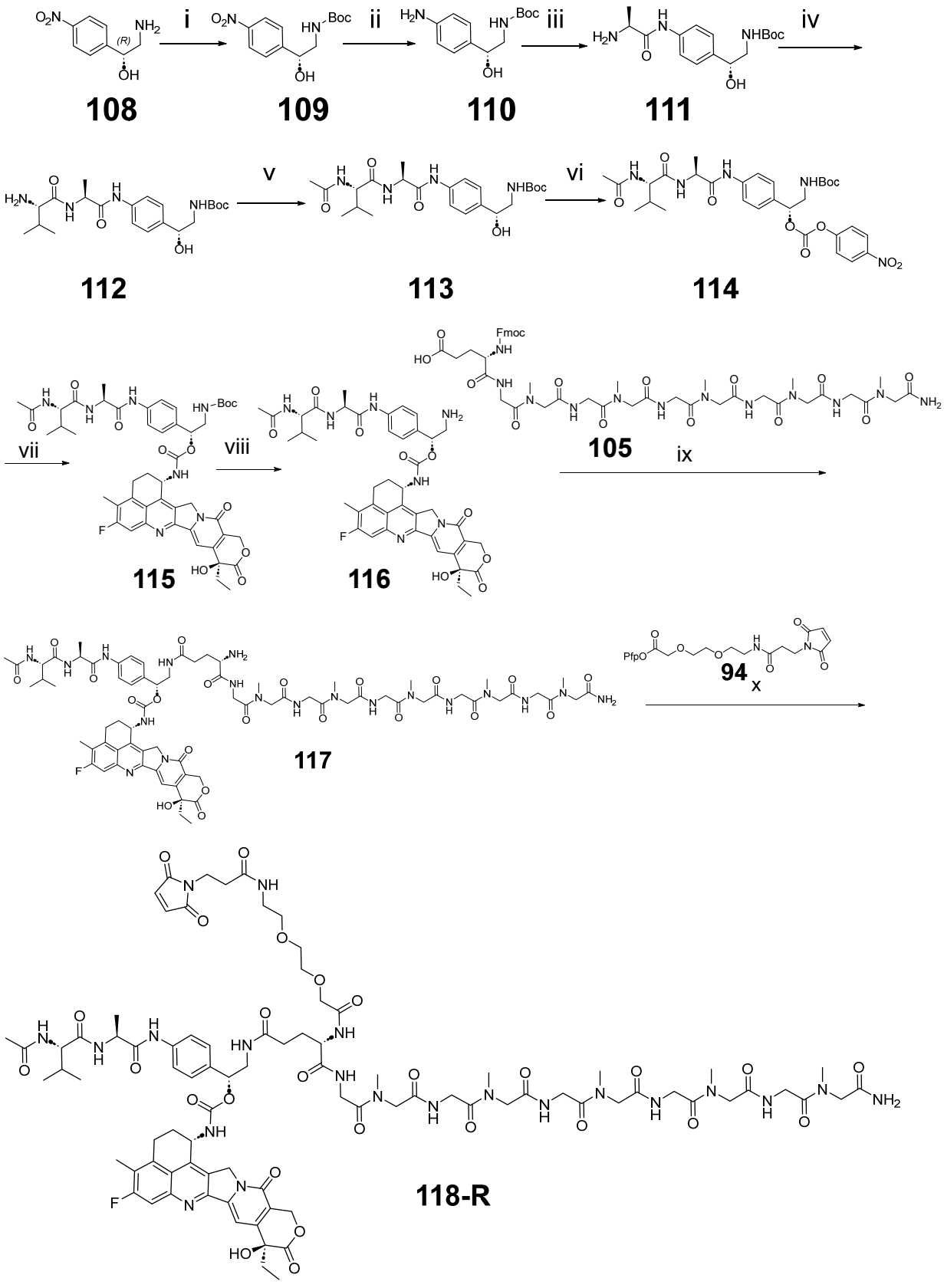
[00369] To a solution of Compound **104** (TFA salt, 30 mg, 32 μmol) in anhydrous DMF (2 mL) was added (S)-32-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-1-amino-3,9,15,21,27-pentamethyl-1,4,7,10,13,16,19,22,25,28,31-undecaoxo-3,6,9,12,15,18,21,24,27,30-decaazapentatriacontan-35-oic acid (Compound **105**) (32 mg, 32 μmol), PyAOP (17 mg, 32 μmol) and DIEA (23 μL). The mixture was stirred at room temperature for a period of 90 min. Then piperidine (150 μL) was added and the stirring continued for an additional 10 min. Then the mixture was purified directly by RP-HPLC to give Compound **106** as a TFA salt (34 mg, 62%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 2-45% B over 20 min, flow 50 mL/min. The desired compound eluted at 17 min.

Step x: (32S,38S)-38-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido)phenyl)-1-amino-32-(2-(2-(2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)ethoxy) ethoxy)acetamido)-3,9,15,21,27-pentamethyl-1,4,7,10,13,16,19,22,25,28,31,35-dodecaoxo-3,6,9,12,15,18,21,24,27,30,36-undecaazaoctatriacontan-38-yl ((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 (Compound 107-S)

[00370] To a solution of Compound **106** (TFA salt, 34 mg, 20 μmol) in anhydrous DMF (1 mL) was added perfluorophenyl 2-(2-(2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido) ethoxy)ethoxy)acetate (Compound **12)** (10 mg, 20 μmol) and DIEA (14 μL). The mixture was stirred at room temperature for a period of 30 min. Then the mixture was purified directly by RP-HPLC to give Compound **107-S** as a pale-yellow solid (26 mg, 69%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 5-50% B over 20 min, flow 50 mL/min. The desired compound eluted at 17 min. MS $[M+2H^+]/2$ = 946.2.

Example 11: Synthesis of Drug-Linker Compound 118-R

Scheme 14 (SEQ ID NOS 54-55 and 26, respectively, in order of appearance)


i
ii
iii
iv
v
vi
vii
viii
ix
x
108
109
110
111
112
113
114
115
116
105
117
94
118-R

[00371] Reagents and conditions: i. Boc_2O, DIEA, DCM; ii. Pd/C, H_2, MeOH, rt, 1 h; iii. Fmoc-Ala-OH, EEDQ, DCM, rt, 20 h. then piperidine/DMF; iv. Fmoc-Val-OH, PyAOP, DIEA, DMF, rt., 20 min, then piperidine, rt., 10 min.; v. HOAc, PyAOP, DIEA, DMF; vi. BisPNP carbonate, DIEA, DMF, rt., 24 h; vii. exatecan mesylate, DIEA, DMF, rt., 48 h; viii. TFA/DCM, 1/3, rt., 15 min; ix. EDC/HOAt, DIEA, DMSO, rt., 1 h, then piperidine, rt., 2 h; x. DIEA, DMSO.

Step i: tert-butyl (R)-(2-hydroxy-2-(4-nitrophenyl)ethyl)carbamate (Compound 109)

[00372] To a solution of (R)-2-amino-1-(4-nitrophenyl)ethan-1-ol (Compound **108)** (318 mg, 1.75 mmol) in anhydrous DMF (3 mL) was added DIEA (0.3 mL, 1.75 mmol), and tert-butoxycarbonyl anhydride (381 mg, 1.75 mmol). The mixture was stirred at RT for a period of 1 h. The solvent was evaporated under vacuum and the residue was purified by silicagel column (DCM 99% / MeOH 1%) to give Compound **109** as a tan solid (466 mg, 94%).

Step ii: tert-butyl (R)-(2-(4-aminophenyl)-2-hydroxyethyl)carbamate (Compound 110)

[00373] To a solution of Compound **109** (238 mg, 0.84 mmol) in methanol (6 mL) was added Pd/C (10% Pd, 50 mg). The mixture was purged with argon gas, then filled with hydrogen, and hydrogenated for a period of 1 h. The catalyst was removed by filtration, and the solvent was evaporated to give Compound **110** as a clear solid (197 mg, 92%).

Step iii: tert-butyl ((R)-2-(4-((S)-2-aminopropanamido)phenyl)-2-hydroxyethyl)carbamate (Compound 111)

[00374] To a solution of Compound **110** (197 mg, 0.78 mmol) in DCM (5 mL)/MeOH (1 mL) mixture was added Fmoc-L-Ala-OH (243 mg, 0.78 mmol) and EEDQ (232 mg, 0.94 mmol). The mixture was stirred at RT over a period of 20 h. The solvent was evaporated under vacuum and the resulting residue was dissolved in 2 mL of DMF. Then piperidine (0.3 mL) was added, and the mixture was stirred for 10 min. Then the mixture was purified by RP-HPLC to give Compound **111** as a TFA salt (258 mg, 76%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 2-30% B over 20 min, flow 50 mL/min. The desired compound eluted at 17 min.

Step iv: tert-butyl ((R)-2-(4-((S)-2-((S)-2-amino-3-methylbutanamido)propanamido)phenyl)-2-hydroxyethyl)carbamate (Compound 112)

[00375] To a solution of Compound **111** (TFA salt, 237 mg, 0.54 mmol) in anhydrous DMF (2 mL) was added Fmoc-L-Val-OH (184 mg, 0.54 mmol), PyAOP (283 mg, 0.54 mmol), and DIEA (0.4 mL). The mixture was stirred at RT over a period of 20 min. Then piperidine (0.2 mL) was added, and the mixture was stirred for 10 min. Then the mixture was purified by RP-HPLC to give Compound 112 as a TFA salt (230 mg, 79%).Preparative HPLC method details:

Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC

Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 2-35% B over 20 min, flow 50 mL/min. The desired compound eluted at 20 min.

Step v: tert-butyl ((R)-2-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido) phenyl)-2-hydroxyethyl)carbamate (Compound 113)

[00376] To a solution of Compound **112** (TFA salt, 230 mg, 0.43 mmol) in anhydrous DMF (2 mL) was added acetic acid (32 mg, 0.53 mol), PyAOP (224 mg, 0.43 mmol) and DIEA (0.3 mL). The mixture was stirred at room temperature for a period of 20 min. Then the mixture was purified directly by RP-HPLC to give Compound **113** as a tan solid (167 mg, 85%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 5-60% B over 20 min, flow 50 mL/min. The desired compound eluted at 18 min.

Step vi and Step vii: (R)-1-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido) phenyl)-2-((tert-butoxycarbonyl)amino)ethyl ((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 (Compound 115)

[00377] To a solution of Compound **113** (104 mg, 0.22 mmol) in anhydrous DMF (2 mL) was added bis(4-nitrophenyl) carbonate (77 mg, 0.25 mol) and DIEA (38 µL). The mixture was stirred at room temperature for a period of 24 h to give a solution of tert-butyl ((R)-2-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido)phenyl)-2-(((4-nitrophenoxy)carbonyl)oxy)ethyl) carbamate (Compound **114)**. Then a solution of exatecan mesylate (133 mg, 0.25 mmol) and DIEA (80 µL) in 1 mL of anhydrous DMF was added, and the stirring continued for 2 d. Then the mixture was purified by RP-HPLC to give Compound 115 as a pale-yellow solid (111 mg, 60%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 15-75% B over 20 min, flow 50 mL/min. The desired compound eluted at 20 min.

Step viii: (R)-1-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido)phenyl)-2-aminoethyl ((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 (Compound 116)

[00378] Compound **115** (70 mg, 75.7 µmol) was dissolved in a mixture of DCM (3 mL) and TFA (1 mL). The mixture was stirred at room temperature for a period of 15 min, then the solvent was removed under vacuum, and the residue was purified by RP-HPLC to give

Compound **116** as a TFA salt (58 mg, 81%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 5-50% B over 20 min, flow 50 mL/min. The desired compound eluted at 17 min.

Step ix: (32S,38R)-38-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido)phenyl)-1,32-diamino-3,9,15,21,27-pentamethyl-1,4,7,10,13,16,19,22,25,28,31,35-dodecaoxo-3,6,9,12,15,18,21,24,27,30,36-undecaazaoctatriacontan-38-yl ((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 (Compound 117)

[00379] To a solution of Compound **116** (TFA salt, 30 mg, 32 μmol) in anhydrous DMF (2 mL) was added Compound **105** (32 mg, 32 μmol), PyAOP (17 mg, 32 μmol) and DIEA (23 μL). The mixture was stirred at room temperature for a period of 90 min. Then piperidine (150 μL) was added and the stirring continued for an additional 10 min. Then the mixture was purified directly by RP-HPLC to give Compound **117** as a TFA salt (34 mg, 62%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 2-45% B over 20 min, flow 50 mL/min. The desired compound eluted at 17 min.

Step x: (32S,38R)-38-(4-((S)-2-((S)-2-acetamido-3-methylbutanamido)propanamido)phenyl)-1-amino-32-(2-(2-(2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)ethoxy) ethoxy)acetamido)-3,9,15,21,27-pentamethyl-1,4,7,10,13,16,19,22,25,28,31,35-dodecaoxo-3,6,9,12,15,18,21,24,27,30,36-undecaazaoctatriacontan-38-yl ((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 (Compound 118-R)

[00380] To a solution of Compound **117** (TFA salt, 34 mg, 20 μmol) in anhydrous DMF (1 mL) was added Compound **94** (10 mg, 20 μmol) and DIEA (14 μL). The mixture was stirred at room temperature for a period of 30 min. Then the mixture was purified directly by RP-HPLC to give Compound **118-R** as a pale-yellow solid (26 mg, 69%). Preparative HPLC method details: Column: Phenomenex Gemini NX 5, C18, 110 Å, 150 x 50 mm. Instrument: Shimadzu LC with CTC IFC. Mobile phase: A) water (0.1% TFA), B) acetonitrile. Gradient: 5-50% B over 20 min, flow 50 mL/min. The desired compound eluted at 17 min. MS $[M+2H^+]/2$ = 946.3

Example 12: Preparation of Antibody-Drug-Conjugates

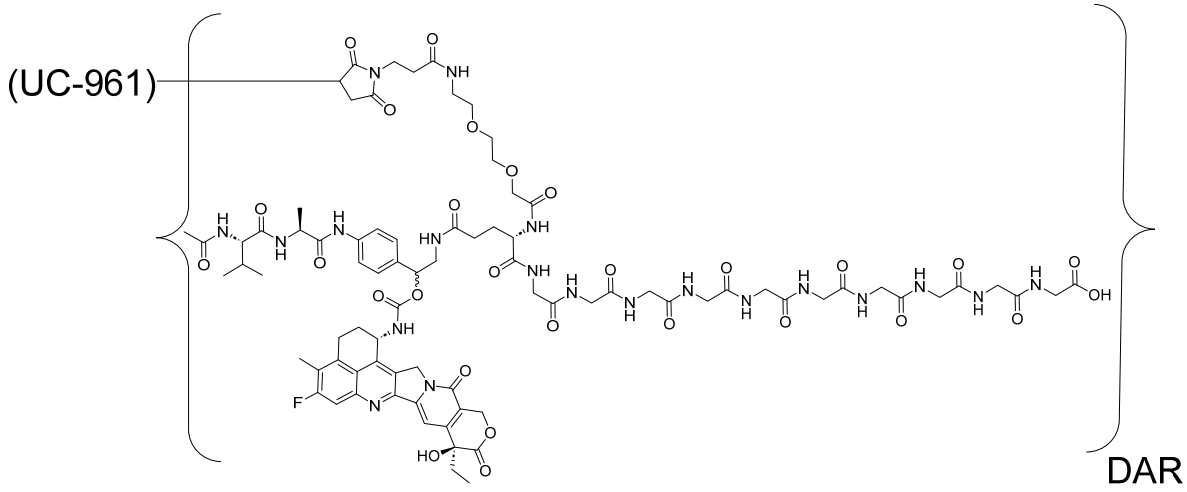
[00381] The conjugates were prepared using the followed conditions using the appropriate Drug-Linker and antibody (e.g., UC-961 antibody or ROR2 antibody).

[00382] 50 mg of mAb(s) for conjugation in various formulations were pH adjusted or buffer exchanged into 5% (v/v) 0.5 M Tris, 0.025 M EDTA, pH 8.5 formulations for reduction. The addition of 0.025 M EDTA in the formulation buffer was added to prevent metal-catalysed disulphide reoxidation. 10 mM TCEP (7 M eq.) was added to reduce a target number of interchain disulphide bonds and generate the desired average number of free thiols per mAb for 90 min at 25 °C. The free thiols were conjugated with an excess of maleimide (MC) containing toxin linker dissolved in a water miscible solvent (12 eq. of 20 mM MC-linker in 10% DMA) for 60 min at 25 °C. Extra solvent was added prior to toxin linker to maintain solubility of the toxin linker upon addition and mixing was performed utilizing stir flasks. Conjugation was ended by the addition of an excess of NAC (110 mM) and further stirred for 30 min to quench unreacted maleimide. Excess quenched toxin linker was removed by incubation with activated carbon for 60 min at room temperature at 15 rpm and/or diafiltration. Conjugates (yields, 93-97%) were exchanged into the final formulation buffer (0.1 M Arg/PBS, pH 7.4) and filtered through 0.22 μm PES before aliquoting and storage at ≤ -60 °C.

Example 13: Preparation of Antibody-drug conjugate (ADC)-7 using Drug-Linker 18 and UC-961 Antibody

[00383] ADC-7 was prepared using example 12 and the Drug-Linker **18** and UC-961 antibody.

ADC-7

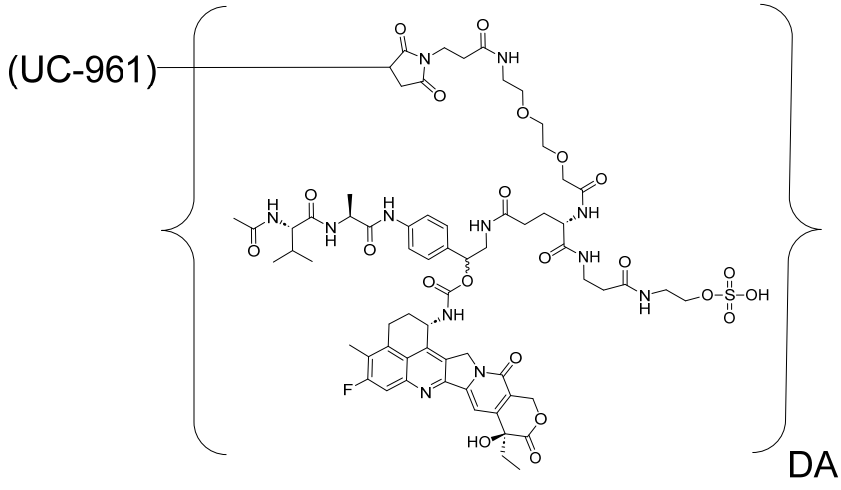


(SEQ ID NO: 24); wherein DAR was 1.6. Using the protocol from example 12, a DAR above 2 was unattainable using Drug-Linker **18** and UC-961 antibody. The sequences of the heavy chain and light chain region of UC-961 antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 14: Preparation of ADC-2 using Drug-Linker 25 and UC-961 Antibody

[00384] ADC-2 was prepared using example 12 and the Drug-Linker **25** and UC-961 antibody.

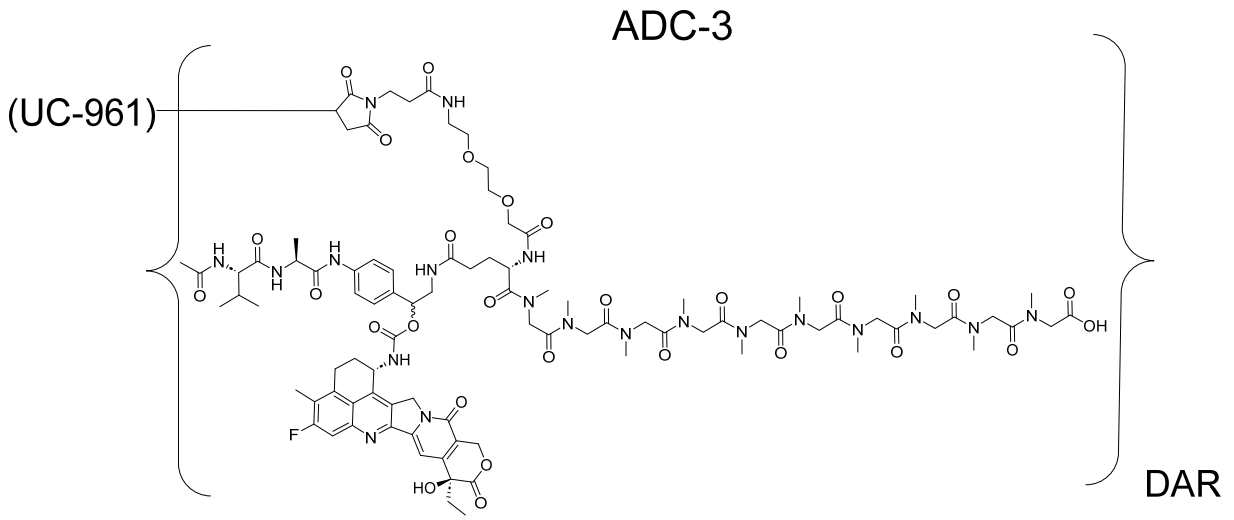
ADC-2



; wherein the DAR value as determined by RP-HPLC was 8.0. The sequences of the heavy chain and light chain region of UC-961 antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 15: Preparation of ADC-3 using of Drug-Linker 34 and UC-961 Antibody

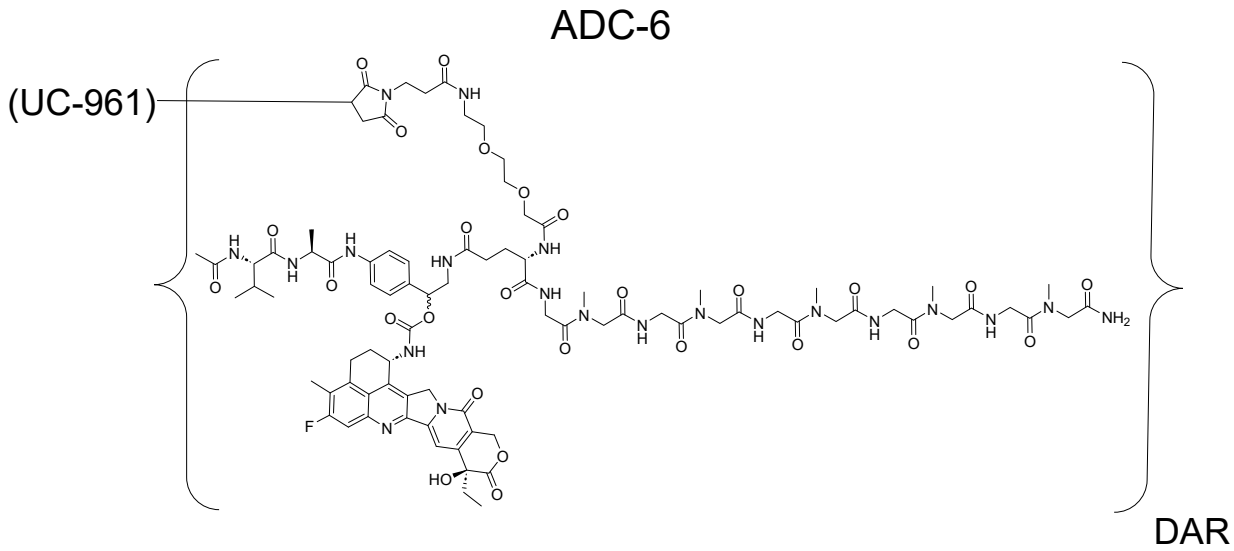
[00385] ADC-3 was prepared using example 12 and the Drug-Linker **34** and UC-961 antibody.



(SEQ ID NO: 25) ; wherein the DAR value as determined by RP-HPLC was 8.0. The sequences of the heavy chain and light chain region of UC-961 antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 16: Preparation of ADC-6 using Drug-Linker 37 and UC-961 Antibody

[00386] ADC-6 was prepared using example 12 and the Drug-Linker **37** and UC-961 antibody.

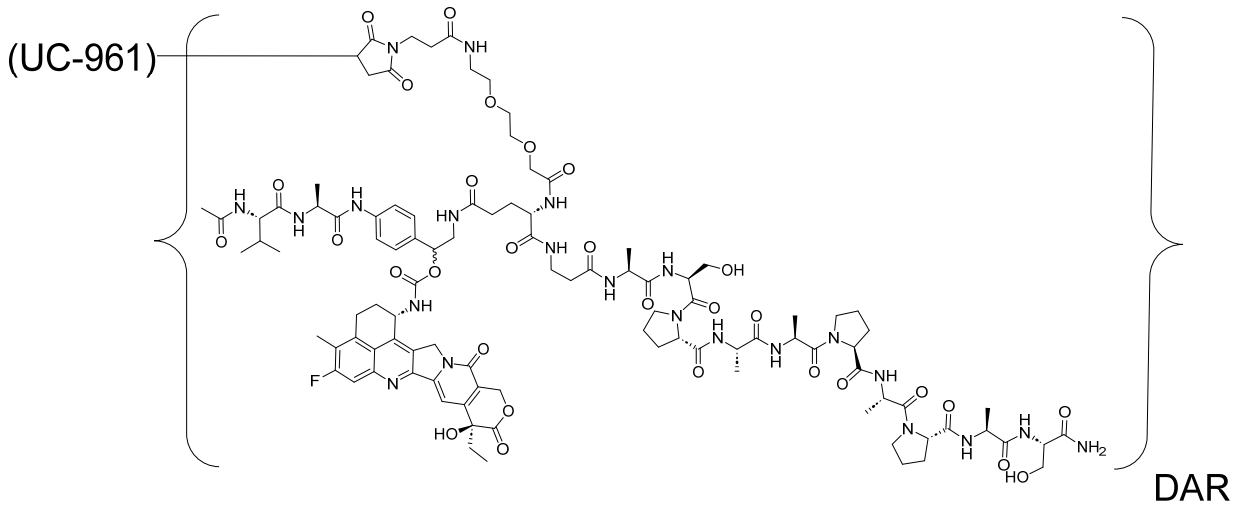


(SEQ ID NO: 26); wherein the DAR value as determined by RP-HPLC was 8.0. The sequences of the heavy chain and light chain region of UC-961 antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 17: Preparation of ADC-4 using Drug-Linker 40 and UC-961 Antibody

[00387] ADC-4 was prepared using example 12 and the Drug-Linker **40** and UC-961 antibody.

ADC-4

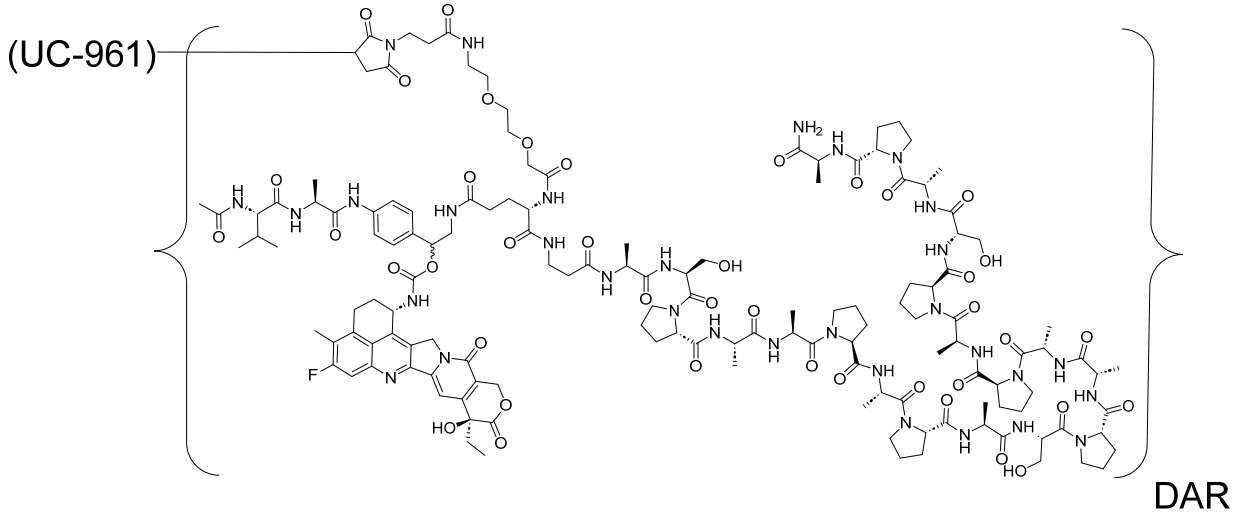


(SEQ ID NO: 27); wherein the DAR value as determined by RP-HPLC was 8.0. The sequences of the heavy chain and light chain region of UC-961 antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 18: Preparation of ADC-5 using Drug-Linker 43 and UC-961 Antibody

[00388] ADC-5 was prepared using example 12 and the Drug-Linker **43** and UC-961 antibody.

ADC-5

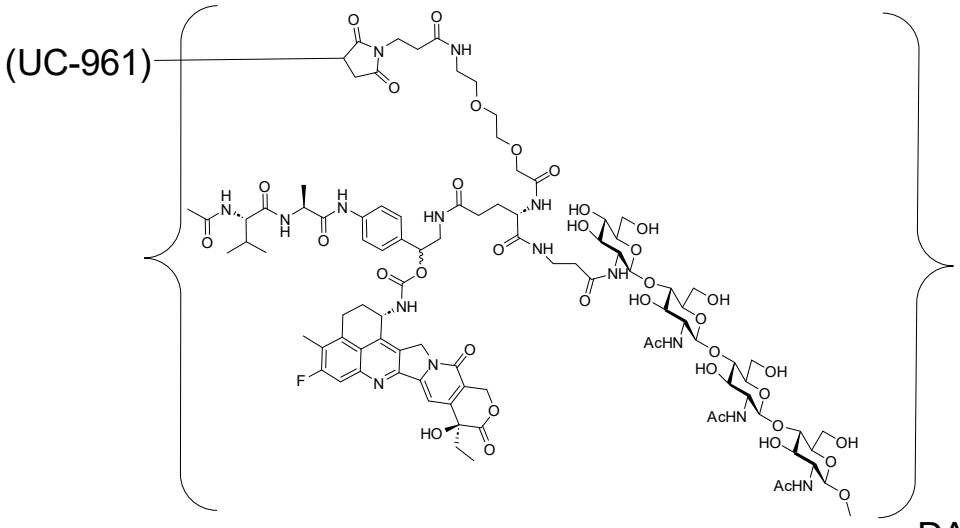


(SEQ ID NO: 28); wherein the DAR value as determined by RP-HPLC was 8.0. The sequences of the heavy chain and light chain region of UC-961 antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 19: Preparation of ADC-8 using Drug-Linker 58 and UC-961 Antibody

[00389] ADC-8 was prepared using example 12 and the Drug-Linker **58** and UC-961 antibody.

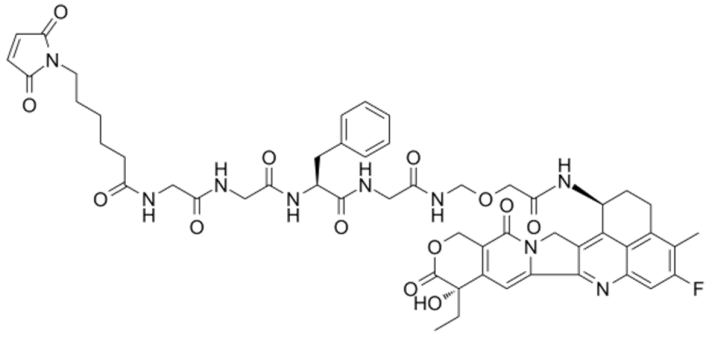
ADC-8



; wherein the DAR value as determined by RP-HPLC was 8. The sequences of the heavy chain and light chain region of UC-961antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 20: Preparation of ADC-1 using Deruxtecan and UC-961 Antibody

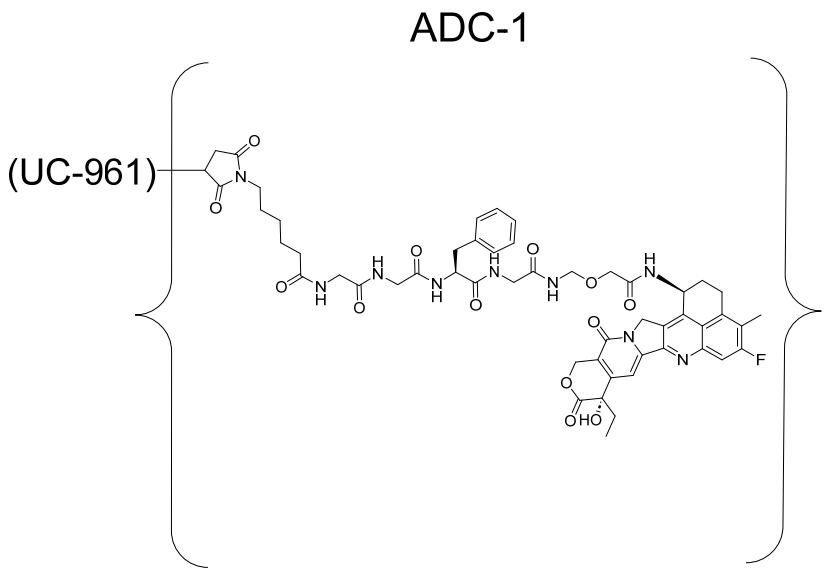
[00390] ADC-1 was synthesized using Deruxtecan in combination with UC-961. Deruxtecan, is a drug-linker composed of an DX-8951 derivative (DXd), and a maleimide-GGFG (SEQ ID NO: 37) peptide linker.



Deruxtecan: (SEQ ID NO: 37)

The sequences of the heavy chain and light chain region of UC-961antibody are shown in Example 41.

[00391] ADC-1 was prepared using example 12 and Deruxtecan and UC-961 antibody.



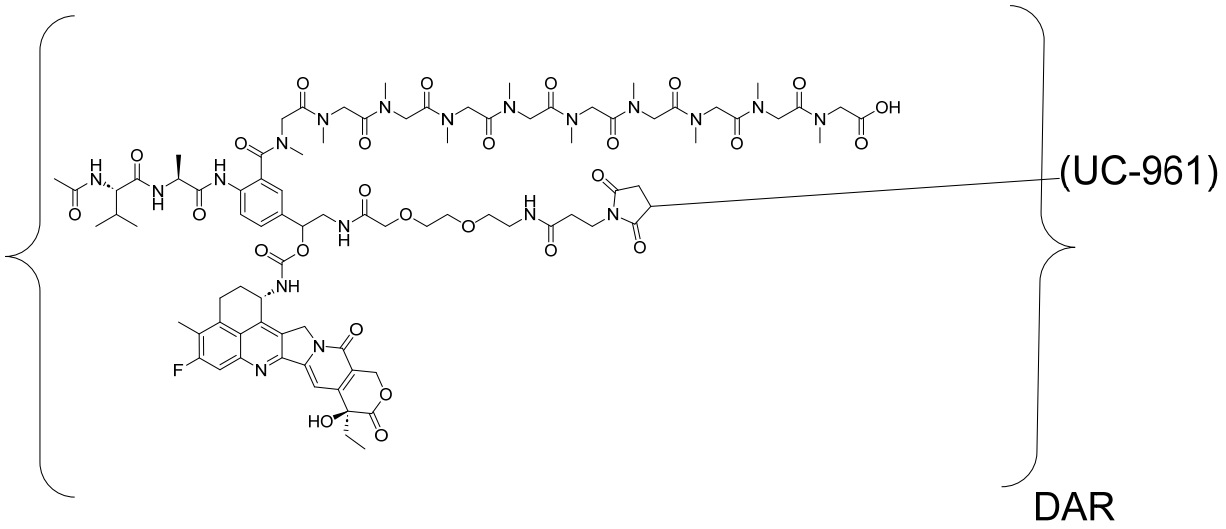
(SEQ ID NO: 37);

wherein the DAR value as determined by RP-HPLC was 7.8. The sequences of the heavy chain and light chain region of UC-961 antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 21: Preparation of Antibody-drug conjugate ADC-9 using Drug-Linker 78 and UC-961 Antibody

[00392] ADC-9 was prepared using example 12 and the Drug-Linker **78** and UC-961 antibody.

ADC-9

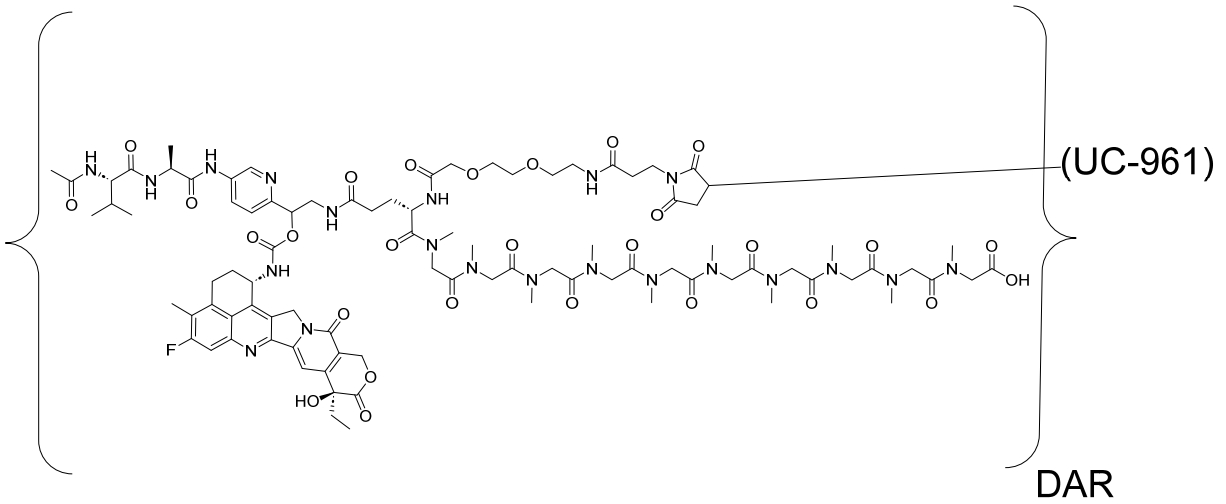


(SEQ ID NO: 29); wherein the DAR value as determined by RP-HPLC was 8. The sequences of the heavy chain and light chain region of UC-961 antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 22: Preparation of Antibody-drug conjugate ADC-10 using Drug-Linker 95 and UC-961 Antibody

[00393] ADC-10 was prepared using example 12 and the Drug-Linker **95** and UC-961 antibody.

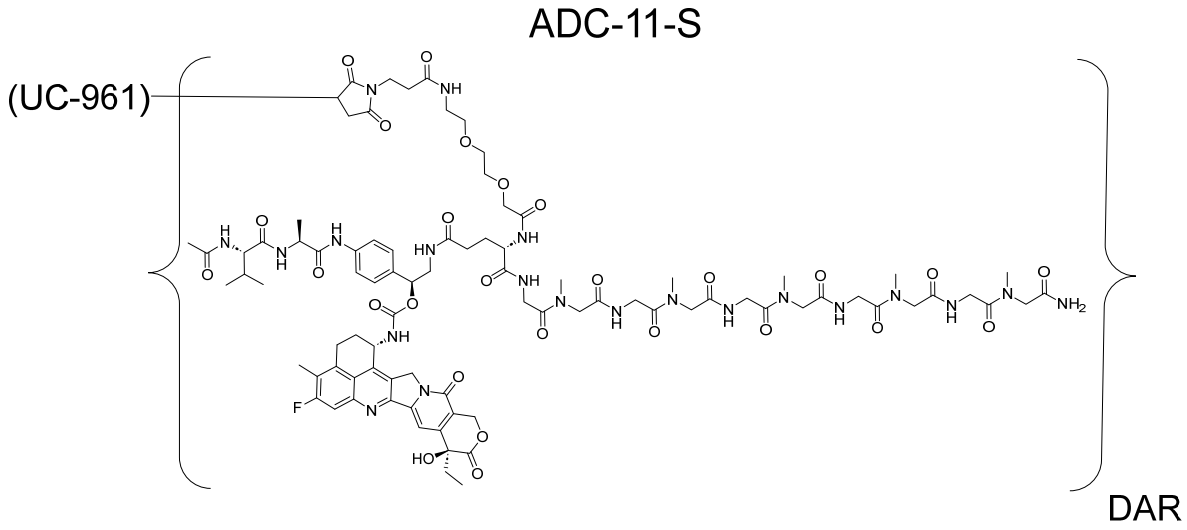
ADC-10



(SEQ ID NO: 25); wherein the DAR value as determined by RP-HPLC was 7.9. The sequences of the heavy chain and light chain region of UC-961antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 23: Preparation of ADC-11-S using Drug-Linker 107-S and UC-961 Antibody

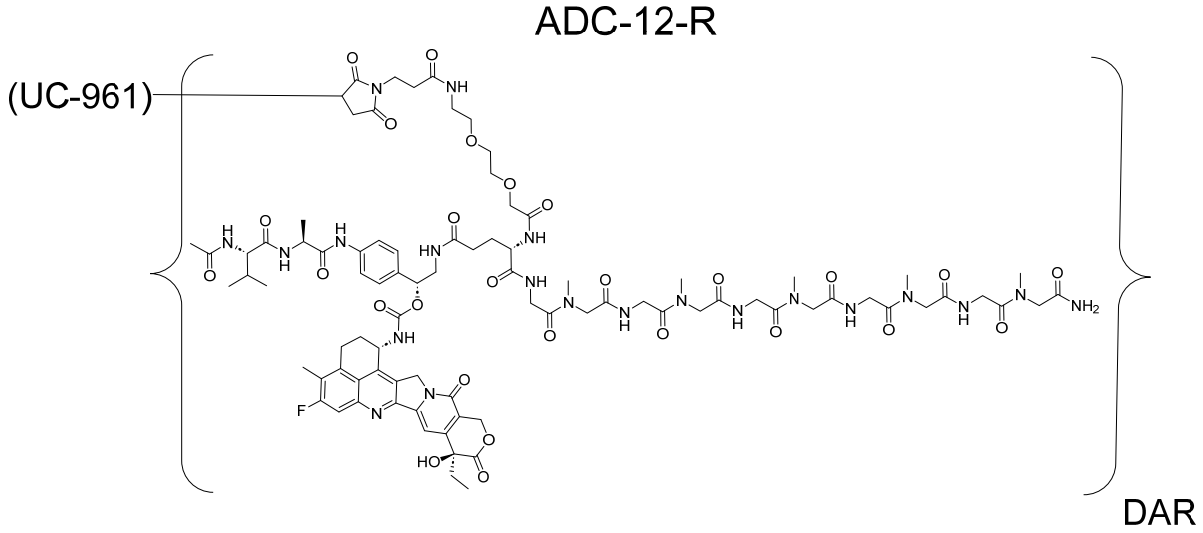
[00394] ADC-11-S was prepared using example 12 and the Drug-Linker **107-S** and UC-961 antibody.



(SEQ ID NO: 26); wherein the DAR value as determined by RP-HPLC was 8.0. The sequences of the heavy chain and light chain region of UC-961antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 24: Preparation of ADC-12-R using Drug-Linker 118-R and UC-961 Antibody

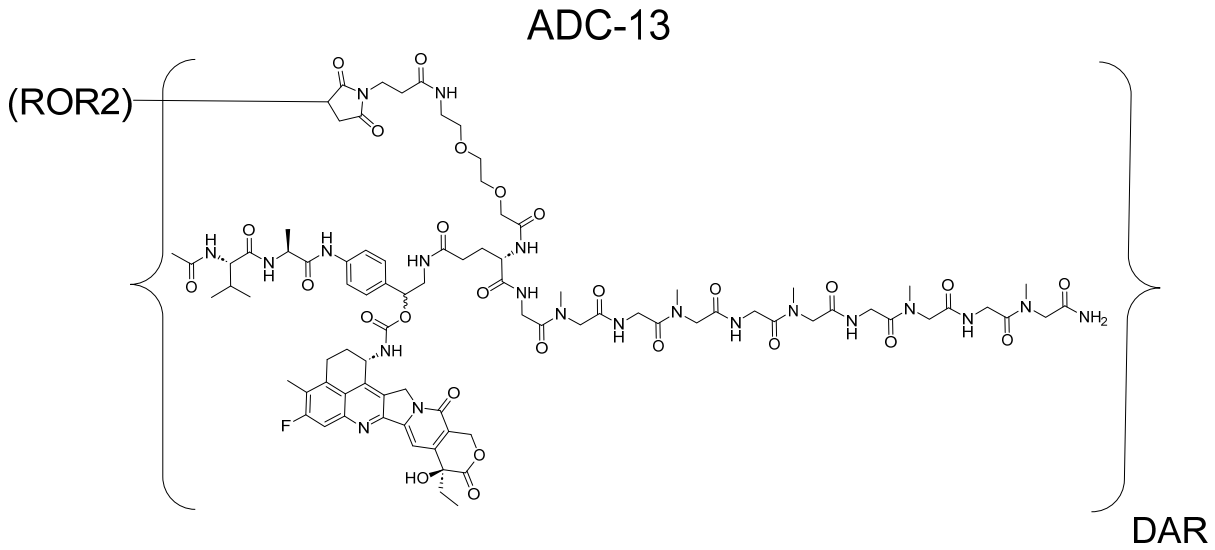
[00395] ADC-12-R was prepared using example 12 and the Drug-Linker 1**18-R** and UC-961 antibody.



(SEQ ID NO: 26); wherein the DAR value as determined by RP-HPLC was 8.0. The heavy chain and light chain region of UC-961 antibody are shown in Example 41 (e.g., SEQ ID NO:1 and SEQ ID NO:2, respectively).

Example 25: Preparation of ADC-13 using Drug-Linker 37 and ROR2 Antibody

[00396] ADC-13 was prepared using example 12 and the Drug-Linker **37** and ROR2 antibody.

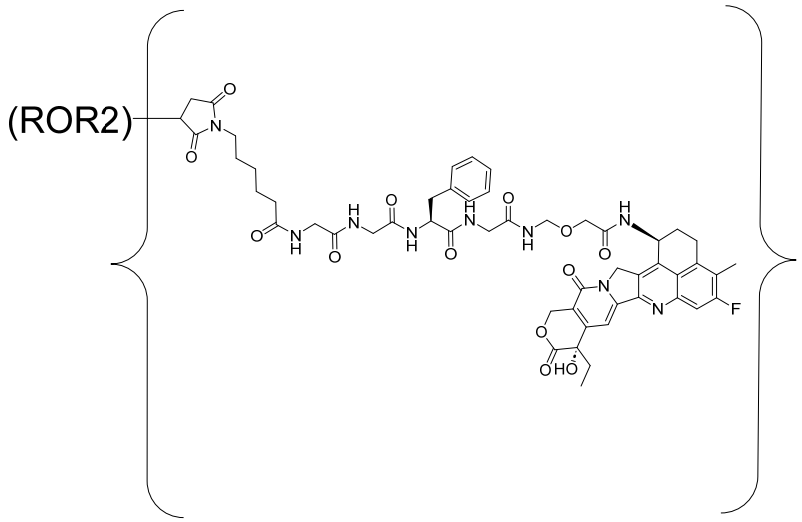


(SEQ ID NO: 26); wherein the DAR value as determined by RP-HPLC was 8 as in example 31. The sequences of the heavy chain and light chain region of ROR2 antibody are shown in Example 42 (e.g., SEQ ID NO:3 and SEQ ID NO:4, respectively).

Example 26: Preparation of ADC-14 using Deruxtecan and ROR2 Antibody

[00397] ADC-14 was prepared using example 12 and Deruxtecan and ROR2 antibody.

ADC-14



(SEQ ID NO: 37);

wherein the DAR value as determined by RP-HPLC was 8. The sequences of the heavy chain and light chain region of ROR2 antibody are shown in Example 42 (e.g., SEQ ID NO:3 and SEQ ID NO:4, respectively).

Characterization of Conjugates

Example 27: Plasma stability

[00398] The plasma stability tests illustrate the stability of the various ADCs in mouse and human plasma. ADCs 1-6, 9 and 10 were tested in both mouse and human plasma.

[00399] ADCs were incubated in IgG depleted plasma at a concentration of 50 µg / mL in a volume of 300 µL. IgG depletion had been performed using a HiTrap Protein G Column (Cytiva). The samples were incubated at 37 °C in Eppendorf tubes for periods of 0, 1, 3, 7 and 15 days. After the appropriate time incubation, samples were transferred to a -80 °C freezer until they could be processed. Samples were incubated in each timepoint in duplicate.

[00400] To separate the ADCs from the plasma, 100 µL of each sample were mixed with 100 µL Protein A magnetic bead slurry (Thermo Pierce) and 900 µL of Sodium Phosphate (50 mM, pH7) with shaking for two hours at room temperature. The ADC should then bind to the beads allowing the excess plasma to be discarded. The beads were then washed to remove nonspecific binding with 1mL of 0.1% Triton, 0.1% IPA, and then twice in 1mL PBS for 30 minutes each with shaking. The ADC was then eluted from the beads in 100 µL of a low pH, high organic mix (40mM Glycine, 2% Formic Acid 50% Acetonitrile) for 60 minutes. The bead slurry was then centrifuged and 50 µL supernatant was injected onto the LC-MS.

[00401] The LC used a 50 mm x 2.1 bioZen XB-C8 column over a seven-minute gradient of H_2O and Acetonitrile each with 0.1% formic acid. The MS was operated in intact protein mode with a source temperature of 500 °C, delustering potential of 200 V, and a mass range of 900-4500 m/z.

[00402] Processing was performed in Sciex OS allowing the addition of up to four payload-linkers per protein. Stability results were shown in **FIG. 1** and **FIG. 11,** for mouse plasma and **FIG. 2** and **FIG. 12**, for human plasma.

[00403] As shown in **FIG. 1** and **FIG. 11**, the stability of the ADC-1, ADC-2, ADC-3, ADC-4, ADC-5, ADC-6, ADC-9 and ADC-10 in mouse plasma were obtained. Additionally, as shown in **FIG. 2** and **FIG. 12**, the stability of ADC-1, ADC-2, ADC-3, ADC-4, ADC-5, ADC-6, ADC-9 and ADC-10 in human plasma were obtained.

Example 28: Cellular Binding

[00404] The ability of an anti-UC-961 conjugate to bind to Jeko-1 cells and LCLC-103H cells was measured using in vitro cellular binding assay.

[00405] For each Jeko-1 cell line, 0.5 million cells were plated in 50 µL on each well of a 96-well deep-well plate (Thermo Scientific #249946). A 1:3 dilution series of primary antibody was made starting with 1-µg/mL starting stock. Thereafter, 50 µL of different concentrations of primary antibody (from 17 pg/mL to 1000 ng/mL final concentration) were placed over the 50 µL containing the cells. Cells and antibodies were mixed and incubated on ice for 20 minutes. For the first wash, 300 µL of FACS buffer was added and cells were centrifuged at 500 × g for 5 minutes at 4 ºC. The supernatant was discarded, and cells were resuspended in 400 µL of FACS buffer for an additional wash. After the second wash, cells were resuspended in 100 µL of goat anti-human IgG secondary phycoerythrin (PE) antibodies (ThermoFisher Scientific #12-4998-82) at 1 µg/mL final concentration and incubated on ice (in the dark) for 20 minutes. Cells were washed twice as described previously and analyzed on the BD FACSVerse with Flowjo software, Version 10. The percentage of maximal binding relative to the highest concentration was graphed and half-maximal effective concentrations (EC_{50}) values were determined using GraphPad Prism Version 7 and shown in **Table 1** and binding percentage of each ADC plotted in **FIG. 3** and **FIG. 13**. **FIG. 4** and **FIG. 14** show the mean fluorescence intensity of each ADC.

Table 1.

Ab/ADC #	UC-961	ADC-1	ADC-2	ADC-3	ADC-4	ADC-5	ADC-6	ADC-9	ADC-10

EC50 (nM)	54	61	83	132	115	180	102	9	10

[00406] For each LCLC-103H cell line, 0.5 million cells were plated in 50 µL on each well of a 96-well deep-well plate (Thermo Scientific #249946). A 1:3 dilution series of primary antibody was made starting with 1-µg/mL starting stock. Thereafter, 50 µL of different concentrations of primary antibody (from 17 pg/mL to 1000 ng/mL final concentration) were placed over the 50 µL containing the cells. Cells and antibodies were mixed and incubated on ice for 20 minutes. For the first wash, 300 µL of FACS buffer was added and cells were centrifuged at 500 × g for 5 minutes at 4 ºC. The supernatant was discarded, and cells were resuspended in 400 µL of FACS buffer for an additional wash. After the second wash, cells were resuspended in 100 µL of goat anti-human IgG secondary phycoerythrin (PE) antibodies (ThermoFisher Scientific #12-4998-82) at 1 µg/mL final concentration and incubated on ice (in the dark) for 20 minutes. Cells were washed twice as described previously and analyzed on the BD FACSVerse with Flowjo software, Version 10. The percentage of maximal binding relative to the highest concentration was graphed and half-maximal effective concentrations (EC_{50}) values were determined using GraphPad Prism Version 7 and are shown in **FIG. 20** and **FIG. 21**. The binding percentage of each ADC are plotted in **FIG. 20** and **FIG. 21** show the median fluorescence intensity of each ADC.

Example 29: Cytotoxicity measurement

[00407] The ability of an anti-UC-961 conjugate to inhibit cell growth was measured using in vitro cytotoxicity assay.

[00408] Jeko-1 cells were cultured in log phase growth and split into 96-well plates. Each cell-line was plated at a slightly different concentration but ranged from $5x10^3$ to $50x10^4$ cells/well. Cells, in duplicate, were incubated with 3-fold serial dilution of a particular immunoconjugate starting at 3000 or 1000 nanomolar (3000, 1000, 333, 111, 37, 12.3, 4.1, 1.37, 0.46, 0.15 nanomolar) for 72 hours at 37° C and 5% CO_2. After treatment the cells were incubated with an equal volume of CellTiter-Glo® reagent (Promega Inc.) for 15 minutes at room temperature, and viability was determined by a luminometer. EC50 values were shown in **Table 2** and percentage of inhibition plotted in **FIG. 5** and **FIG. 15**. Another experiment was conducted for ADC-6, ADC-12-R, and ADC11-S. EC50 values were 134.4, 120.9, and 129.5, for ADC-6, ADC-12-R, and ADC-11-S respectively. The percentage of inhibition plotted in **FIG. 23**.

Table 2.

Ab/ADC #	UC-961	ADC-1	ADC-2	ADC-3	ADC-4	ADC-5	ADC-6	ADC-9	ADC-10
EC50 (nM)	N/A	160	76	81	88	93	90	221	88

[00409] LCLC-103H cells were cultured in log phase growth and split into 96-well plates. Each cell-line was plated at a slightly different concentration but ranged from $5x10^3$ to $50x10^4$ cells/well. Cells, in duplicate, were incubated with 3-fold serial dilution of a particular immunoconjugate starting at 3000 or 1000 nanomolar (3000, 1000, 333, 111, 37, 12.3, 4.1, 1.37, 0.46, 0.15 nanomolar) for 72 hours at 37° C and 5% CO_2. After treatment the cells were incubated with an equal volume of CellTiter-Glo® reagent (Promega Inc.) for 15 minutes at room temperature, and viability was determined by a luminometer. EC50 values were 331.5, 314.7, and 320.2, for ADC-6, ADC-12-R, and ADC-11-S respectively, and percentage of inhibition plotted in **FIG. 24**.

Example 30: Internalization

[00410] MDA-MB-468 cells were harvested, washed with cold PBS and resuspended at a concentration of 1×10^7 cells/mL in cold FACS buffer comprising PBS and 2% FBS. Aliquots of 1×10^6 cells were added to microcentrifuge tubes or wells. Primary antibody was diluted to create 10× stock solutions of 300 µg/mL or 1 mg/mL to allow addition of 10 µl of each solution to the appropriate tubes.

[00411] Control groups comprised of unstained and secondary antibody only (goat anti-human IgG-PE, Fc-gamma specific) (ThermoFisher Scientific #12-4998-82). Test groups comprised cells subjected to the following conditions with evaluation at 30 µg/mL (203 nM) or 100 µg/mL (676 nM) of primary antibody depending upon the experiment: Cells were kept on ice for 20 minutes in addition to controls centrifuged at 300 × g for 4 minutes, washed twice with 200 µl FACS buffer, resuspended in 100 µl of FACS buffer, and incubated at 37°C for 30, 60, 120, or 240 minutes. After incubation, cells were centrifuged at 250 × g and washed twice with FACS buffer and resuspended in 100 µl of FACS buffer. A 10× stock of the secondary antibody was diluted 1:2000 in FACS buffer and 10 µl per tube was added to the appropriate tubes. Cells were incubated on ice for 20 minutes, washed twice with FACS buffer and resuspended in 100 µl of fixation buffer (4% paraformaldehyde in PBS). FACS analysis was then performed, assessing median fluorescence intensity (MFI). The relative magnitude of primary antibody internalization was determined by comparing MFI values for each timepoint with that for the primary antibody control at Time 0 are shown in **FIG. 6** and **FIG. 16**.

Antibody internalization assay (no wash, quench method using PCR machine):

[00412] Materials: Cells: LCLC-103H; FACS staining buffer—2% FBS in RPMI; Wash buffer—2% FBS in 1XPBS + 2mM EDTA; Secondary antibody: Goat anti-human FcyfabAF488 (Jackson ImmunoResearch #109-547-008); Quench antibody: Rabbit anti-AlexaFluor 488 polyclonal Ab (ThermoFisher #710369); (15µg/mL) 2% PFA (paraformaldehyde) in 1XPBS 0.2ml PCR strip tubes; and PCR machine. Method: Count were cells counted, then resuspend to 2X at $2.0X10^6$ cells/ml ($1.0X10^5$ cells/well). On ice, a 50µl mix of 2X primary antibody at a saturating amount and 2X secondary antibody in PCR strip tubes were prepared. For the primary antibody for example 20µg/ml per sample (10µg/ml final). For secondary antibody, use 120µg/ml per sample (60µg/ml final). Then, 50µl of 2X concentration of cells was added, mixed gently, and incubated on ice for 30 min. Strip tubes were transferred to PCR machine with the program for the appropriate time at 37°*C*; starting with the longest incubation time first (3, 2, 1, and 0.5 hrs). The time course tubes were harvest all at once. Then contents were transferred to appropriate well in staining plate. The plate was washed 3X with FACS buffer and spun at 500g for 3min at 4°C. The supernatant was removed by flicking. Following, 100µl of quench antibody (15µg/ml) was added to appropriate wells. After mixing, it incubated in the dark for 30 min on ice. Afterwards it was washed it 200µl of FACS Buffer and the plate spun at 500g for 3min at 4°C, for three times. It was fixed in 100µl of 2% PFA in 1X PBS and then incubated at RT in the dark for 10min. Subsequently, the plate was washed with 200µl of FACS Buffer and spun at 500g for 3 min. Then, resuspend in 150µl of FACS Buffer and analyze by FACS. Note 1: If primary antibody was washed off prior to incubation at 37°C, no need to wash plate prior to addition of quench antibody. Note 2: If primary antibody was not washed off prior to incubation; Wash 3X with cold wash buffer and spin plate at 500g for 3min at 4°C. The relative magnitude of primary antibody internalization was determined by comparing MFI values for each timepoint with that for the primary antibody control at Time 0 are shown in **FIG. 22**.

Example 31: DAR by RP-HPLC

[00413] RP-HPLC of the ADCs was used to determine the drug to antibody ratio (DAR) of each ADC. As shown in the below **Table 4**, reversed phase HPLC was used to obtain the drug to antibody ratio (DAR) of the ADCs.

[00414] RP-HPLC conditions: Column – Phenomenex Kinetex 100 Å, 50 x 4.6 mm, 2.6 µm, Part Number: PL1912-1502. MPA – 0.1% TFA/H20, MPB – 0.1% TFA/CAN

[00415] Method: Flow rate – 1 mL/min, Gradient – see **Table 3**. Column temp. – 50 C.

[00416] Sample temp – RT. DAD 214 nm, BW 16 nm; Reference 440 nm, BW 80 nm; Peak width > 0.4 min (8 s response time (0.62 Hz); Spectrum: 200 – 600 nm, step 1.2 nm, slit 8 nm.

[00417] Sample – neat injection, ~ 5 ug.

Table 3: RP-HPLC Method Flow rate Gradient

Time (min)	B%
0	30
2	30
10	41
11.5	90
15.5	90
16.5	30
20	30

Table 4: DAR of Various ADCs generated from UC961 antibody

ADC	Monomer (%)	DAR
ADC-1	96	7.8
ADC-2	97	8.0
ADC-3	97	8.0
ADC-4	97	8.0
ADC-5	97	8.0
ADC-6	97	8.0
ADC-7	97	1.6
ADC-8	96	8
ADC-9	99	8
ADC-10	99	7.9

Example 32: Hydrophobicity of drug-linkers by RP-HPLC analysis

[00418] As shown in **Table 5**, reversed phase HPLC analysis was used to obtain the relative hydrophobicity of the drug-linkers.

[00419] Column – Phenomenex Kinetex 100 Å, 50 x 4.6 mm, 2.6 µm, Part Number: 00B-4497-E0. MPA – 0.05% TFA/H20, MPB – 0.05% TFA/CAN.

[00420] Method: Flow rate – 2 mL/min. Gradient – see Table 6. Column temp. – 60 C. Sample temp – RT. DAD 214 nm, BW 4 nm + 360 nm, BW 4 nm. Reference 440 nm, BW 40

nm. Peak width > 0.1 min (2 s response time (2.5 Hz). Spectrum: 200 – 400 nm, step 2 nm, slit 2 nm

[00421] Sample – Injection mass, 5 – 100 pmols, dilution of DMA toxin stock in MeOH.

[00422] **Table 6** shows the retention times of the various Drug-Linkers. Drug-Linkers Deruxtecan, 18, 25, 34, 37, 40, 43, 58, 78 and 95 were synthesized as enantiomers hence the two retention time values. Based off the first retention times for each Drug-Linker from the RP-HPLC, the hydrophobicity increases as follows: **18** < **58** < **25** < **37** < **43** < **40** < **78** < **34** < **78** < **Deruxtecan**. The drug-linker **25** shorter sulphate side chain demonstrates that the benefits of increasing the hydrophilicity, which in turn increases the ADC's $T_{1/2}$ life and AUC, and ultimately its in vivo efficacy, is more of an overall ionic effect and less of a physical masking effect of a larger side chain.

Table 5: RP-HPLC Method Flow rate Gradient

Time (min)	**B%**
0	5
8	95
8.1	100
9	100
9.1	5
10	5

Table 6: Retention Times of Drug-Linkers using RP-HPLC

Drug-Linker	Deruxtecan (DxD-GGFG (SEQ ID NO: 37))	**25**	**18**	**34**	**40**	**43**	**37**	**58**	**78**	**95**
RT1	3.774	3.064	3.036	3.227	3.191	3.184	3.068	3.049	3.262	3.225
RT2	N/A	3.177	3.156	3.329	3.293	3.274	3.177	3.168	3.375	3.254

Example 33: Payload release

[00423] Conjugates were incubated with papain or β-glucuronidase buffer overnight and monitored for the release of exatecan. A stock of papain at 10mg/ml in 1.1mM EDTA, 0.067 mM DTT and 5.5 mM Cysteine was prepared. 50 µg of ADC (10 µl) and 1 µl of papain stock so the final concentration was 1 mg/ml, incubated at 37 °C for 4 hours before analysis. As shown in **FIG. 7** and **FIG. 17**, XIC for all samples show a strong signal for release of payload. All six ADCs present a peak at 436.16 (matching a MSMS fragment assigned to exatecan).

Example 34: In Vivo efficacy

[00424] The antitumor activity of ADCs was evaluated in the xenograft models of Jeko-1 mantle cell lymphoma, H1975 non-small cell lung tumors, LCLC-103H large-cell lung-cancer tumors, CTG-2215 triple-negative breast cancer (TNBC), and NCI-H526 small-cell lung-cancer (SCLC). The tumor bearing mice were randomized based on their individual tumor and given iv injection dose. As shown in **FIG. 8**, at 5 mg/Kg single iv injection dose, ADCs were shown to have antitumor activity in Jeko-1 model. Whereas in **FIG. 9**, at 10 mg/Kg, once weekly iv injection dose for 3 weeks (days 1, 8, 15), ADCs were shown to have antitumor activity in H1975 model. Whereas in **FIG. 25**, at 10 mg/Kg, once weekly iv injection dose for 3 weeks (days 1, 8, 15), ADCs were shown to have antitumor activity in LCLC-103H model. Whereas, in **FIG. 26**, at 5mg/Kg or 10 mg/Kg, once weekly iv injection dose for 4 weeks (days 1, 8, 15, 22), ADC was shown to have antitumor activity in CTG-2215 model. Whereas, in **FIG. 27**, at 10 mg/Kg, once weekly iv injection dose for 3 weeks (days 1, 8, 15). ADC was shown to have antitumor activity in NCI-H526 model. Whereas, in **FIG. 28**, shows dose titration at 2.5 mg/kg, 5 mg/Kg, or 10 mg/Kg, once weekly iv injection dose for 2 weeks (days 1, 8) for select ADC in LCLC-103H model.

Example 35: Pharmacokinetics Preparation

[00425] **a-HuROR1 ELISA ("Total ADC") Procedure:** wells of a 96-well plate were coated with biotin-ROR1 antigen (Biotinylated Human / Cynomolgus / Rhesus macaque ROR1 Protein, Avitag™; 200 ug/ml, AcroBiosystem) at 0.2 μg/well/25 ul and place overnight at 4 ℃. The wells were then washed with 100 μl/ well Washing Buffer for 4 times and blocked with 5%MILK + PBS for 90 min at 37 ℃. A standard curve of ADC-Dxd and/or ADC-Exatecan (25 ul/well) were added as well as the diluted mouse plasma PK samples. The plate was incubated at 37 ℃ for 60 min and subsequently washed. 25 ul/well of Goat anti-Human Kappa- HRP (Sothernbiotech, cat#2061-05, Lot# i1519-YD22B) at 1: 5,000 - 1: 20,000 dilution was added, and the plate was incubated for 60 min at 37 ℃. The plate was then washed and developed in TMB/Stop solution and read on the Spectramax at 450 OD.

[00426] **a-Dxd ELISA ("Free Payload") Procedures:** 0.2 μg/well/25 ul of biotin-ROR1 for antigen coating o/n 4 ℃. (Biotinylated Human / Cynomolgus / Rhesus macaque ROR1 Protein, Avitag™; 200 ug/ml, AcroBiosystem). Wash with 100 µl per well Washing Buffer for 4 times. Block with 5%MILK+PBS 90 min 37 ℃. Add 25 ul of ADC-Dxd and/or ADC-Exatecan as standards and mouse plasma samples. Incubate 60 min 37 ℃. Washing was performed. Add

anti-Dxd (0.025 ug/25 ul/well; AcroBiosystems, cat# DXD-S222) 60 min 37. Washing was then performed. Goat a-Mouse-Kappa-HRP was added @ 1: 5K - 1: 20. (Bethyl Lab, 1 mg/ml, Lot#33, Cat#A90-119P). Washing was then performed. Develop in TMB/Stop Soln and was read @ OD 450. "Free Payload" = anti-HuROR1 ELISA Values ("Total" ADC) – anti-Dxd ELISA Values (ADCs containing Payloads).

Example 36: Calculation of Pharmacokinetic Parameters

[00427] Pharmacokinetic analyses were performed on plasma concentration-versus-time data for all analytes using Phoenix WinNonlin (v 7.0) non-compartmental analysis function (linear trapezoidal rule for AUC calculations). Nominal dose values and sampling times were used for calculations. For the purpose of PK calculations, any concentration reported as "BLQ" was set equal to zero. As the data permitted, the terminal rate constant (lambda z, λz) for each of the analytes was determined. The value of λz was calculated by the slope of the regression line of the natural log transformed concentrations vs. time with the following constraints: Data points were randomly distributed around a single straight line; At least three data points post the Cmax were used in the regression; The correlation coefficient (R2) of regression was >0.90; The period over which the regression is determined was at least 2-fold greater than the calculated half-life itself.

[00428] To optimize the reliability of the identified terminal phase (λz), the data points used to define the λz were manually selected. When lambda z profiles did not meet the guidelines stated above, the AUCINF, t1/2, CL, or Vz parameters for that animal profile were not reported. When possible, AUCINF was calculated as: AUClast + (Clast / λz). CL was calculated as: Dose / (AUCINF) and Vz was calculated as: Dose / (AUCINF * λz). Terminal half-life (t1/2) was calculated as: ln(2) / λz. Mean plasma concentration-versus-time data are presented as mean only (N=2) and are reported to 3 significant figures. PK parameter values are presented as mean only (N=2). Individual Tmax (where applicable) and t1/2 values are reported to 2 significant figures, while all other values are reported to 3 significant figures. Pharmacokinetic data was presented in **FIG. 10** and **FIG. 18**.

Example 40: Determination of Enantiopurity

[00429] Chiral RP-HPLC was used to determine enantiopurity of select ADCs. **FIG. 19** displays the chromatogram of **Compound 37** (RT = 3.119; and RT = 3.225) and the corresponding, separated diastereomers **Compound 107-S** (RT = 3.116) and **Compound 118-R** (RT = 3.221). Note: The GGFG linker (SEQ ID NO: 37) RT = 3.774 was not observed **FIG. 19**. As shown in the below **Table 7**, reversed phase HPLC was used to obtain the drug to antibody ratio (DAR) of the ADCs

[00430] RP-HPLC conditions: Column – Kinetex C18 Column 100 Å, 50 x 4.6 mm, 2.6 µm, Part Number: PL1912-1502. MPA – 0.1% TFA/H20, MPB – 0.1% TFA/CAN

[00431] Method: Flow rate – 1 mL/min, Gradient – see **Table 3**. Column temp. – 50 C.

[00432] Sample temp – RT. DAD 214 nm, BW 16 nm; Reference 440 nm, BW 80 nm; Peak width > 0.4 min (8 s response time (0.62 Hz); Spectrum: 200 – 600 nm, step 1.2 nm, slit 8 nm.

[00433] Sample – neat injection, ~ 5 ug.

Table 7: DAR of Various ADCs generated from UC961 antibody.

ADC	Monomer (%)	DAR	Yield
ADC-11-S	98	8.0	87
ADC-12-R	98	8.0	84

Example 41: UC-961 Antibody Heavy Chain and Light Chain Sequences

[00434] UC-961 is a humanized IgG1/kappa antibody. UC-961 was expressed transiently in CHO-K1 cells and was purified in a single step using protein A chromatography resin and the final buffer composition was 100 mM Tris-HCl, 85 mM acetate, 10 mM glycine, pH 7.0 (WuXi Biologics). The heavy chain and light chain sequences of the UC-961 antibody are shown below.

[00435] **Heavy Chain (SEQ ID NO:1)**

[00436] QVQLQESGPGLVKPSQTLSLTCTVSGYAFTAYNIHWVRQAPGQGLEWMGSF
DPYDGGSSYNQKFKDRLTISKDTSKNQVVLTMTNMDPVDTATYYCARGWYYFDYWG
HGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP
PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00437] **Light Chain (SEQ ID NO:2)**

[00438] DIVMTQTPLSLPVTPGEPASISCRASKSISKYLAWYQQKPGQAPRLLIYSGSTL
QSGIPPRFSGSGYGTDFTLTINNIESEDAAYYFCQQHDESPYTFGEGTKVEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Example 42: ROR2 Antibody Heavy Chain and Light Chain Sequences

[00439] The ROR2 antibody is a humanized IgG1/kappa antibody. The ROR2 antibody was expressed transiently in CHO-K1 cells and was purified in a single step using protein A

chromatography resin and the final buffer composition was 20 mM histidine, 150 mM sodium chloride, pH 5.5 (WuXi Biologics). The heavy chain and light chain sequences of the ROR2 antibody are shown below.

[00440] Heavy Chain (SEQ ID NO:3)

[00441] EVQLVESGGGLVKPGGSLRLSCAASGFTFSTYGVSWVRQAPGKGLEWVSTIS
SGGGYTHYAGSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARHPRDFSYALDY
WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH
TCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALAAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00442] Light Chain (SEQ ID NO:4)

[00443] EIVMTQSPATLSVSPGERATLSCRASQDVGHYLAWYQQKPGQAPRLLIYWA
STRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNIYPWTFGQGTKVEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD
STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC