ANTIBODY-DRUG CONJUGATES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Application Nos. 63/581,306, filed September 8, 2023, 63/591,078, filed June October 17, 2023, and 63/550,023, filed February 5, 2024, the entirety of each of which is incorporated herein by reference.

BACKGROUND

[0002] Antibody-drug conjugates (ADCs) can provide an effective means of delivering a drug to a targeted site in a tissue or organism. Recognition of a target, such as a tumor, by the antibody minimizes exposure of non-target tissues to toxic chemotherapeutic agents and limits adverse effects associated with the toxicity of "free" drugs (i.e., unbound to a carrier such as an antibody). Therefore, a need exists for the development of new therapeutic modalities, such as ADCs, optimized to deliver a drug to a targeted site in a tissue or organism and minimize adverse effects.

SUMMARY

[0003] Among other things, the present disclosure encompasses the recognition that conjugate designs, e.g., ADC designs, can impact their structures, properties, activities, etc. In some examples, the present disclosure provides conjugates that can provide various benefits and advantages, e.g., improved properties, improved activities, etc. In some examples, provided conjugates have, among other things, improved solubility, reduced aggregation, improved activities, etc. In some examples, provided conjugates comprise moieties (e.g., carbohydrate moieties, PEG moieties, etc.) that can improve solubility and/or reduce aggregation. In some examples, provided conjugates comprise $-(CH_2CH_2O)n-$ as described herein. In some examples, n is 1-24. In some examples, $-(CH_2CH_2O)n-$ is in the chain of bonds from a target binding moiety to a payload moiety (compared to in a side chain off the chain of bonds from a target binding moiety to a payload moiety).

[0004] In some examples, the present disclosure provides conjugates comprising:

i) a target binding moiety;

ii) a payload moiety; and

iii) a linker that connects the target binding moiety and the payload moiety;

wherein:

the linker comprises $-(CH_2CH_2O)n-$ and L^C;

n is 0-24;

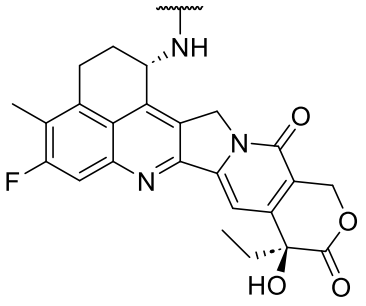
L^C is bonded to a payload moiety and is $-L^{C1}-L^{CO}-$;

L^{C1} is or comprises a cleavable unit; and

L^{CO} is a covalent bond, or a spacer moiety.

[0004a] In an aspect, the present disclosure provides a conjugate, comprising:

i) a target binding moiety targeting HHLA2;

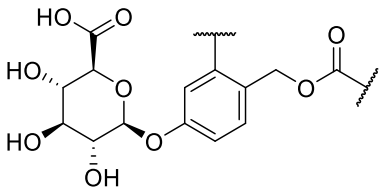
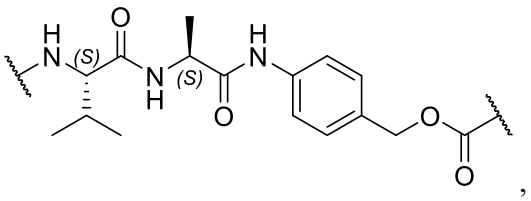
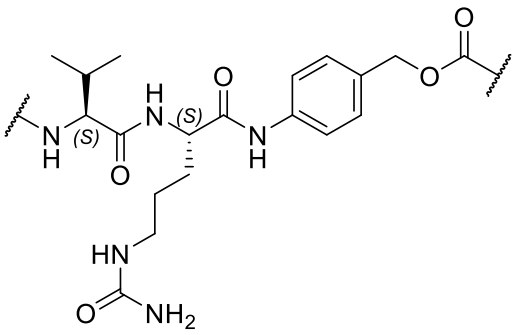
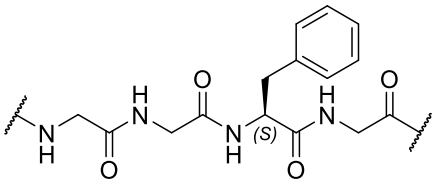
ii) a payload moiety having the structure of  ; and

iii) a linker that connects the target binding moiety and the payload moiety;

wherein:

the linker comprises $–(CH_2CH_2O)n–$ and L^C; wherein

n is 8, or wherein n is 0-24;

L^C is  ,  ,  , or  , wherein the carbonyl is bonded to the payload moiety,

optionally wherein the target binding moiety is an antibody selected from Hu2C4-H3L3, 65872, 65889, or 887-1DE.

[0005] In some examples, the present disclosure provides conjugates comprising:

i) a target binding moiety;

ii) a payload moiety; and

iii) a linker that connects the target binding moiety and the payload moiety;

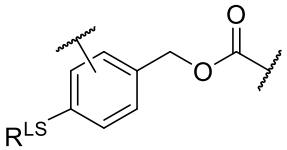
wherein:

the linker comprises −(CH_2CH_2O)n− and L^C;

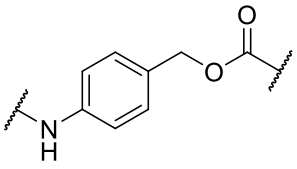
n is 0-24;

L^C is bonded to a payload moiety and is $-L^{C1}-L^{CO}-$;

L^{C1} is −Gly−Gly−Phe−Gly−, −Val−Ala−, −Val–Cit–, L^{C1S}, −Gly−Gly−Phe−Gly−N(R')−L^{C1S}–, −Val−Ala−N(R')−L^{C1S}–, or −Val–Cit–N(R')−L^{C1S}–;

L^{C1S} is 

, wherein the phenyl ring and the −CH_2− is optionally substituted, and the carbonyl is bonded to L^{CO}, and R^{LS} is or comprises a sugar moiety;

L^{CO} is a covalent bond, or optionally substituted 

wherein the carbonyl is bonded to a payload moiety;

each R' is independently −R, −C(O)R, −CO_2R, or −$S(O)_2$R, or two or more R' are taken together with their intervening atom(s) to form an optionally substituted 3-20 membered ring having, in addition to the intervening atom(s), 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

each R is independently hydrogen, or an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur.

[0005a] In another aspect, the present disclosure provides a conjugate, comprising:

i) a target binding moiety;

ii) a payload moiety; and

iii) a linker that connects the target binding moiety and the payload moiety;

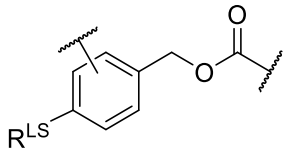
wherein:

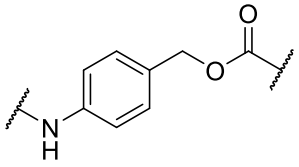
the linker comprises –(CH_2CH_2O)n− and L^C;

n is 0-24;

L^C is bonded to a payload moiety and is $-L^{C1}-L^{CO}-$;

L^{C1} is a cleavable unit; and/or L^{C1} is −Gly−Gly−Phe−Gly−, −Val−Ala−, −Val–Cit–, L^{C1S}, −Gly−Gly−Phe−Gly−N(R')−L^{C1S}–, −Val−Ala−N(R')−L^{C1S}–, or −Val–Cit–N(R')−L^{C1S}–;

L^{C1S} is , wherein the phenyl ring and the $-CH_2-$ is optionally substituted, and the carbonyl is bonded to L^{CO}, and R^{LS} is or comprises a sugar moiety;

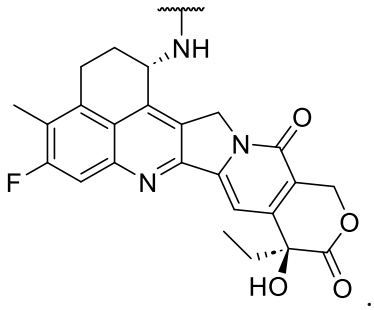
L^{CO} is a covalent bond, or a spacer moiety (e.g., optionally substituted  wherein the carbonyl is bonded to a payload moiety);

each R' is independently $-R$, $-C(O)R$, $-CO_2R$, or $-S(O)_2R$, or two or more R' are taken together with their intervening atom(s) to form an optionally substituted 3-20 membered ring having, in addition to the intervening atom(s), 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

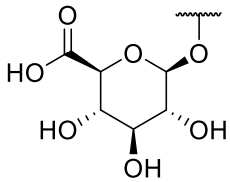
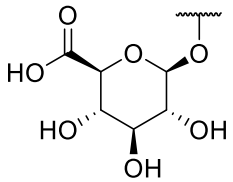
each R is independently hydrogen, or an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, optionally wherein:

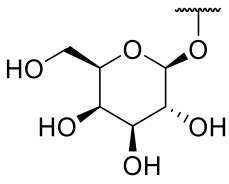
(a) the target binding moiety comprises an antibody or an antigen-binding fragment thereof; and/or

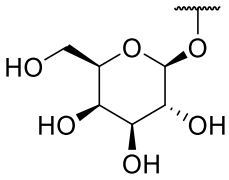
(b) the payload moiety is

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[0006] In some examples, R^{LS} is or comprises a sugar moiety so that L^C is cleavable, e.g., by an enzyme. In some examples, R^{LS} is or comprises a glucuronide moiety. In some examples, L^C can be cleaved by a β-glucuronidase. In some examples, R^{LS} is or comprises a galactoside moiety. In some examples, L^C can be cleaved by a β-galactosidase. In some examples, R^{LS} is or comprises

 or a derivative thereof. In some examples, R^{LS} is . In some

examples, R^{LS} is or comprises  or a derivative thereof. In some examples, R^{LS}



is . In some examples, L^{C1} is L^{C1S} as described herein. In some examples, L^{CO} is a covalent bond. In some examples, L^{C} is L^{C1} as described herein. In some examples, L^{C} is L^{C1S} as described herein. In some examples, the phenyl ring the $-CH_2-$ in L^{C1S} is unsubstituted.

[0007] In some examples, n is 1-24.

[0008] In some examples, the present disclosure provides a conjugate, wherein the conjugate is a compound of formula A-1 or a salt thereof:

$$\left[R^{A}\right]_{s}\left[\left[-L^{T}-L^{RX}\right]_{a}L^{X'}\left[(CH_2CH_2O)_n-L^{ZP}-L^{C}-R^{P}\right]_{b}\right]_{t},$$

A-1

wherein:

each R^A is independently a target binding moiety;

s is 1-20;

each L^T is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^T are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

each L^{RX} is independently a covalent bond, a moiety that results from a reaction between a group present on the unconjugated target binding moiety and a group present on an agent comprising $L^{X'}$, or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

each of a and b is independently 1-10;

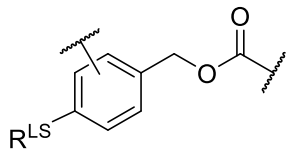
each $L^{X'}$ is independently a covalent bond or an optionally substituted bivalent or polyvalent straight or branched C_{1-30} aliphatic wherein 1-10 methylene units of $L^{X'}$ are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

each n is independently 0-24;

each L^{ZP} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

each L^C is independently $-L^{C1}-L^{CO}-$;

each L^{C1} is independently a cleavable unit, or each L^{C1} is independently −Gly−Gly−Phe−Gly−, −Val−Ala−, −Val–Cit–, L^{C1S}, −Gly−Gly−Phe−Gly−N(R')−L^{C1S}–, −Val−Ala−N(R')−L^{C1S}–, or −Val–Cit–N(R')−L^{C1S}–;

L^{C1S} is , wherein the phenyl ring and the $-CH_2-$ is optionally substituted, and the carbonyl is bonded to L^{CO}, and R^{LS} is or comprises a sugar moiety;

each L^{CO} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{CO} are optionally and independently replaced by a group selected from $-O-$, $-N(R')-$, $-C(O)-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)N(R')-$, $-S(O)_2(NR')-$, and $-Cy-$;

each R^P is independently a payload moiety;

t is 1-20;

each –Cy– is independently an optionally substituted bivalent 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

each R' is independently $-R$, $-C(O)R$, $-CO_2R$, or $-S(O)_2R$, or two or more R' are taken together with their intervening atom(s) to form an optionally substituted 3-20 membered ring having, in addition to the intervening atom(s), 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

each R is independently hydrogen, or an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur.

[0008a] In another aspect, the present disclosure provides a conjugate, wherein the conjugate is a compound of formula A-1 or a salt thereof:

$$\left[R^A\right]_s\left[\left[-L^T-L^{RX}\right]_a L^{X'}\left[(CH_2CH_2O)_n-L^{ZP}-L^C-R^P\right]_b\right]_t,$$

A-1

wherein:

each R^A is independently a target binding moiety;

s is 1-20;

each L^T is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^T are optionally and independently replaced by a group selected from $-O-$, $-N(R')-$, $-C(O)-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)N(R')-$, $-S(O)_2(NR')-$, and $-Cy-$;

each L^{RX} is independently a covalent bond, a moiety that results from a reaction between a group present on the unconjugated target binding moiety and a group present on an agent comprising $L^{X'}$, or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from $-O-$, $-N(R')-$, $-C(O)-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)N(R')-$, $-S(O)_2(NR')-$, and $-Cy-$; or each L^{RX} is independently a covalent bond or an

optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each of a and b is independently 1-10;

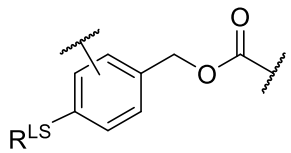
each $L^{X'}$ is independently a covalent bond or an optionally substituted bivalent or polyvalent straight or branched C_{1-30} aliphatic wherein 1-10 methylene units of $L^{X'}$ are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each n is independently 0-24;

each L^{ZP} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each L^{C} is independently −L^{C1}–L^{CO}–;

each L^{C1} is independently a cleavable unit, or each L^{C1} is independently −Gly−Gly−Phe−Gly−, −Val−Ala−, −Val–Cit–, L^{C1S}, −Gly−Gly−Phe−Gly−N(R')−L^{C1S}–, −Val−Ala−N(R')−L^{C1S}–, or −Val–Cit–N(R')−L^{C1S}–;

L^{C1S} is 

, wherein the phenyl ring and the −CH_2− is optionally substituted, and the carbonyl is bonded to L^{CO}, and R^{LS} is or comprises a sugar moiety;

each L^{CO} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{CO} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each R^{P} is independently a payload moiety;

t is 1-20;

each –Cy– is independently an optionally substituted bivalent 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

each R' is independently −R, −C(O)R, −CO_2R, or −$S(O)_2$R, or two or more R' are taken together with their intervening atom(s) to form an optionally substituted 3-20 membered ring having, in addition to the intervening atom(s), 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

each R is independently hydrogen, or an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur,

optionally wherein:

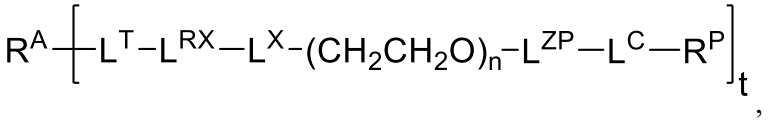
(a) s is 1;

(b) an occurrence of a is 2-10; and/or

(c) an occurrence of b is 2-10.

[0009] In some examples, a is 1 and b is 1.

[0010] In some examples, the present disclosure provides a conjugate (e.g., a conjugate of formula A-1), wherein the conjugate is a compound of formula A-2 or a salt thereof:



A-2

wherein:

R^A is a target binding moiety;

each L^T is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^T are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each L^{RX} is independently a covalent bond, a moiety that results from a reaction between a group present on the unconjugated target binding moiety and a group present on an agent comprising −L^X–(CH_2CH_2O)n−L^{ZP}–L^C–R^P, or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

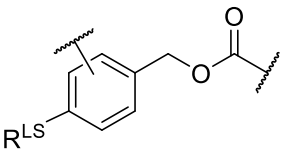
each L^X is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^X are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each n is independently 0-24;

each L^{ZP} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each L^C is independently $-L^{C1}-L^{CO}-$;

each L^{C1} is independently a cleavable unit, or each L^{C1} is independently −Gly−Gly−Phe−Gly−, −Val−Ala−, −Val–Cit–, L^{C1S}, −Gly−Gly−Phe−Gly−N(R')−L^{C1S}–, −Val−Ala−N(R')−L^{C1S}–, or −Val–Cit–N(R')−L^{C1S}–;

L^{C1S} is , wherein the phenyl ring and the −CH_2− is optionally substituted, and the carbonyl is bonded to L^{CO}, and R^{LS} is or comprises a sugar moiety;

each L^{CO} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{CO} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each R^P is independently a payload moiety;

t is 1-20;

each –Cy– is independently an optionally substituted bivalent 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

each R' is independently −R, −C(O)R, −CO_2R, or −$S(O)_2$R, or two or more R' are taken together with their intervening atom(s) to form an optionally substituted 3-20 membered ring having, in addition to the intervening atom(s), 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

each R is independently hydrogen, or an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur.

[0010a] In another aspect, the present disclosure provides a conjugate, wherein the conjugate is a compound of formula A-2 or a salt thereof:

$$R^A\left[-L^T-L^{RX}-L^X-(CH_2CH_2O)_n-L^{ZP}-L^C-R^P\right]_t,$$

A-2

wherein:

R^A is a target binding moiety;

each L^T is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^T are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each L^{RX} is independently a covalent bond, a moiety that results from a reaction between a group present on the unconjugated target binding moiety and a group present on an agent comprising $-L^X-(CH_2CH_2O)n-L^{ZP}-L^C-R^P$, or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each L^X is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^X are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each n is independently 0-24;

each L^{ZP} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each L^C is independently $-L^{C1}-L^{CO}-$;

each L^{C1} is independently a cleavable unit;

each L^{CO} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{CO} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each R^P is independently a payload moiety;

t is 1-20;

each –Cy– is independently an optionally substituted bivalent 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

each R' is independently −R, −C(O)R, $-CO_2R$, or $-S(O)_2R$, or two or more R' are taken together with their intervening atom(s) to form an optionally substituted 3-20 membered ring having, in addition to the intervening atom(s), 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

each R is independently hydrogen, or an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur,

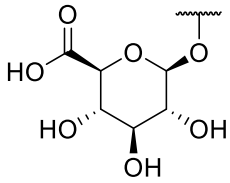
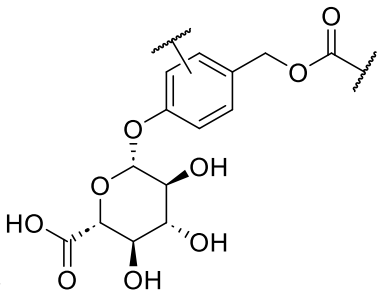
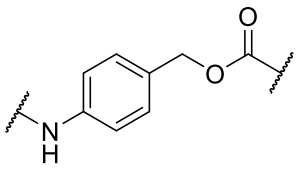
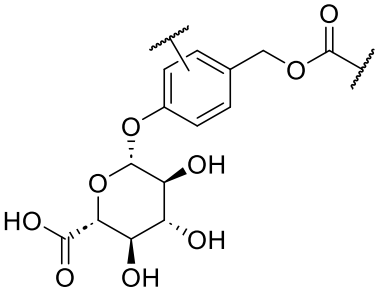
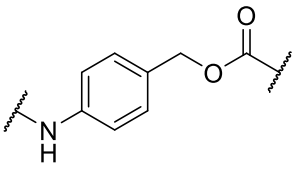
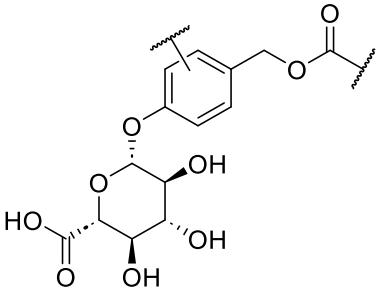
optionally

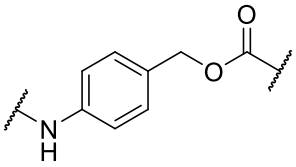
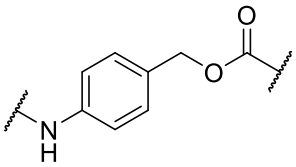
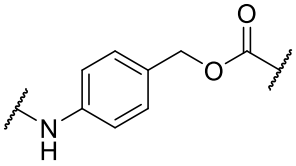
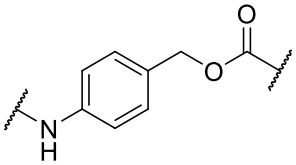
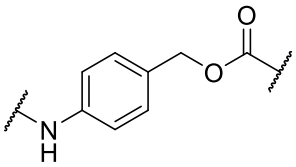
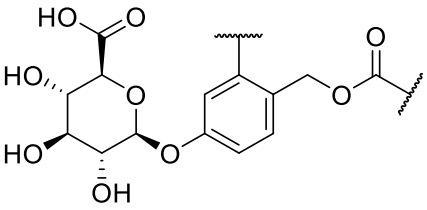
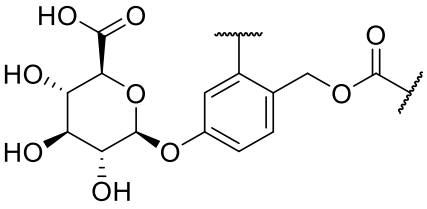
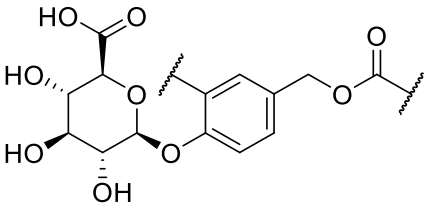
wherein:

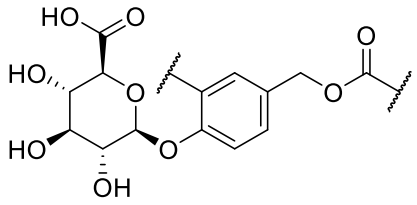
(a) R^A is or comprises an antibody or an antigen-binding fragment thereof; and/or

(b) an occurrence of L^X is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^X are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−.

[0011] In some examples, each L^{C1} is independently a cleavable unit. In some examples, each L^{C1} is independently −Gly−Gly−Phe−Gly−, −Val−Ala−, −Val–Cit–, L^{C1S}, −Gly−Gly−Phe−Gly−N(R')−L^{C1S}–, −Val−Ala−N(R')−L^{C1S}–, or −Val–Cit–N(R')−L^{C1S}–, wherein each variable is independently as described herein. In some examples, each L^{C1} is independently −Gly−Gly−Phe−Gly−, −Val−Ala−, −Val–Cit–, or L^{C1S}. In some examples, each L^{C1} is independently −Val−Ala−, −Val–Cit–, or L^{C1S}. In some examples, each L^{C1} is independently −Val−Ala−, −Val–Cit–, or L^{C1S}, wherein R^{LS} is or comprises a glucuronide moiety. In some examples, each L^{C1} is

independently −Val−Ala−, −Val–Cit–, or L^{C1S}, wherein R^{LS} is . In some examples, each L^{C1} is independently −Gly−Gly−Phe−Gly−, −Val−Ala−, –Val–Cit–, or , and each L^{CO} is independently a covalent bond or optionally substituted  wherein the carbonyl is bonded to a payload moiety. In some examples, at least one occurrence of n is 1-24. In some examples, each occurrence of n is independently 1-24. In some examples, each L^{C1} is independently −Gly−Gly−Phe−Gly−, −Val−Ala−, –Val–Cit–, or , each L^{CO} is independently a covalent bond or optionally substituted  wherein the carbonyl is bonded to a payload moiety, and at least one occurrence of n is independently 1-24. In some examples, each L^{C1} is independently −Gly−Gly−Phe−Gly−, −Val−Ala−, –Val–Cit–, or , each L^{CO} is independently a covalent bond or

optionally substituted  wherein the carbonyl is bonded to a payload moiety, and each occurrence of n is independently 1-24. In some examples, each L^{C1} is independently −Val−Ala−. In some examples, each L^{C1} is independently −Val−Ala− and each L^{CO} is independently optionally substituted . In some examples, each L^{C1} is independently −Val−Ala− and each L^{CO} is . In some examples, each L^{C1} is independently −Val−Cit−. In some examples, each L^{C1} is independently −Val−Cit− and each L^{CO} is independently optionally substituted . In some examples, each L^{C1} is independently −Val−Cit− and each L^{CO} is . In some examples, each L^{C1} is independently . In some examples, each L^{C1} is independently  and each L^{CO} is a covalent bond. In some examples, each L^{C1} is independently . In some examples, each L^{C1} is independently

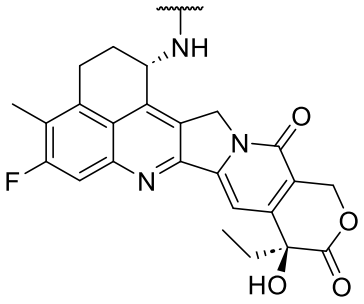


and each L^{CO} is a covalent bond.

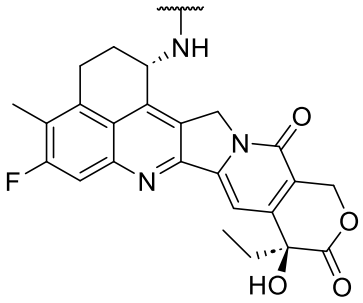
[0012] In some examples, a target binding moiety binds to a polypeptide. In some examples, a target binding moiety binds to HHLA2 or a fragment thereof.

[0013] In some examples, a target binding moiety is or comprises an antibody or an antigen-binding fragment thereof. In some examples, a target binding moiety is or comprises an anti-HHLA2 antibody or an antigen-binding fragment thereof.

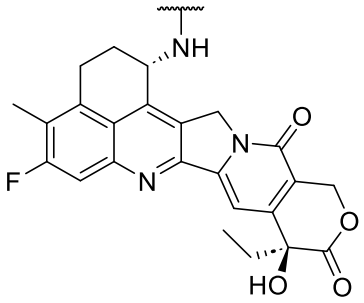
[0014] Those skilled in the art appreciate that various payload moieties, e.g., those reported for antibody-drug conjugates, can be utilized in accordance with the present disclosure. In some examples, a payload moiety is or comprises camptothecin or a derivative or an analog thereof. In some examples, a payload moiety



is or comprises . In some examples, a payload is



. In some examples, each payload is

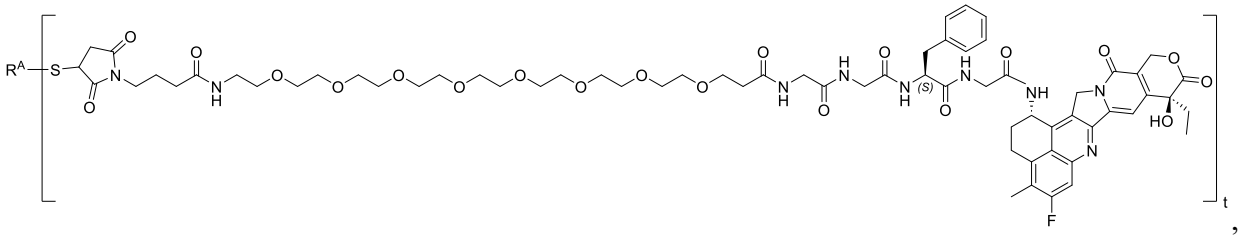


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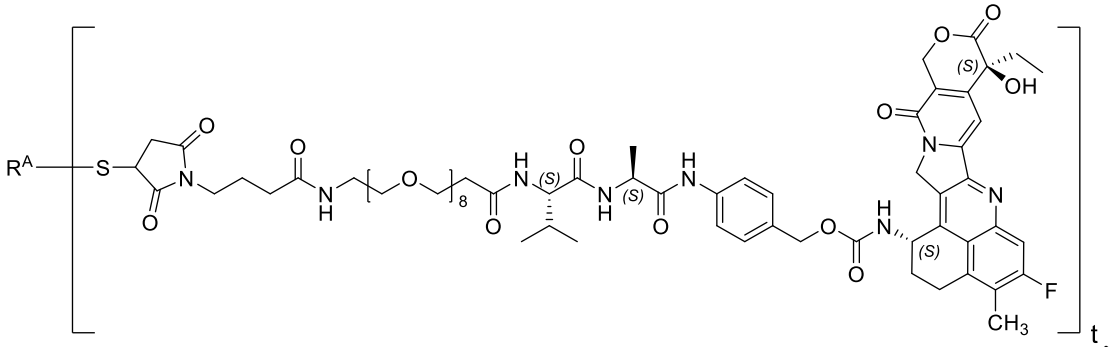
[0015] In some examples, the present disclosure provides various linkers. In some examples, provided linkers comprise PEG moieties. In some examples, provided linkers comprise $-(CH_2CH_2O)n-$, wherein n is 1-24. In some examples, provided linkers comprise cleavable units, e.g., GGFG, that directly bonded to payload moieties. In some examples, a cleavable unit can be cleaved by an enzyme, e.g., an enzyme present at a target site. In some examples, a cleavable unit is or comprises a polypeptide, e.g., GGFG, Val-Ala, Val-Cit, etc. In some examples, a polypeptide is

bonded to a provided method at its C-terminus through −C(O)−. Among other things, the present disclosure provides antibody-drug conjugates in which there are no moieties (e.g., no spacer moieties) between cleavable units and payload moieties. In some examples, there are moieties, e.g., spacer moieties, between cleavable units and payload moieties. In some examples, a linker is or comprises $-L^{ZP}-L^{C}-$ wherein each variable is independently as described herein. In some examples, a linker is or comprises $-(CH_2CH_2O)n-L^{ZP}-L^{C}-$ wherein each variable is independently as described herein. In some examples, a linker is or comprises $-L^{X}-(CH_2CH_2O)n-L^{ZP}-L^{C}-$ wherein each variable is independently as described herein.

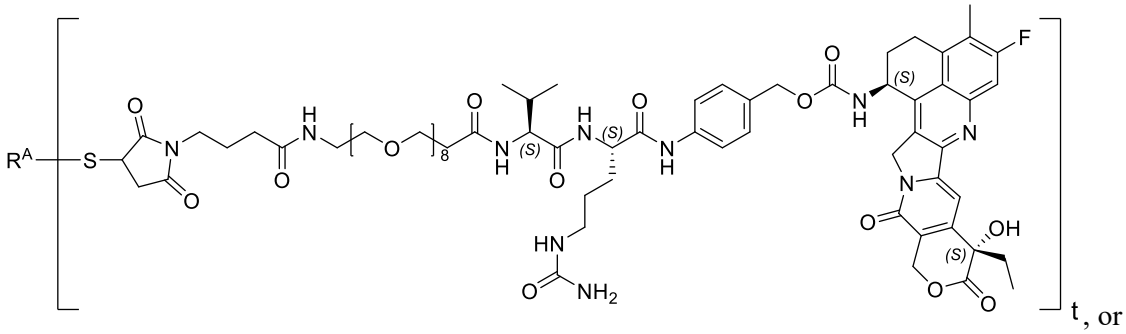
[0015a] In another aspect, the present disclosure provides a conjugate, wherein the conjugate is a compound having the structure of



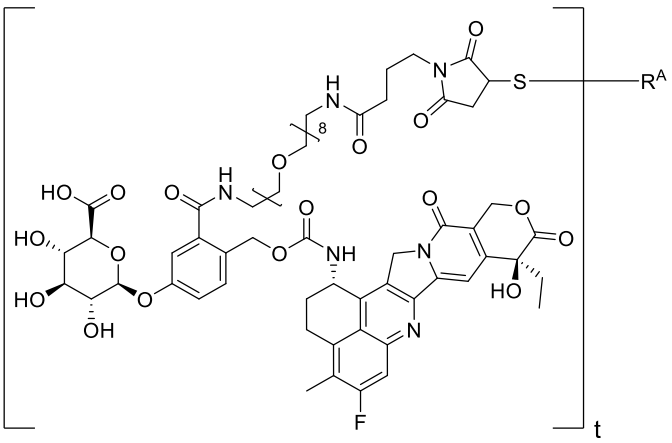
,



t,



t, or



t , or a salt thereof, wherein R^A is Hu2C4-H3L3,

887-1DE, 65889, or 65872 in Table 1, each −S− is independently of a Cys residue, and t is about 1-8, optionally wherein t is about 2-8.

[0016] In some examples, the present disclosure provides pharmaceutical compositions comprising provided conjugates and pharmaceutically acceptable carriers. Among other things, provided technologies, e.g., compounds, conjugates, agents, compositions, etc., are useful for preventing or treating various conditions, disorders or diseases. In some examples, when utilized as therapeutics, provided compounds, conjugates, agents, e.g., are provided in pharmaceutical compositions. Compounds, conjugates, agents, etc., may be various forms, e.g., salt forms. In some examples, they may exist in various pharmaceutically acceptable salt forms. In some examples, in a composition a compound, conjugate, agent, etc., may exist in one or more forms, e.g., in one or more pharmaceutically acceptable salt forms.

[0016a] In another aspect, the present disclosure provides a composition comprising one or more conjugates each of which is independently a conjugate as disclosed herein, optionally wherein:

(a) the ratio of the payload moiety to the target binding moiety of the composition is about 4-8;

(b) the composition is a pharmaceutical composition; and/or

(c) the composition comprises a pharmaceutically acceptable carrier.

[0016b] In another aspect, the present disclosure provides a kit comprising a conjugate as disclosed herein or a composition as disclosed herein, and optionally instructions for use and/or administration.

[0017] In some examples, the present disclosure provides methods for preventing or treating various conditions, disorders or diseases. In some examples, the present disclosure provides a method for preventing a condition, disorder or disease, comprising administering or delivering to a subject susceptible thereto an effective amount of a provided compound, conjugate, agent or composition. In some examples, the present disclosure provides a method for treating a condition, disorder or disease, comprising administering or delivering to a subject suffering therefrom an effective amount of a provided compound, conjugate, agent or composition. In some examples, a condition, disorder or disease is cancer. In some examples, a subject has or is at risk of developing a cancer. In some examples, a subject has a solid tumor or a hematological cancer. In some examples, a solid tumor is or comprises one or more of: a renal cancer, a bone cancer, a skin cancer, a breast cancer, a cervical cancer, a colorectal cancer, an endometrial cancer, a lung cancer, an ovarian cancer, a liver cancer, cholangiocarcinoma, or a thyroid cancer. In some examples, a hematological cancer comprises or is a leukemia or lymphoma. In some examples, a leukemia comprises or is acute lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic leukemia, or acute leukemia. In some examples, a lymphoma comprises or is Hodgkin lymphoma (HL), non-Hodgkin's lymphoma, lymphocytic lymphoma, or diffuse large B cell lymphoma (DLBCL). In some examples, a condition, disorder or disease is associated with aberrant expression of an agent that a target binding moiety can bind, e.g., HHLA2. In some examples, a conjugate is administered parenterally. In some examples, parenteral

administration is or comprises subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion. In some examples, a conjugate is administered in combination with another therapeutic agent.

[0017a] In another aspect, the present disclosure provides use of the conjugate or composition as disclosed herein in the manufacture of a medicament for treating a subject having a disease, disorder, or condition wherein the medicament is to be administered or delivered to a subject in need thereof a therapeutically effective amount of the conjugate or the composition, optionally wherein:

(a) the subject has cancer;

(b) the subject has a solid tumor, or wherein the subject has a renal cancer, a bone cancer, a skin cancer, a breast cancer, a cervical cancer, a colorectal cancer, an endometrial cancer, a lung cancer, an ovarian cancer, a liver cancer, a prostate cancer, a pancreatic cancer, cholangiocarcinoma, or a thyroid cancer, or wherein the subject has a hematological tumor, or wherein the subject has leukemia, or wherein the subject has acute lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic leukemia, or acute leukemia, or wherein the subject has lymphoma, or wherein the subject has Hodgkin lymphoma (HL), non-Hodgkin's lymphoma, lymphocytic lymphoma, or diffuse large B cell lymphoma (DLBCL), or wherein the subject is at risk of developing a cancer;

(c) the disease, disorder, or condition is associated with aberrant HHLA2 expression; and/or

(d) the conjugate is to be administered in combination with a second agent.

[0017b] In another aspect, the present disclosure provides use of a conjugate or composition as disclosed herein in the manufacture of a medicament for inhibiting proliferation of diseased cells in a system, wherein the diseased cells expresses or comprise an agent that a target binding moiety of the conjugate can bind.

[0017c] In another aspect, the present disclosure provides use of a conjugate or composition as disclosed herein in the manufacture of a medicament for reducing number of diseased cells in a system, wherein the diseased cells expresses or comprise an agent that a target binding moiety of the conjugate can bind.

[0017d] In another aspect, the present disclosure provides use of a conjugate or composition as disclosed herein in the manufacture of a medicament for delivering a payload to a target in a system, wherein:

a payload moiety of the conjugate is a moiety of the payload; and

the target expresses or comprises an agent that a target binding moiety of the conjugate can bind.

[0018] In some examples, the present disclosure provides technologies, e.g., methods, reagents, intermediates, etc., for manufacturing various compounds, e.g., conjugates described herein.

[0018a] In another aspect, the present disclosure provides a method for preparing a conjugate or composition as disclosed herein, comprising reacting a target binding agent and a payload agent, wherein:

the target binding agent comprises a target binding moiety and a target binding agent reactive group;

the payload agent comprises a payload moiety and a payload agent reactive group; and

the target binding agent reactive group reacts with the payload agent reactive group to conjugate the payload moiety to the target binding moiety optionally through a linker,

optionally wherein the payload agent is Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, LP-A, LP-B, LP-C or LP-D.

[0019] Various features, objects, and advantages of provided technologies are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating embodiments of provided technologies, is given by way of illustration only, not limitation. Various changes and modifications of provided technologies will become apparent to those skilled in the art from the present disclosure including the detailed description.

BRIEF DESCRIPTION OF DRAWINGS

[0020] Figures 1A, 1B and 1C. Provided conjugates can bind to targets. Figures 1A, 1B and 1C depict certain binding curves for anti-HHLA2 antibody drug conjugates binding to HHLA2+ A204 cells. Naked antibody, exatecan conjugates with DAR about 4 (Exatecan_DAR4), and exatecan conjugates with DAR about 8 (Exatecan_DAR8) for each of Hu2C4-H3L3 (1A), 65872 (1B), and 887-1DE (1C) were tested. Controls include human IgG1 isotype (IgG1 Control) and exatecan conjugates of human IgG1 isotype with DAR about 8 (IgG1-Exatecan_DAR8).

[0021] Figure 2. Provided conjugates can be internalized. Figure 2 depicts examples of induction of internalization in A204 cells by anti-HHLA2 antibodies: Hu2C4-H3L3, 65872, and 887-1DE.

[0022] Figures 3A and 3B. Provided conjugates can kill target cells. Figures 3A and 3B depict dose-response curves for data from example assessment of anti-HHLA2 antibody drug conjugates: Hu2C4-H3L3, 65872, and 887-1DE. 3A: DAR is about 4. 3B: DAR is about 8. Data for exatecan conjugates of human IgG1 isotype with DAR about 8 (IgG1-Exatecan_DAR8) and exatecan are also included.

[0023] Figure 4. Provided conjugates can bind to targets. Figure 4 depicts certain binding curves for anti-HHLA2 antibody drug conjugates binding to HEK cells overexpressing B7H7. Depicted are Hu2C4-H3L3 conjugates of LP-A, LP-B, and LP-C at DAR 8, and 65872 conjugates of LP-A, LP-B, and LP-C at DAR 8. Controls include Hu2C4-H3L3-PEG8-GGFG-Exatecan DAR8 and GGFG-Exatecan conjugates of human IgG1 isotype with DAR about 8. As demonstrated herein, provided conjugates can bind to targets.

[0024] Figure 5. Provided conjugates can kill target cells. Figure 5 depicts certain dose-response curves for data from example assessment of anti-HHLA2 antibody drug conjugates. Depicted are Hu2C4-

H3L3 conjugates of LP-A, LP-B, and LP-C at DAR 8, and 65872 conjugates of LP-A, LP-B and LP-C at DAR 8. Controls include Hu2C4-H3L3-PEG8-GGFG-Exatecan DAR8 and GGFG-Exatecan conjugates of human IgG1 isotype with DAR about 8. As demonstrated herein, provided conjugates can effectively kill target cells.

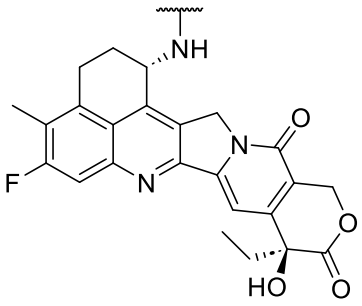
DEFINITIONS

[0025] In order for provided technologies to be more readily understood, certain terms are first defined below. Additional definitions for the following terms and other terms are set forth throughout the specification. The publications (e.g., patents, patent application publications, non-patent publications,

CLAIMS

1. A conjugate, comprising:

i) a target binding moiety targeting HHLA2;

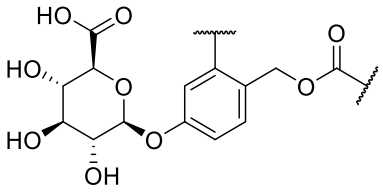
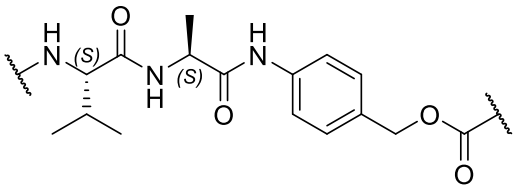
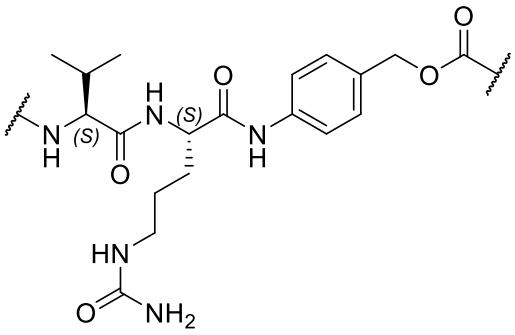
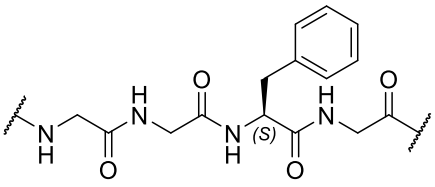
ii) a payload moiety having the structure of  ; and

iii) a linker that connects the target binding moiety and the payload moiety;

wherein:

the linker comprises –$(CH_2CH_2O)n$– and L^C; wherein

n is 8, or wherein n is 0-24;

L^C is  ,  ,  , or  , wherein the carbonyl is bonded to the payload moiety,

optionally wherein the target binding moiety is an antibody selected from Hu2C4-H3L3, 65872, 65889, or 887-1DE.

2. A conjugate, comprising:

i) a target binding moiety;

ii) a payload moiety; and

iii) a linker that connects the target binding moiety and the payload moiety;

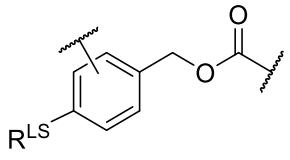
wherein:

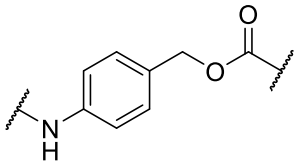
the linker comprises –$(CH_2CH_2O)n$– and L^C;

n is 0-24;

L^C is bonded to a payload moiety and is –L^{C1}–L^{CO}–;

L^{C1} is a cleavable unit; and/or L^{C1} is –Gly–Gly–Phe–Gly–, –Val–Ala–, –Val–Cit–, L^{C1S}, –Gly–Gly–Phe–Gly–N(R')–L^{C1S}–, –Val–Ala–N(R')–L^{C1S}–, or –Val–Cit–N(R')–L^{C1S}–;

L^{C1S} is , wherein the phenyl ring and the $-CH_2-$ is optionally substituted, and the carbonyl is bonded to L^{CO}, and R^{LS} is or comprises a sugar moiety;

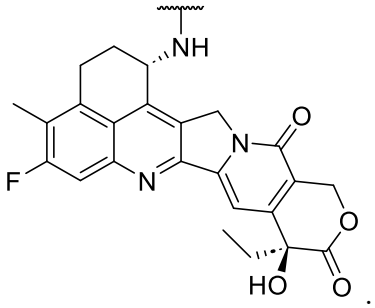
L^{CO} is a covalent bond, or a spacer moiety (e.g., optionally substituted  wherein the carbonyl is bonded to a payload moiety);

each R' is independently $-R$, $-C(O)R$, $-CO_2R$, or $-S(O)_2R$, or two or more R' are taken together with their intervening atom(s) to form an optionally substituted 3-20 membered ring having, in addition to the intervening atom(s), 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

each R is independently hydrogen, or an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, optionally wherein:

(a) the target binding moiety comprises an antibody or an antigen-binding fragment thereof; and/or

(b) the payload moiety is

.

3. The conjugate of claim 1 or claim 2, wherein:

(a) the payload moiety to target binding moiety ratio of the conjugate (DAR) is about 2-8; and/or

(b) the linker comprises $-(CH_2CH_2O)n-L^{ZP}-L^{C}-$, wherein:

L^{ZP} is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from $-O-$, $-N(R')-$, $-C(O)-$, $-S-$, $-S(O)-$, $-S(O)_2-$,$-C(O)N(R')-$, $-S(O)_2(NR')-$, and $-Cy-$;

each $-Cy-$ is independently an optionally substituted bivalent 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

R is optionally substituted C_{1-6} aliphatic,

optionally wherein L^{ZP} is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, and −S(O)$_2$(NR')−, such as wherein L^{ZP} is –(CH$_2$)z−N(R')C(O)−, –(CH$_2$)z−C(O)−, or −(CH$_2$)z−C(O)N(R')−, wherein z is 1-19.

4. The conjugate of any one of the preceding claims, wherein:

(a) the linker comprises $-L^X-(CH_2CH_2O)n-L^{ZP}-L^C-$, wherein:

L^X is a covalent bond or an optionally substituted bivalent or polyvalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^X are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

L^{ZP} is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

each −Cy− is independently an optionally substituted 3-12 membered ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

(b) the linker is or comprises $-L^{RX}-L^X-(CH_2CH_2O)n-L^{ZP}-L^C-$, wherein:

L^{RX} is a covalent bond or a moiety that results from a reaction between a group present on the unconjugated target binding moiety and a group present on an agent comprising $-L^X-(CH_2CH_2O)n-L^{ZP}-L^C-$ and a payload moiety, wherein $-L^C-$ is bonded to the payload moiety; or L^{RX} is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

L^X is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^X are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

L^{ZP} is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

each −Cy− is independently an optionally substituted 3-12 membered ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

and/or

(c) the linker is or comprises $-L^T-L^{RX}-L^X-(CH_2CH_2O)n-L^{ZP}-L^C-$, wherein:

L^T is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^T are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

L^{RX} is a covalent bond or a moiety that results from a reaction between a group present on the

unconjugated target binding moiety and a group present on an agent comprising $-L^X-(CH_2CH_2O)n-L^{ZP}-L^C-$ and a payload moiety, wherein $-L^C-$ is bonded to the payload moiety; or L^{RX} is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

L^X is a covalent bond or an optionally substituted bivalent or polyvalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^X are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

L^{ZP} is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each −Cy− is independently an optionally substituted 3-12 membered ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic,

optionally wherein L^{ZP} is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, and $-S(O)_2(NR')-$, such as wherein L^{ZP} is $-(CH_2)z-N(R')C(O)-$, $-(CH_2)z-C(O)-$, or $-(CH_2)z-C(O)N(R')-$, wherein z is 1-19.

5. The conjugate of any one of claims 2-4, wherein L^C is −Gly−Gly−Phe−Gly−, −Val−Ala−PABA−, −Val−Cit−PABA−, mGlu or oGlu.

6. The conjugate of any one of the preceding claims, wherein n is 8.

7. The conjugate of any one of claims 4-6, wherein:

(a) L^X is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^X are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

(b) each L^{RX} is independently $-L^{RX1}-L^{RX2}-$, wherein:

each L^{RX1} is independently a covalent bond or an optionally substituted bivalent or polyvalent straight or branched C_{1-10} aliphatic wherein 1-5 methylene units of L^{RX1} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each L^{RX2} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-10} aliphatic wherein 1-5 methylene units of L^{RX2} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each −Cy− is independently an optionally substituted 3-12 membered ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each L^{RX2} is bonded to L^X; and

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

(c) L^T is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^T are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, and −S(O)$_2$(NR')−;

(d) L^T is –CH_2−; and/or

(e) the target binding moiety comprises an amino acid residue, and L^T is bonded to the backbone atom of the amino acid residue.

8. The conjugate of claim 2 or claim 3, wherein the linker is or comprises:

(a) $\left[-L^{RX}\right]_a-L^{X'}-\left[(CH_2CH_2O)_n-L^{ZP}-L^{C}-\right]_b$, wherein:

each L^{RX} is independently a covalent bond or a moiety that results from a reaction between a group present on the unconjugated target binding moiety and a group present on an agent comprising $L^{X'}$ and optionally a payload moiety, wherein –L^C– is bonded to the payload moiety; or each L^{RX} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

each of a and b is independently 1-10;

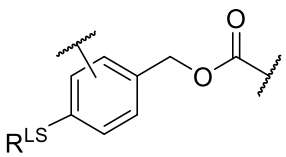
$L^{X'}$ is a covalent bond or an optionally substituted bivalent or polyvalent straight or branched C_{1-30} aliphatic wherein 1-10 methylene units of $L^{X'}$ are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

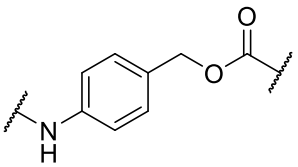
each n is independently 0-24;

each L^{ZP} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −S(O)$_2$−, −C(O)N(R')−, −S(O)$_2$(NR')−, and −Cy−;

each L^C is independently −L^{C1}–L^{CO}–;

each L^{C1} is independently −Gly−Gly−Phe−Gly−, −Val−Ala−, −Val–Cit–, L^{C1S}, −Gly−Gly−Phe−Gly−N(R')−L^{C1S}–, −Val−Ala−N(R')−L^{C1S}–, or −Val–Cit–N(R')−L^{C1S}–;

each L^{C1S} is independently , wherein the phenyl ring and the −CH_2− is optionally substituted, and the carbonyl is bonded to L^{CO}, and R^{LS} is or comprises a sugar moiety;

each L^{CO} is independently absent or optionally substituted  wherein the carbonyl is bonded to a payload moiety;

each L^C is independently bonded to a payload moiety;

each −Cy− is independently an optionally substituted 3-12 membered ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R' is independently −R, −C(O)R, −CO_2R, or −$S(O)_2$R, or two or more R' are taken together with their intervening atom(s) to form an optionally substituted 3-20 membered ring having, in addition to the intervening atom(s), 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

or

(b) $\left[-L^{T}-L^{RX}\right]_{a}-L^{X'}-\left[(CH_2CH_2O)_n-L^{ZP}-L^{C}-\right]_{b}$, wherein:

each L^T is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^T are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each L^{RX} is independently a covalent bond or a moiety that results from a reaction between a group present on the unconjugated target binding moiety and a group present on an agent comprising $L^{X'}$ and optionally a payload moiety, wherein –L^C– is bonded to the payload moiety; or each L^{RX} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each of a and b is independently 1-10;

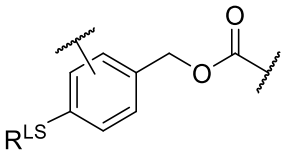
$L^{X'}$ is a covalent bond or an optionally substituted bivalent or polyvalent straight or branched C_{1-30} aliphatic wherein 1-10 methylene units of $L^{X'}$ are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

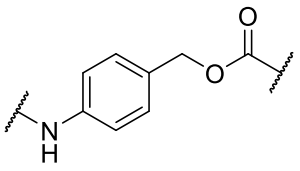
each n is independently 0-24;

each L^{ZP} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each L^C is independently −L^{C1}–L^{CO}–;

each L^{C1} is independently −Gly−Gly−Phe−Gly−, −Val−Ala−, −Val–Cit–, L^{C1S}, −Gly−Gly−Phe−Gly−N(R')−L^{C1S}–, −Val−Ala−N(R')−L^{C1S}–, or −Val–Cit–N(R')−L^{C1S}–;

each L^{C1S} is independently , wherein the phenyl ring and the −CH_2− is optionally substituted, and the carbonyl is bonded to L^{CO}, and R^{LS} is or comprises a sugar moiety;

each L^{CO} is independently absent or optionally substituted  wherein the carbonyl is bonded to a payload moiety;

each L^{C} is independently bonded to a payload moiety;

each −Cy− is independently an optionally substituted 3-12 membered ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R' is independently −R, −C(O)R, −CO_2R, or −$S(O)_2$R, or two or more R' are taken together with their intervening atom(s) to form an optionally substituted 3-20 membered ring having, in addition to the intervening atom(s), 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

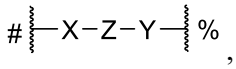
each R is independently hydrogen or optionally substituted C_{1-6} aliphatic, optionally

wherein:

(i) each L^{T} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{T} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, and −$S(O)_2$(NR')−; and/or

(ii) each occurrence of L^{T} is −CH_2−.

9. The conjugate of any one of the preceding claims, wherein the linker is or comprises a structure of formula B:



B

wherein:

represents the point of attachment to the target binding moiety;

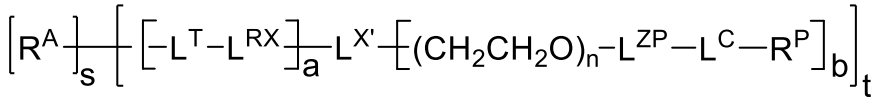
% represents the point of attachment to a payload moiety;

X is a moiety that results from the reaction of an unbound linker and a group present on the target binding moiety;

Y is L^{C}; and

Z is or comprises –(CH_2CH_2O)n−.

10. A conjugate, wherein the conjugate is a compound of formula A-1 or a salt thereof:



A-1

wherein:

each R^{A} is independently a target binding moiety;

s is 1-20;

each L^T is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^T are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each L^{RX} is independently a covalent bond, a moiety that results from a reaction between a group present on the unconjugated target binding moiety and a group present on an agent comprising $L^{X'}$, or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−; or each L^{RX} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each of a and b is independently 1-10;

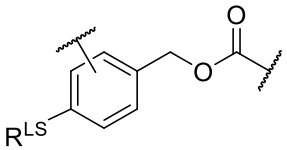
each $L^{X'}$ is independently a covalent bond or an optionally substituted bivalent or polyvalent straight or branched C_{1-30} aliphatic wherein 1-10 methylene units of $L^{X'}$ are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each n is independently 0-24;

each L^{ZP} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each L^C is independently $-L^{C1}-L^{CO}-$;

each L^{C1} is independently a cleavable unit, or each L^{C1} is independently −Gly−Gly−Phe−Gly−, −Val−Ala−, −Val–Cit–, L^{C1S}, −Gly−Gly−Phe−Gly−N(R')−L^{C1S}–, −Val−Ala−N(R')−L^{C1S}–, or −Val–Cit–N(R')−L^{C1S}–;

L^{C1S} is 

, wherein the phenyl ring and the −CH_2− is optionally substituted, and the carbonyl is bonded to L^{CO}, and R^{LS} is or comprises a sugar moiety;

each L^{CO} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{CO} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

each R^P is independently a payload moiety;

t is 1-20;

each –Cy– is independently an optionally substituted bivalent 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

each R' is independently −R, −C(O)R, −CO_2R, or −$S(O)_2$R, or two or more R' are taken together

with their intervening atom(s) to form an optionally substituted 3-20 membered ring having, in addition to the intervening atom(s), 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

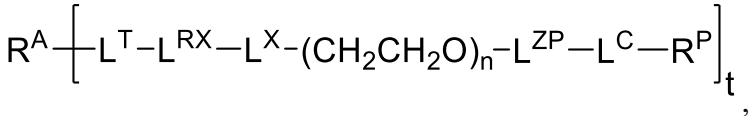
each R is independently hydrogen, or an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, optionally wherein:

(a) s is 1;

(b) an occurrence of a is 2-10; and/or

(c) an occurrence of b is 2-10.

11. A conjugate, wherein the conjugate is a compound of formula A-2 or a salt thereof:



A-2

wherein:

R^A is a target binding moiety;

each L^T is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^T are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each L^{RX} is independently a covalent bond, a moiety that results from a reaction between a group present on the unconjugated target binding moiety and a group present on an agent comprising $-L^X-(CH_2CH_2O)n-L^{ZP}-L^C-R^P$, or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each L^X is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^X are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each n is independently 0-24;

each L^{ZP} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each L^C is independently $-L^{C1}-L^{CO}-$;

each L^{C1} is independently a cleavable unit;

each L^{CO} is independently a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{CO} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

each R^P is independently a payload moiety;

t is 1-20;

each –Cy– is independently an optionally substituted bivalent 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

each R' is independently −R, −C(O)R, $-CO_2R$, or $-S(O)_2R$, or two or more R' are taken together with their intervening atom(s) to form an optionally substituted 3-20 membered ring having, in addition to the intervening atom(s), 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; and

each R is independently hydrogen, or an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, optionally

wherein:

(a) R^A is or comprises an antibody or an antigen-binding fragment thereof; and/or

(b) an occurrence of L^X is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^X are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−.

12. The conjugate of claim 10 or claim 11, wherein:

(a) an occurrence of L^T is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^T are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−;

(b) an occurrence of L^T is $–CH_2–$;

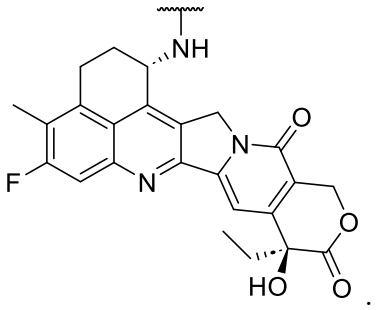
(c) an occurrence of L^{RX} is a covalent bond or a moiety that results from a reaction between a group present on the unconjugated target binding moiety and a group present on an agent comprising $-L^X-(CH_2CH_2O)n-L^{ZP}-L^C-$ and a payload moiety, or wherein an occurrence of L^{RX} is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{RX} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, $-S(O)_2-$, −C(O)N(R')−, $-S(O)_2(NR')-$, and −Cy−, wherein each −Cy− is independently an optionally substituted 3-12 membered ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

(d) an occurrence of n is 8;

(e) an occurrence of L^{ZP} is a covalent bond or an optionally substituted bivalent straight or branched C_{1-20} aliphatic wherein 1-10 methylene units of L^{ZP} are optionally and independently replaced by a group selected from −O−, −N(R')−, −C(O)−, −S−, −S(O)−, −$S(O)_2$−, −C(O)N(R')−, −$S(O)_2$(NR')−, and −Cy−;

and/or

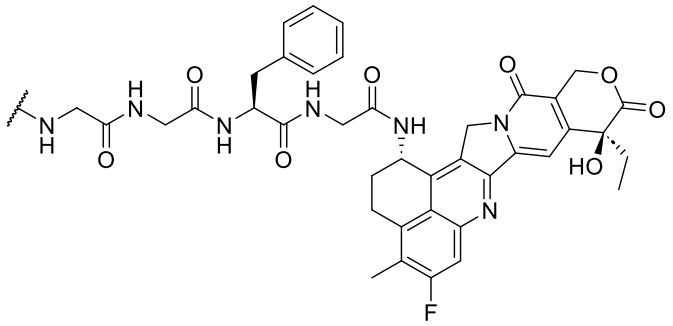
(f) each R^P is



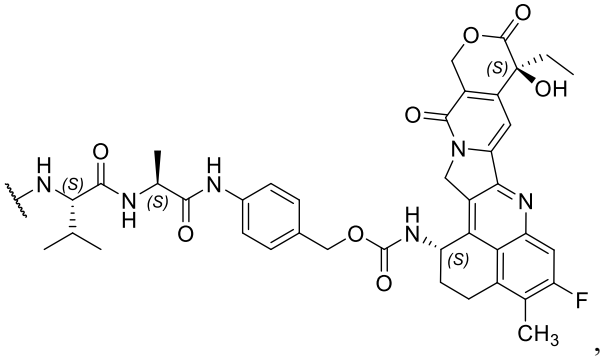
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13. The conjugate of claim 10 or claim 11, wherein:

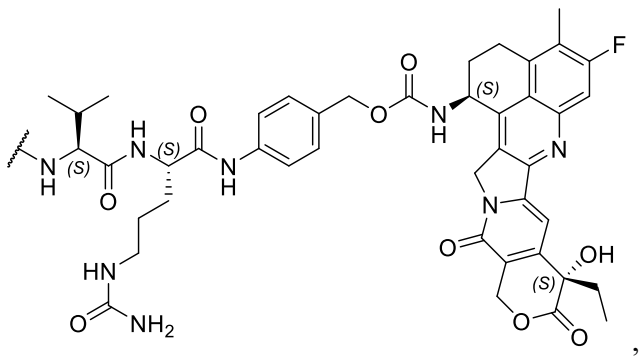
(a) each $-L^C-R^P$ is independently



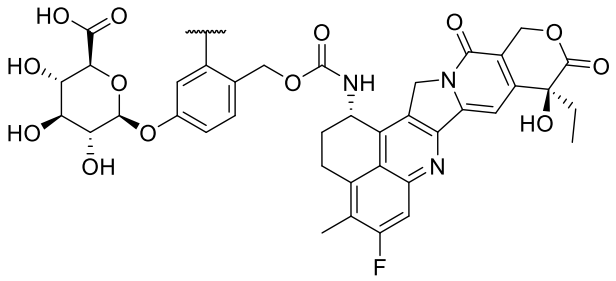
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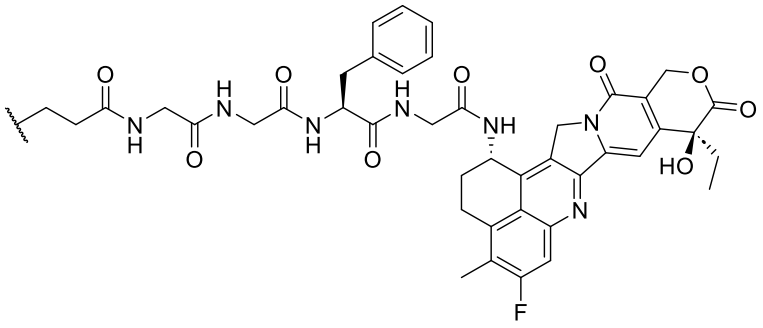


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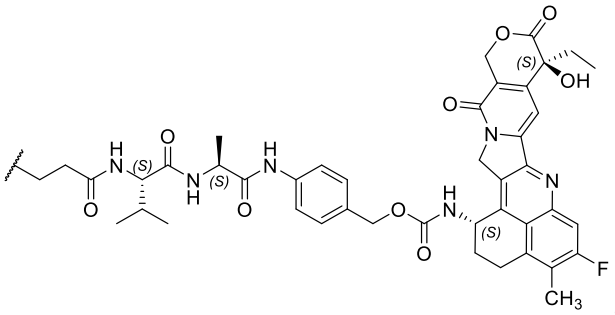


or ;

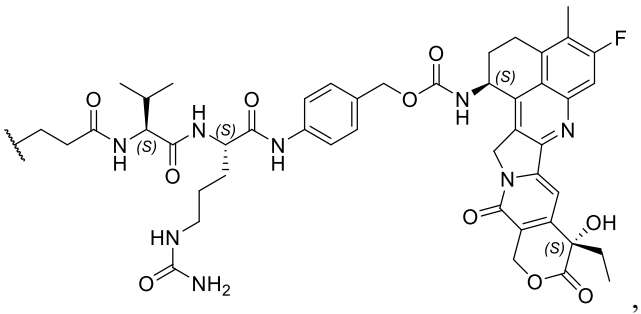
(b) each occurrence of $-L^{ZP}-L^C-R^P$ is or comprises



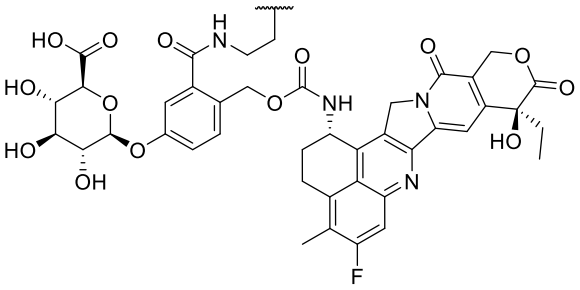
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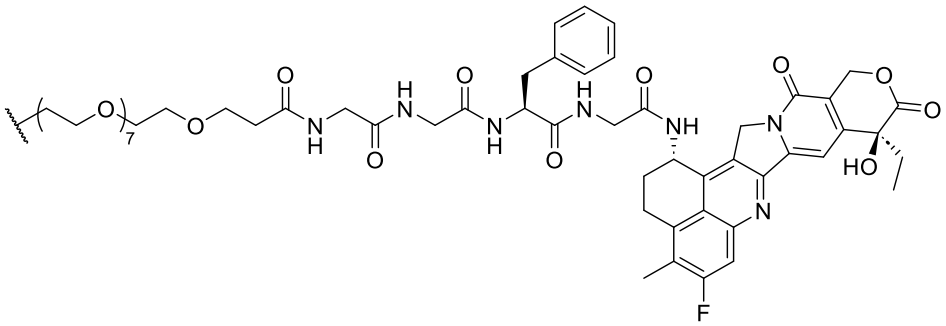


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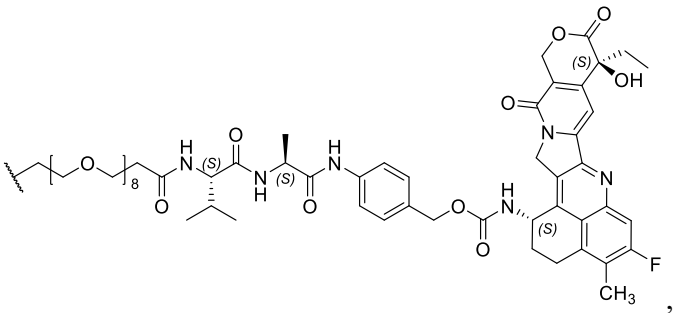


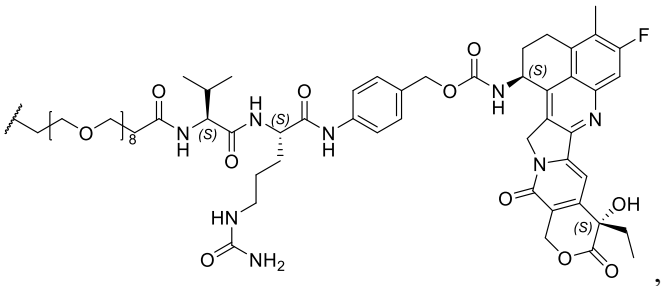
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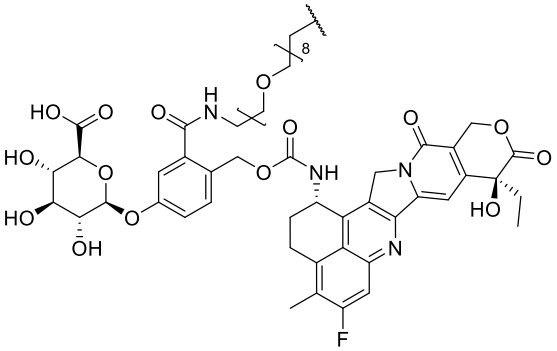
(c) each occurrence of $-(CH_2CH_2O)n-L^{ZP}-L^{C}-R^{P}$ is or comprises



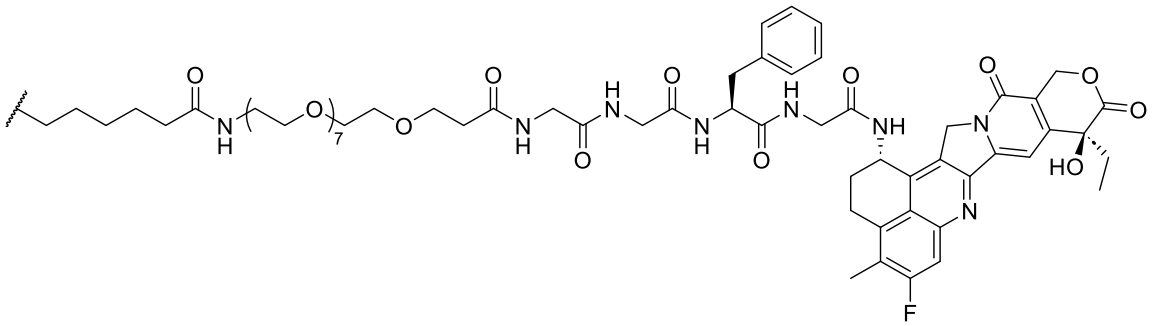
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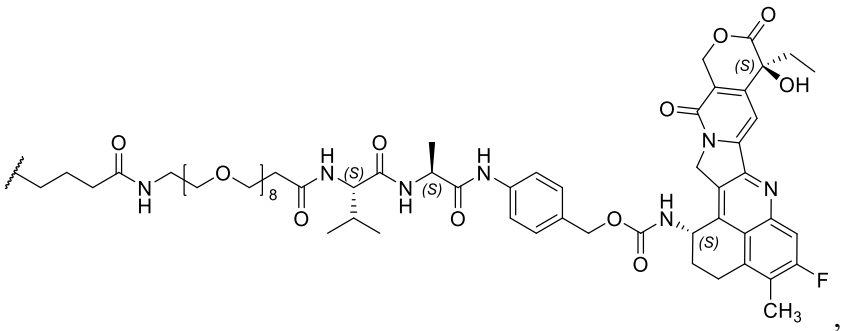

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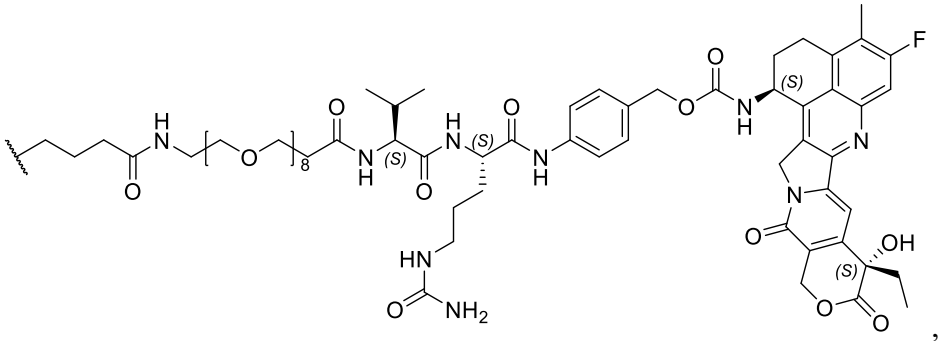

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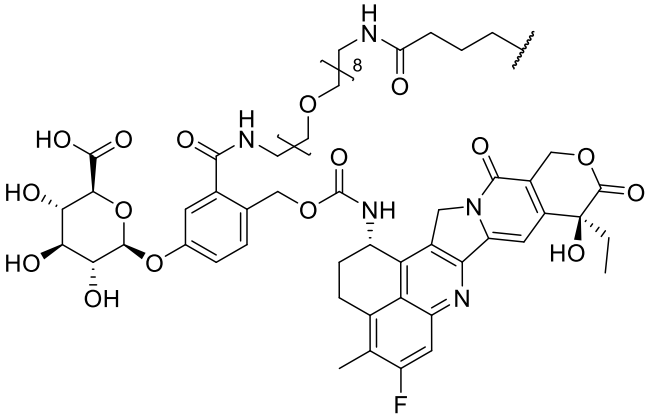
(d) an occurrence of $-L^X-(CH_2CH_2O)n-L^{ZP}-L^C-R^P$ is or comprises


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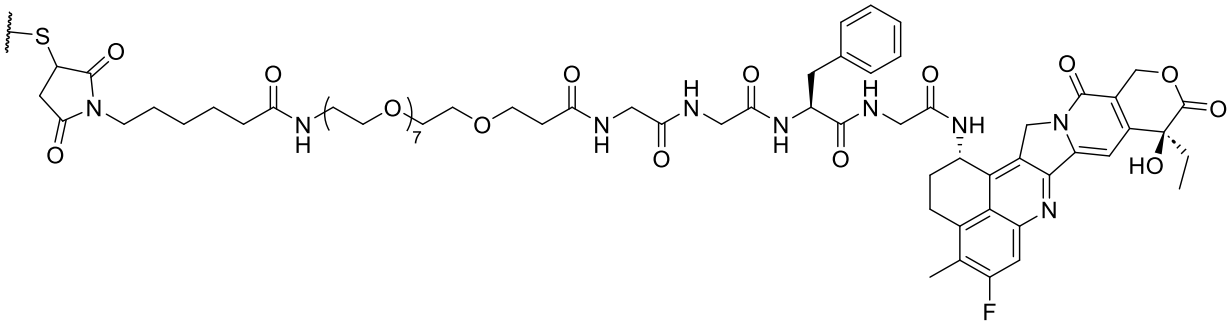


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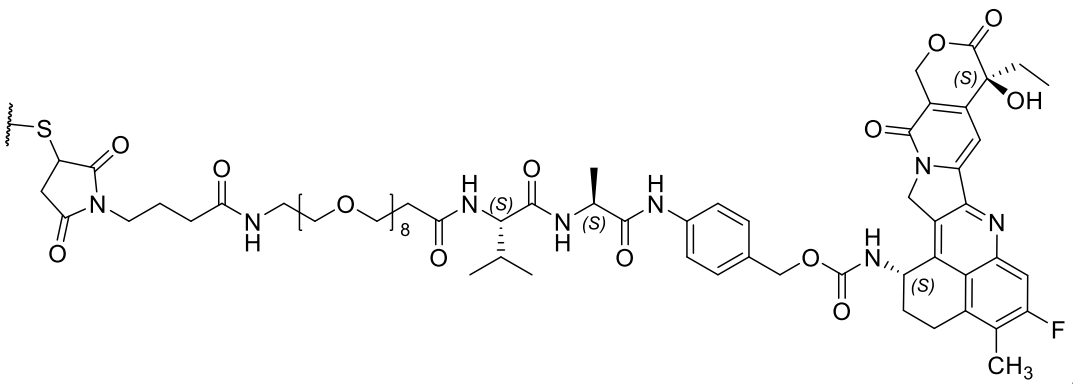


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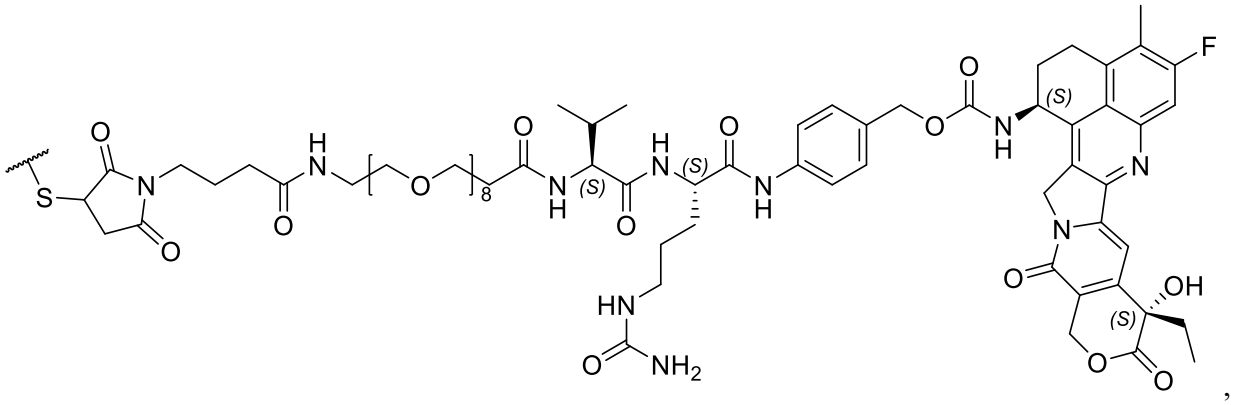
(e) each occurrence of $-L^{RX}-L^{X}-(CH_2CH_2O)n-L^{ZP}-L^{C}-R^{P}$ is or comprises



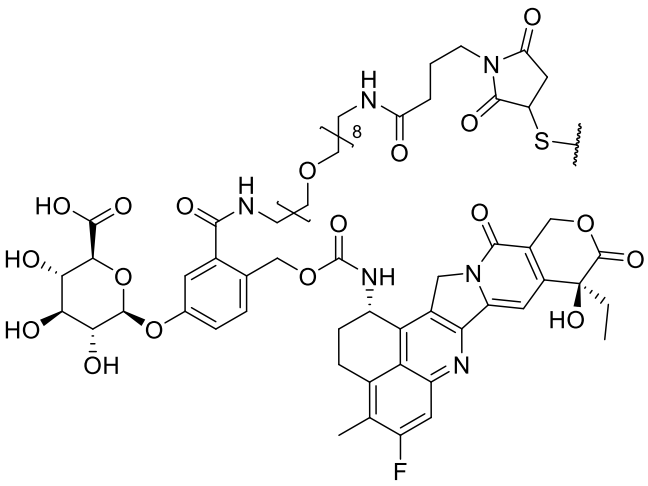
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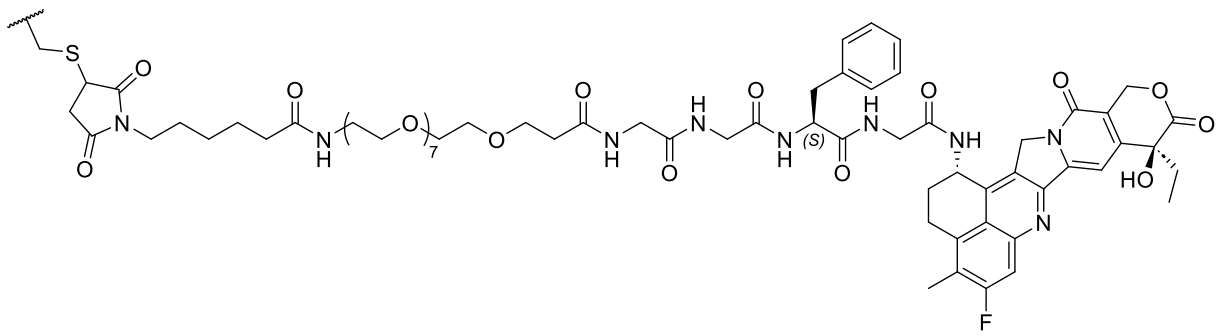
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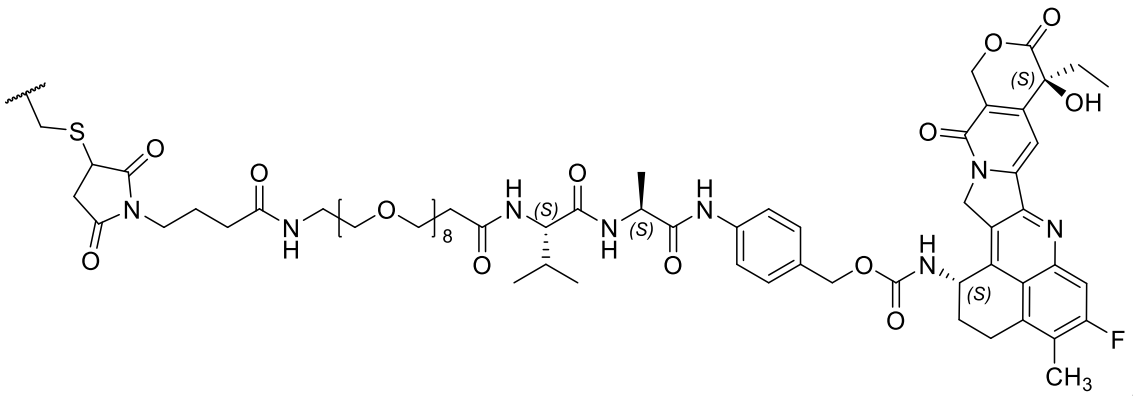
or

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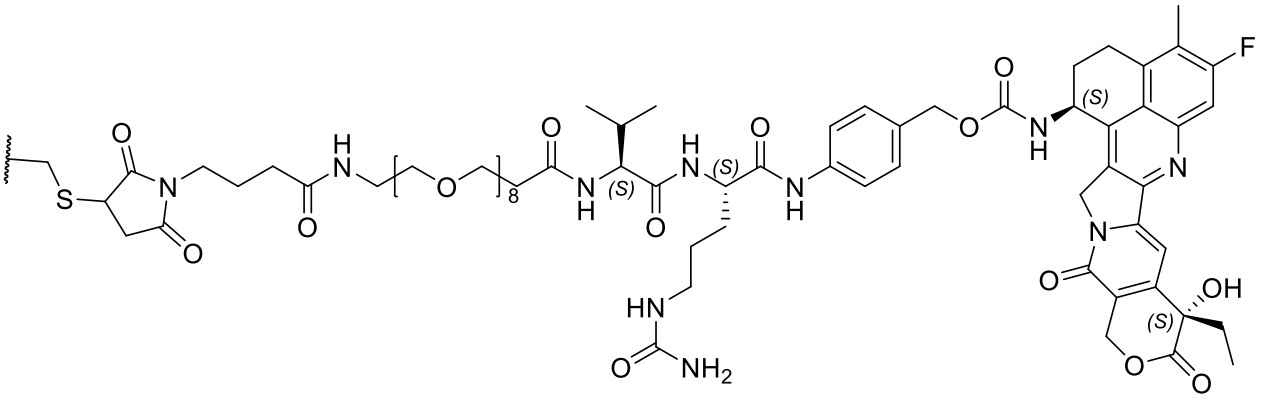
(f) each occurrence of $-L^{T}-L^{RX}-L^{X}-(CH_2CH_2O)n-L^{ZP}-L^{C}-R^{P}$ is or comprises

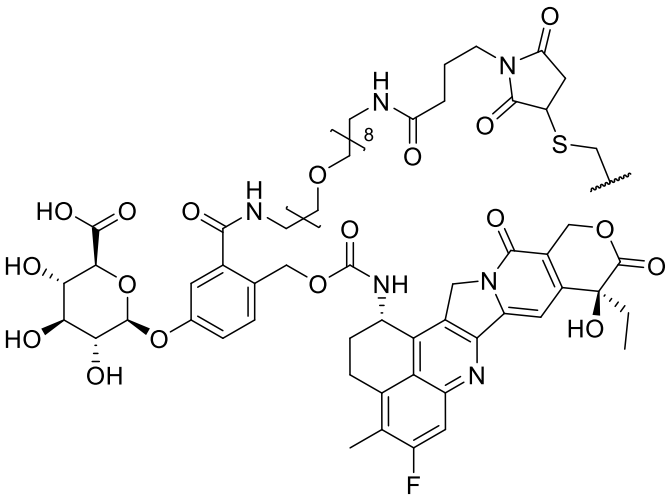


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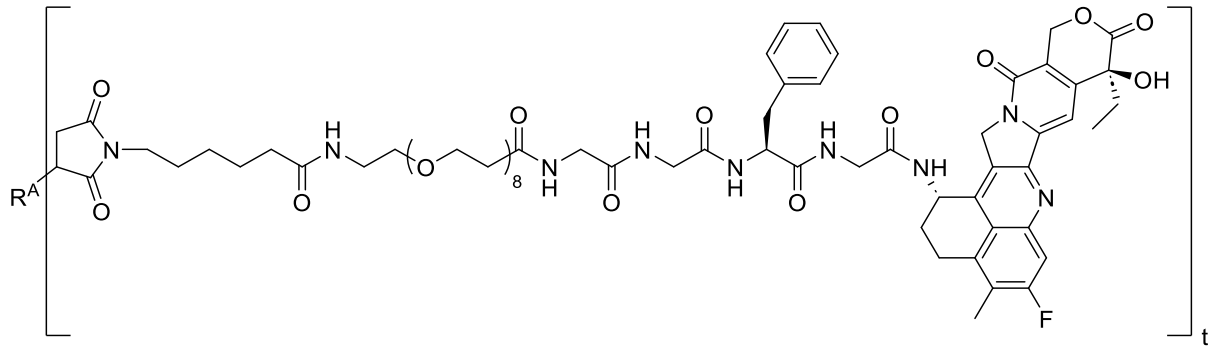


or .

14. The conjugate of any one of claims 10-13, wherein the target binding moiety comprises an amino acid residue, and $-L^{T}-L^{RX}-L^{X}-(CH_2CH_2O)n-L^{ZP}-L^{C}-R^{P}$ is bonded to the backbone atom of the amino acid residue.

15. The conjugate of claim 2, having a structure of:

(a) formula X-C:



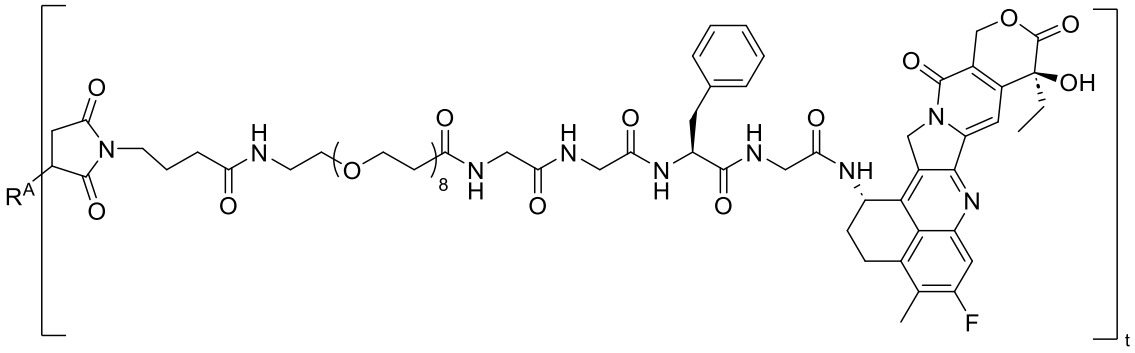
X-C

or a pharmaceutically acceptable salt thereof, wherein:

R^{A} is a target binding moiety; and

t is an integer between 1 and 16;

(b) formula X-C':



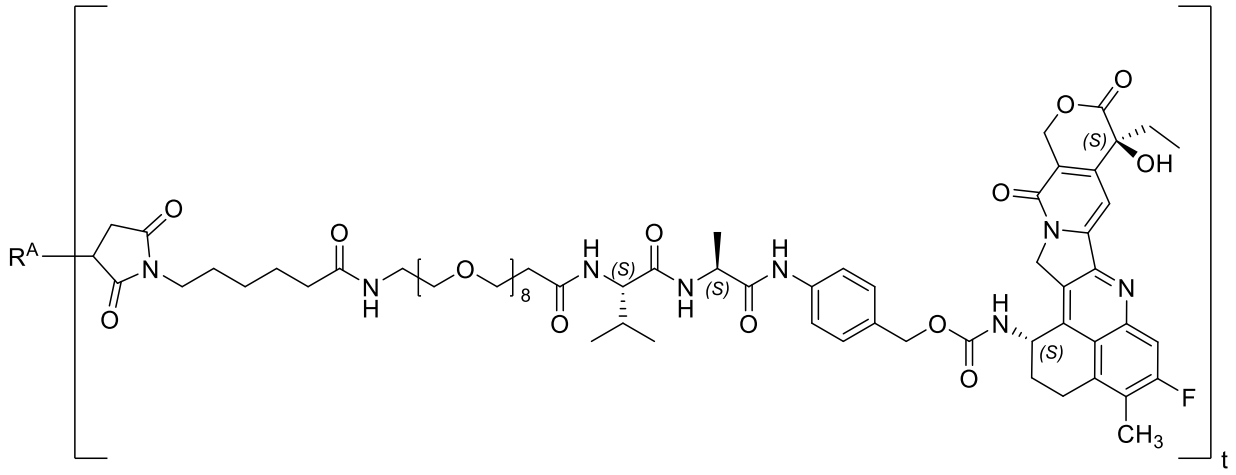
X-C’

or a pharmaceutically acceptable salt thereof, wherein:

R^A is a target binding moiety; and

t is an integer between 1 and 16;

(c) formula X-G’:



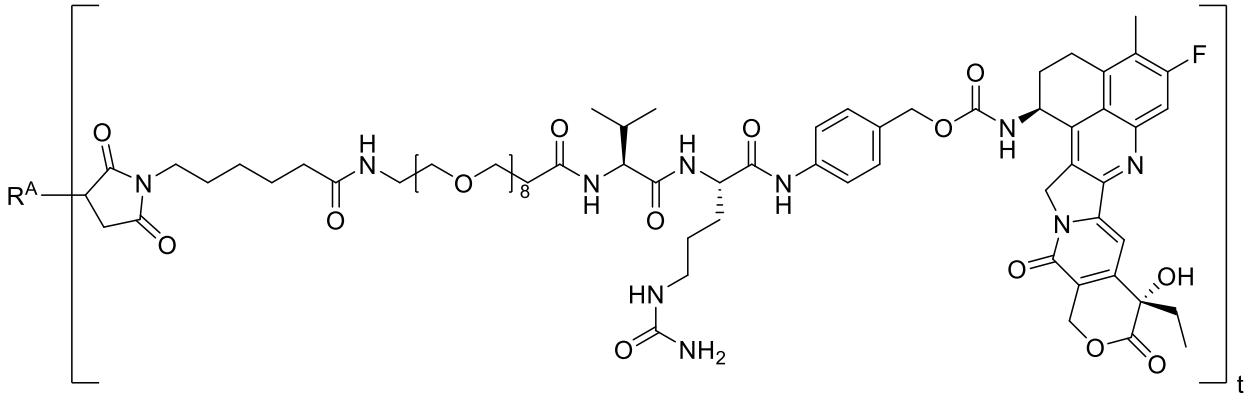
X-G’

or a pharmaceutically acceptable salt thereof, wherein:

R^A is a target binding moiety; and

t is an integer between 1 and 16;

(d) formula X-H’:



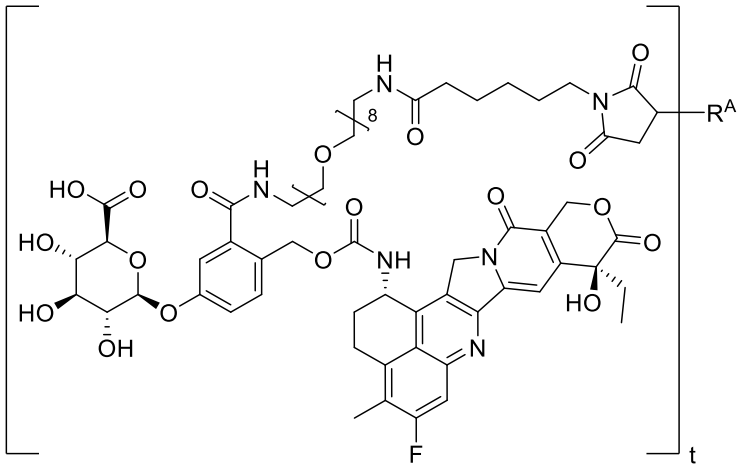
X-H’

or a pharmaceutically acceptable salt thereof, wherein:

R^A is a target binding moiety; and

t is an integer between 1 and 16;

(e) formula X-I':



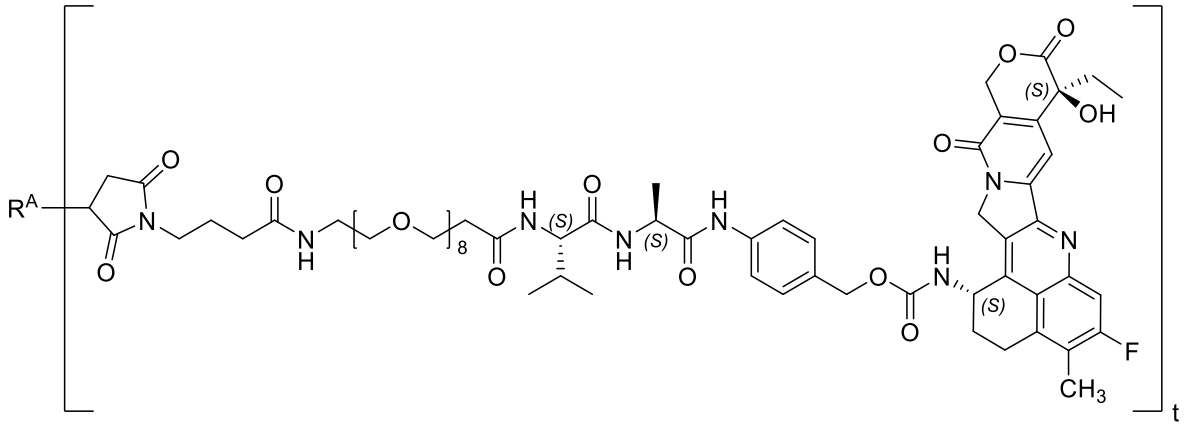
X-I'

or a pharmaceutically acceptable salt thereof, wherein:

R^A is a target binding moiety; and

t is an integer between 1 and 16;

(f) formula X-J':



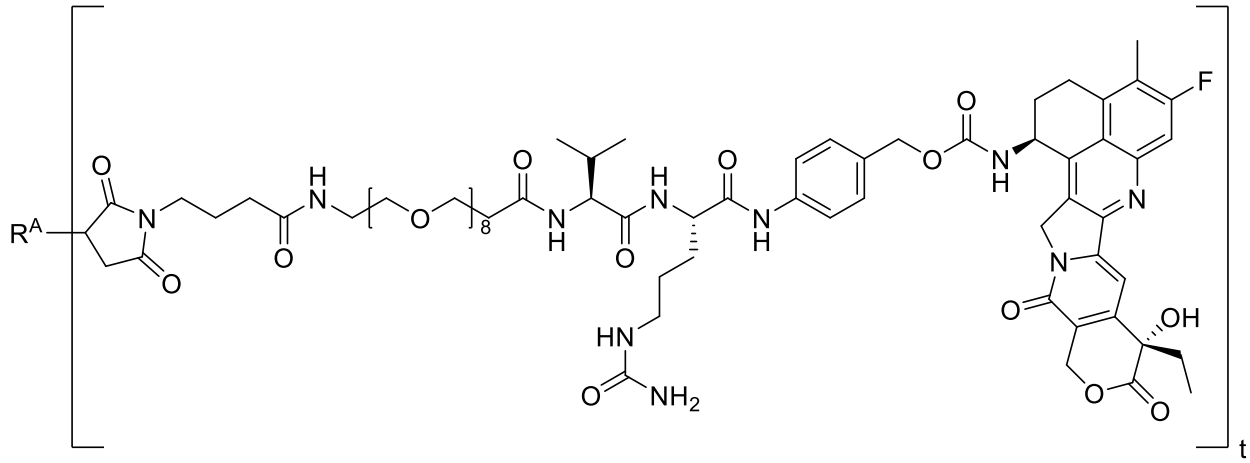
X-J'

or a pharmaceutically acceptable salt thereof, wherein:

R^A is a target binding moiety; and

t is an integer between 1 and 16;

(g) formula X-K':



X-K’

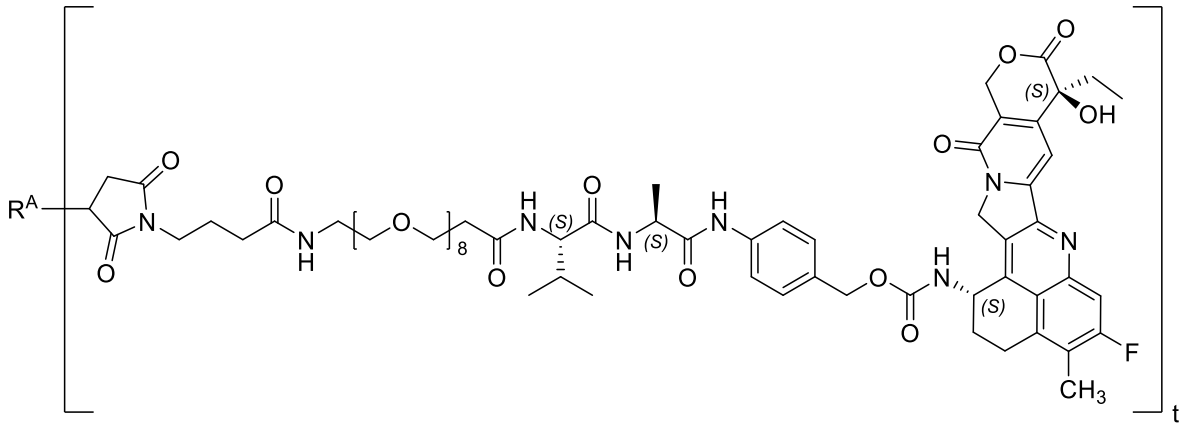
or a pharmaceutically acceptable salt thereof, wherein:

R^A is a target binding moiety; and

t is an integer between 1 and 16;

or

(h) formula X-L’:



X-L’

or a pharmaceutically acceptable salt thereof, wherein:

R^A is a target binding moiety; and

t is an integer between 1 and 16.

16. The conjugate of any one of claims 10-15, wherein t is about 2-8.

17. The conjugate of any one of the preceding claims, wherein each target binding moiety is independently an antibody or an antigen-binding fragment thereof.

18. The conjugate of any one of claims 2-16, wherein each target binding moiety is an anti-HHLA2 antibody or an antigen-binding fragment thereof, optionally wherein the anti-HHLA2 antibody or an antigen-binding fragment thereof is or comprises:

(a) a heavy chain variable region (VH) comprising one, two, or three VH CDR sequences each with at least about 90% identity to a VH CDR of Table 1; and

a light chain variable region (VL) comprising one, two, or three VL CDR sequences each with at least about 90% identity to a VL CDR of Table 1;

(b) a VH comprising or consisting of a VH of Table 1; and

a VL comprising or consisting of a VL of Table 1;

(c) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 79;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 80;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 81;

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 92;

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 93; and

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 94;

(d) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 82;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 83;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 84;

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 95;

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 96; and

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 97;

(e) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 85;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 86;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 87;

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 98;

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 99; and

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 100; or

(f) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 1;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 2;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO:

3;

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 14;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 15; and
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 16;

(g) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 4;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 5;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 6;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 17;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 18; and
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 19;

(h) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 7;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 8;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 9;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 20;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 21; and
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 22;

(i) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 27;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 28;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 29;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 40;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID

NO: 41; and
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 42;
(j) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 30;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 31;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 32;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 43;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 44; and
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 45;
(k) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 33;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 34;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 35;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 46;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 47; and
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 48;
(l) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 53;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 54;
a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 55;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 66;
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 67; and
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID

NO: 68;

(m) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 56;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 57;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 58;

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 69;

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 70; and

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 71;

(n) a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 59;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 60;

a heavy chain variable region (VH) comprising a VH CDR amino acid sequence of SEQ ID NO: 61;

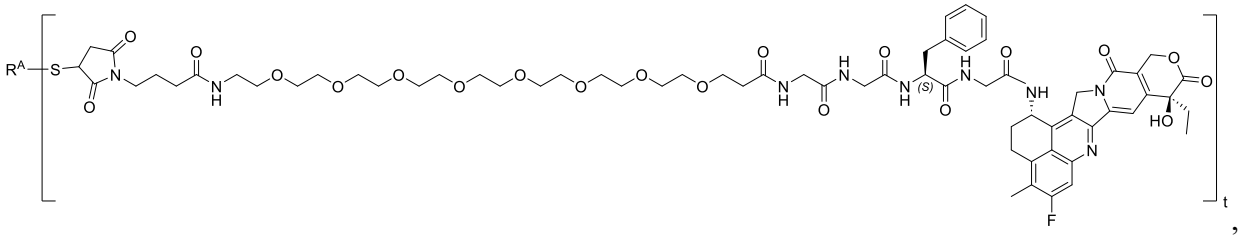
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 72;

a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 73; and

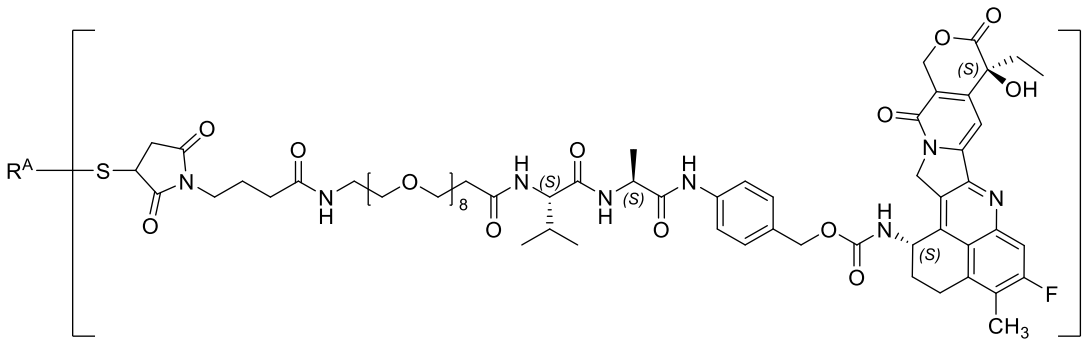
a light chain variable region (VL) comprising a VL CDR amino acid sequence of SEQ ID NO: 74; or

(o) Hu2C4-H3L3, 887-1DE, 65889, or 65872 in Table 1, optionally wherein the conjugate binds HHLA2 with a K_D of about 15 nM or less.

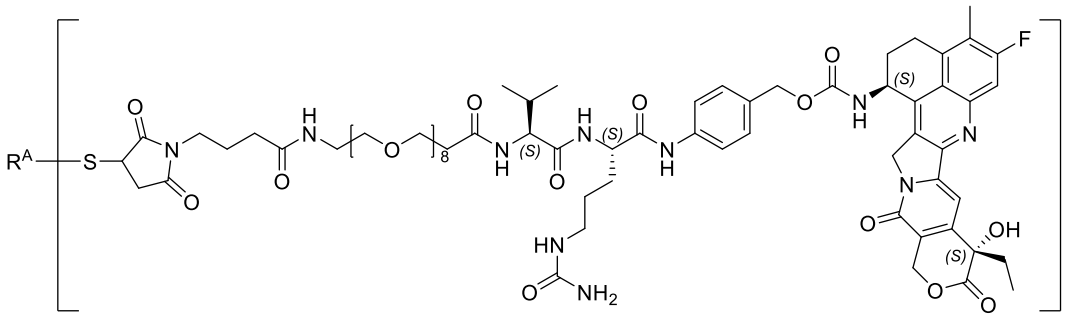
19. A conjugate, wherein the conjugate is a compound having the structure of



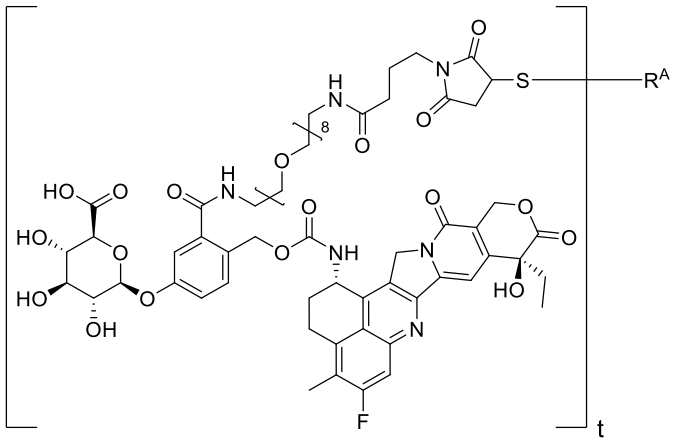
,



t,



t, or



t , or a salt thereof, wherein R^A is Hu2C4-H3L3, 887-1DE, 65889, or 65872 in Table 1, each −S− is independently of a Cys residue, and t is about 1-8, optionally wherein t is about 2-8.

20. The conjugate of any one of the preceding claims, wherein the conjugate is in a pharmaceutically acceptable salt form.

21. A composition comprising one or more conjugates each of which is independently a conjugate of any one of the preceding claims, optionally wherein:

(a) the ratio of the payload moiety to the target binding moiety of the composition is about 4-8;

(b) the composition is a pharmaceutical composition; and/or

(c) the composition comprises a pharmaceutically acceptable carrier.

22. A kit comprising a conjugate of any one of claims 1-20 or a composition of claim 21, and optionally instructions for use and/or administration.

23. Use of the conjugate or composition of any one of claims 1-21 in the manufacture of a medicament for treating a subject having a disease, disorder, or condition wherein the medicament is to be administered or delivered to a subject in need thereof a therapeutically effective amount of the conjugate or the composition, optionally wherein:

(a) the subject has cancer;

(b) the subject has a solid tumor, or wherein the subject has a renal cancer, a bone cancer, a skin cancer, a breast cancer, a cervical cancer, a colorectal cancer, an endometrial cancer, a lung cancer, an ovarian cancer, a liver cancer, a prostate cancer, a pancreatic cancer, cholangiocarcinoma, or a thyroid cancer, or wherein the subject has a hematological tumor, or wherein the subject has leukemia, or wherein the subject has acute lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic leukemia, or acute leukemia, or wherein the subject has lymphoma, or wherein the subject has Hodgkin lymphoma (HL), non-Hodgkin's lymphoma, lymphocytic lymphoma, or diffuse large B cell lymphoma (DLBCL), or wherein the subject is at risk of developing a cancer;

(c) the disease, disorder, or condition is associated with aberrant HHLA2 expression; and/or

(d) the conjugate is to be administered in combination with a second agent.

24. Use of a conjugate or composition of any one of claims 1-21 in the manufacture of a medicament for inhibiting proliferation of diseased cells in a system, wherein the diseased cells expresses or comprise an agent that a target binding moiety of the conjugate can bind.

25. Use of a conjugate or composition of any one of claims 1-21 in the manufacture of a medicament for reducing number of diseased cells in a system, wherein the diseased cells expresses or comprise an agent that a target binding moiety of the conjugate can bind.

26. Use of a conjugate or composition of any one of claims 1-21 in the manufacture of a medicament for delivering a payload to a target in a system, wherein:

a payload moiety of the conjugate is a moiety of the payload; and

the target expresses or comprises an agent that a target binding moiety of the conjugate can bind.

27. A method for preparing a conjugate or composition of any one of claims 1-21, comprising reacting a target binding agent and a payload agent, wherein:

the target binding agent comprises a target binding moiety and a target binding agent reactive group;

the payload agent comprises a payload moiety and a payload agent reactive group; and

the target binding agent reactive group reacts with the payload agent reactive group to conjugate the payload moiety to the target binding moiety optionally through a linker,

optionally wherein the payload agent is Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, LP-A, LP-B, LP-C or LP-D.