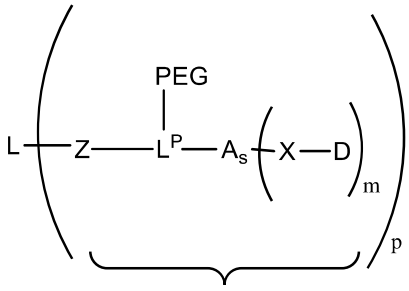
BRIEF SUMMARY

[0034] The disclosure provides *inter alia,* Ligand- Drug Conjugates (LDCs), methods of preparing and using them, and intermediates thereof. The Ligand- Drug Conjugates are stable in circulation, yet capable of inflicting cell death on targeted cells or inhibiting proliferation of targeted cells once its drug cargo is released in the vicinity or within targeted cells.

[0034a] In one aspect, the preent disclosure relates to a Ligand-Drug Conjugate compound of formula (I):



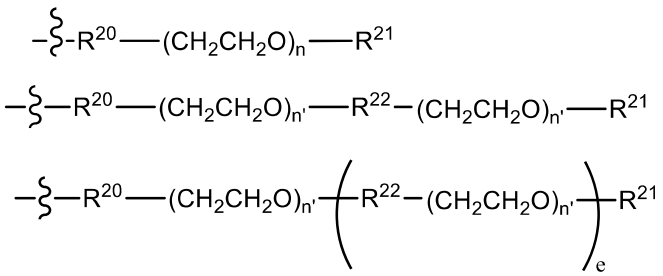
(I)

or a pharmaceutically acceptable salt thereof, wherein,

L is a Ligand Unit, wherein the Ligand Unit is an antibody or antigen-binding fragment thereof;

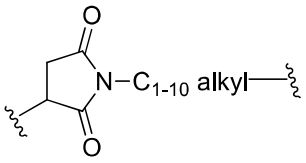
D is a hydrophobic Drug Unit, wherein the Drug Unit corresponds in structure to a hydrophobic cytotoxic, cytostatic, or immunosuppressive agent;

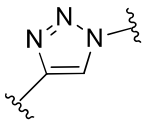
PEG is a Polyethylene Glycol Unit, wherein the PEG Unit has the formula of:



wherein the wavy line indicates the site of attachment of the PEG Unit to L^P,

R^{20} is a PEG Attachment Unit, wherein each R^{20} is –C(O)-, -O-, -S-, -S(O)-, -NH-, -C(O)O-, -C(O)C_{1-10} alkyl, -C(O)C_{1-10} alkyl-O-, -C(O)C_{1-10}alkyl-CO_2-, -C(O)C_{1-10} alkyl-NH-, -C(O)C_{1-10} alkyl-S-, -C(O)C_{1-10} alkyl-C(O)-NH-, -C(O)C_{1-10} alkyl-NH-C(O)-, -C_{1-10} alkyl,

-C_{1-10}alkyl-O-, -C_{1-10}alkyl-CO_2-, -C_{1-10}alkyl-NH-, -C_{1-10}alkyl-S-, -C_{1-10}alkyl-C(O)-NH-, -C_{1-10}alkyl-NH-C(O)-, -$CH_2CH_2SO_2$-C_{1-10}alkyl-, -CH_2C(O)-C_{1-10} alkyl-, =N-(O or N)-C_{1-10}alkyl-O-, =N-(O or N)-C_{1-10}alkyl-NH-, =N-(O or N)-C_{1-10}alkyl-CO_2-, =N-(O or N)-C_{1-10}alkyl-S-, 

, or 

,

R^{21} is a PEG Capping Unit, wherein each R^{21} is independently -C_{1-10} alkyl, -C_{2-10} alkyl-CO_2H, -C_{2-10} alkyl-OH, -C_{2-10} alkyl-NH_2, C_{2-10} alkyl-NH(C_{1-3} alkyl), or C_{2-10} alkyl-N(C_{1-3} alkyl)$_2$,

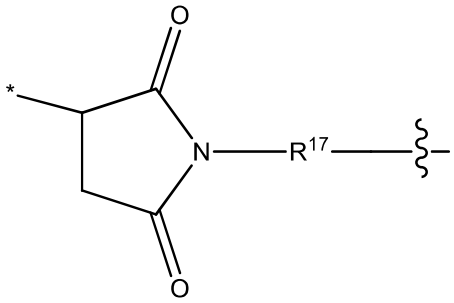
R^{22} is a PEG Coupling Unit, wherein each R^{22} is independently -C_{1-10} alkyl-C(O)-NH-, -C_{1-10} alkyl-NH-C(O)-, -C_{2-10} alkyl-NH-, -C_{2-10} alkyl-O- , -C_{1-10} alkyl-S-, or –C_{2-10} alkyl-NH-,

each n is independently an integer from 8 to 72,

e is an integer from 2 to 5,

and each n' is independently an integer from 6 to 72;

Z is a Stretcher Unit, wherein the Stretcher Unit comprises a succinimide moiety that is connected to a thiol functional group from the antibody or antigen-binding fragment thereof to form a thio-substituted succinimide moiety, or wherein the Stretcher Unit has the structure of:



,

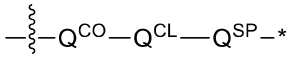
wherein the asterisk indicates covalent attachment of each Z to the Ligand Unit and wavy line adjacent to R^{17} indicates the site of covalent attachment to L^P, and

R^{17} is -C_1-C_{10} alkylene-, -C_1-C_{10} heteroalkylene-, -C_3-C_8 carbocyclo-, -O-(C_1-C_8 alkyl)-, -arylene-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_3-C_8 heterocyclo-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-,

-(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-, or -C_1-C_{10} alkylene-C(=O)-,
-C_1-C_{10} heteroalkylene-C(=O)-, -C_3-C_8 carbocyclo-C(=O)-, -O-(C_1-C_8 alkyl)-C(=O)-,
-arylene-C(=O)-, -C_1-C_{10} alkylene-arylene-C(=O)-, -arylene-C_1-C_{10} alkylene-C(=O)-,
-C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-C(=O)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-C(=O)-,
-C_3-C_8 heterocyclo-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-C(=O)-,
-(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-NH-, C_1-C_{10} heteroalkylene-NH-,
-C_3-C_8 carbocyclo-NH-, -O-(C_1-C_8 alkyl)-NH-, -arylene-NH-, -C_1-C_{10} alkylene-arylene-NH-,
-arylene-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-NH-,
-(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-NH-, -C_3-C_8 heterocyclo-NH-,
-C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-NH-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-NH-,
-C_1-C_{10} alkylene-S-, C_1-C_{10} heteroalkylene-S -, -C_3-C_8 carbocyclo-S -, -O-(C_1-C_8 alkyl)-S -,
-arylene-S-, -C_1-C_{10} alkylene-arylene-S-, -arylene-C_1-C_{10} alkylene-S-,
-C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-S-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-S-,
-C_3-C_8 heterocyclo-S-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-S- or
-(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-S-,

wherein R^{17} is optionally substituted by $-(CH_2)_xNH_2$, $-(CH_2)_xNHR^a$ or $-(CH_2)_xNR^a{}_2$, wherein subscript x is an integer selected from 1-4 and each R^a is independently C_{1-6} alkyl, or two R^a groups are combined with the nitrogen atom to which they are attached to form an azetidinyl, pyrrolidinyl or piperidinyl;

X is a Releasable Assembly Unit, wherein each Releasable Assembly Unit is capable of releasing free drug upon enzymatic cleavage of the Releasable Assembly Unit, and wherein the Releasable Assembly Unit has the formula of:



wherein Q^{CO} is an optional Covalent Attachment Unit,

Q^{SP} is an optional Spacer Unit,

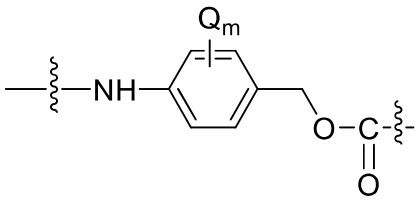
Q^{CL} is a Cleavable Unit,

the asterisk indicates the site of covalent attachment to the Drug Unit and the wavy line indicates covalent attachments to L^P or A,

wherein the Cleavable Unit is a peptide Cleavable Unit comprising an amino acid or is a peptide sequence with a cleavable bond to Q^{SP} or D, depending on the presence or absence,

respectively, or Q^{SP}, wherein said cleavable bond is capable of enzymatic cleavage by a tumor associated protease for said releasing of free drug,

wherein the Spacer Unit, when present, comprises a para-aminobenyzyl (PAB) moiety that is linked to the amino acid or peptide sequence of the peptide Cleavable Unit via the amino acid nitrogen atom of the PAB moiety, and is connected directly to the Drug Unit via a carbonate, carbamate, or ether functional group that is part of the Spacer Unit, or wherein the Spacer Unit has the formula of:



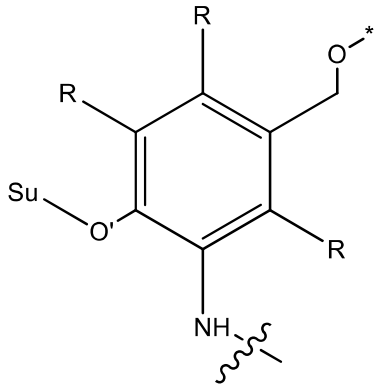
wherein Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano,

subscript m is an integer from 0 to 4, and

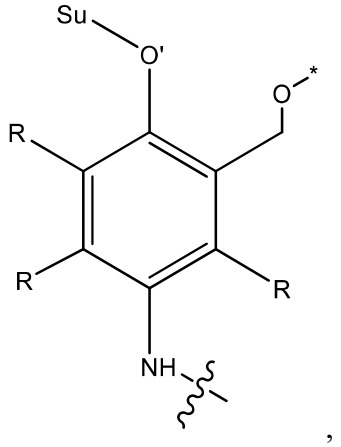
the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to the dipeptide of the peptide Cleavable Unit and the wavy line adjacent to the carbonyl indicates the site of covalent attachment to an oxygen or nitrogen atom of the Drug Unit,

or

wherein the Cleavable Unit has the formula of:



or



,

wherein Su is a sugar moiety,

-O'- is an oxygen glycosidic bond that is capable of enzymatic cleavage by a glycosidase for said free drug release,

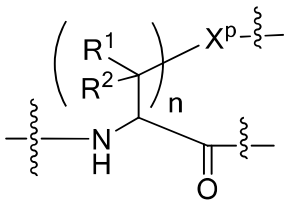
each R is independently selected from the group consisting of hydrogen, halogen, -CN, and $-NO_2$,

the wavy line indicates the site of covalent attachment to L^P or A, depending on the absence or presence of A, either directly or indirectly through the Covalent Attachment Unit, and

the asterisk indicates the site of covalent attachment to the Drug Unit, either directly or indirectly through the Spacer Unit, and

the Spacer Unit, when present, is -C(=O)-;

L^P is a Parallel Connector Unit that connects the Stretcher Unit to the hydrophobic Drug Unit(s) through intermediacy of a Releasable Assembly Unit for each Drug Unit and connects the Polyethylene Glycol in parallel orientation relative to the hydrophobic Drug Unit(s), wherein the Parallel Connector Unit or subunit thereof has the structure of:



wherein subscript n is an integer from 1 to 4,

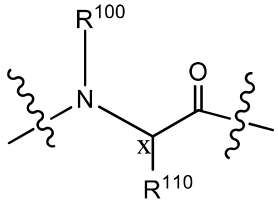
X^P is selected from the group consisting of -O-, -NH-, -S-, -S(=O)-, -C(=O)-, and $-C_2$-C_8 heterocyclo,

R^1 and R^2 are independently selected from the group consisting of -H, $-C_1$-C_3 alkyl, -phenyl and $-C_2$-C_5 heterocycle, and

the wavy lines indicate the sites of covalent attachment to the remainder of the Ligand-Drug Conjugate compound structure,

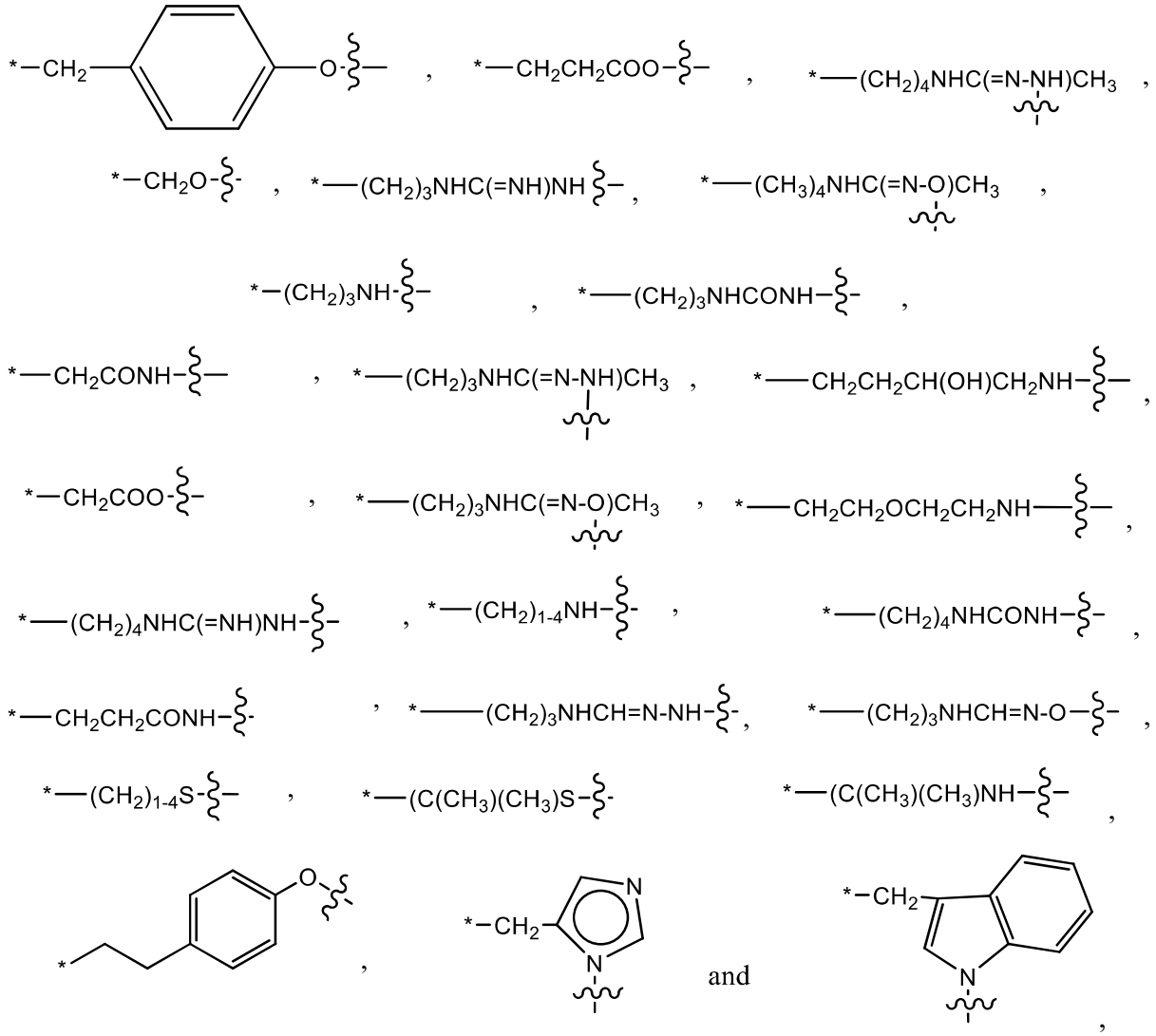
or

the Parallel Connector Unit or subunit thereof has the formula of:



wherein R^{100} is independently selected from the group consisting of -H and $-C_1$-C_3 alkyl,

R^{110} is selected from the group consisting of:



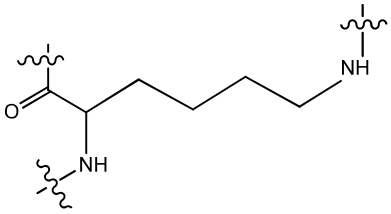
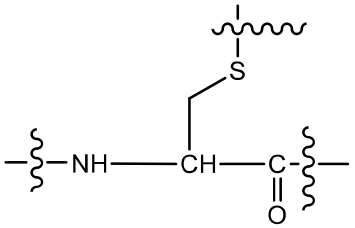
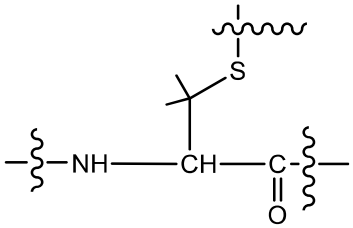
wherein the asterisk indicates the site of covalent attachment to the carbon labeled x and the wavy lines indicate the sites of covalent attachments within the Ligand-Drug Conjugate compound,

or

the Parallel Connector Unit or subunit thereof is a trifunctional amino acid residue,

or

has the structure of:



, or 
,

wherein the wavy lines indicate the sites of covalent attachment within the Ligand-Drug Conjugate compound;

A is an optional Branching Unit;

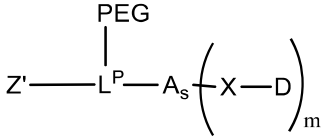
the subscript p is an integer ranging from 1 to 14;

the subscript m is an integer ranging from 1 to 4; and

the subscript s is 0 or 1,with the proviso that when s is 0, m is 1 and when s is 1, m is 2, 3 or 4.

[0034b] In yet another aspect, the present disclosure relates to a pharmaceutical composition comprising a population of Ligand-Drug Conjugate compounds, or pharmaceutically acceptable salts thereof, as described herein, and a pharmaceutically acceptable carrier, wherein the average p value of the Ligand-Drug Conjugate compounds in the composition is from 4 to 14.

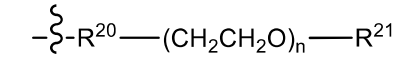
[0034c] In yet another aspect, the present disclosure relates to a Drug-Linker Compound wherein the Drug-Linker Compound is represented by the structure of formula IV:

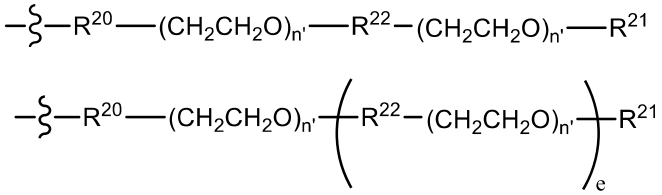

(IV)

or a pharmaceutically acceptable salt thereof, wherein

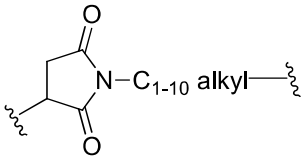
D is a hydrophobic Drug Unit, wherein the Drug Unit corresponds in structure to a hydrophobic cytotoxic, cytostatic, or immunosuppressive agent;

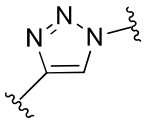
PEG is a Polyethylene Glycol Unit, wherein the PEG Unit has the formula of:




or

wherein the wavy line indicates the site of attachment of the PEG Unit to L^P,

R^{20} is a PEG Attachment Unit, wherein each R^{20} is –C(O)-, -O-, -S-, -S(O)-, -NH-, -C(O)O-, -C(O)C_{1-10} alkyl, -C(O)C_{1-10} alkyl-O-, -C(O)C_{1-10}alkyl-CO_2-, -C(O)C_{1-10} alkyl-NH-, -C(O)C_{1-10} alkyl-S-, -C(O)C_{1-10} alkyl-C(O)-NH-, -C(O)C_{1-10} alkyl-NH-C(O)-, -C_{1-10} alkyl, -C_{1-10}alkyl-O-, -C_{1-10}alkyl-CO_2-, -C_{1-10}alkyl-NH-, -C_{1-10}alkyl-S-, -C_{1-10}alkyl-C(O)-NH-, -C_{1-10}alkyl-NH-C(O)-, -$CH_2CH_2SO_2$-C_{1-10}alkyl-, -CH_2C(O)-C_{1-10} alkyl-, =N-(O or N)-C_{1-10}alkyl-O-, =N-(O or N)-C_{1-10}alkyl-NH-, =N-(O or N)-C_{1-10}alkyl-CO_2-, =N-(O or N)-C_{1-10}alkyl-S-, 

, or 

,

R^{21} is a PEG Capping Unit, wherein each R^{21} is independently -C_{1-10} alkyl, -C_{2-10} alkyl-CO_2H, -C_{2-10} alkyl-OH, -C_{2-10} alkyl-NH_2, C_{2-10} alkyl-NH(C_{1-3} alkyl), or C_{2-10} alkyl-N(C_{1-3} alkyl)$_2$,

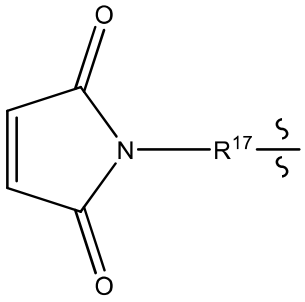
R^{22} is a PEG Coupling Unit, wherein each R^{22} is independently -C_{1-10} alkyl-C(O)-NH-, -C_{1-10} alkyl-NH-C(O)-, -C_{2-10} alkyl-NH-, -C_{2-10} alkyl-O- , -C_{1-10} alkyl-S-, or –C_{2-10} alkyl-NH-,

each n is independently an integer from 8 to 72,

e is an integer from 2 to 5,

and each n' is independently an integer from 6 to 72;

Z' is a Stretcher Unit, wherein the Stretcher Unit comprises a maleimide moiety capable of reacting with a thiol functional group from an antibody or antigen-binding fragment thereof to form a thio-substituted succinimide moiety, or wherein the Stretcher Unit has the structure of:



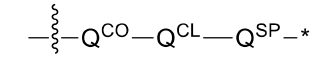
,

wherein the asterisk indicates covalent attachment of Z' to the Ligand Unit and wavy line adjacent to R^{17} indicates the site of covalent attachment to L^P, and

R^{17} is -C_1-C_{10} alkylene-, -C_1-C_{10} heteroalkylene-, -C_3-C_8 carbocyclo-, -O-(C_1-C_8 alkyl)-, -arylene-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_3-C_8 heterocyclo-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-, or -C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} heteroalkylene-C(=O)-, -C_3-C_8 carbocyclo-C(=O)-, -O-(C_1-C_8 alkyl)-C(=O)-, -arylene-C(=O)-, -C_1-C_{10} alkylene-arylene-C(=O)-, -arylene-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-C(=O)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_3-C_8 heterocyclo-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-C(=O)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-NH-, C_1-C_{10} heteroalkylene-NH-, -C_3-C_8 carbocyclo-NH-, -O-(C_1-C_8 alkyl)-NH-, -arylene-NH-, -C_1-C_{10} alkylene-arylene-NH-, -arylene-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-NH-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-NH-, -C_3-C_8 heterocyclo-NH-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-NH-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-S-, C_1-C_{10} heteroalkylene-S -, -C_3-C_8 carbocyclo-S -, -O-(C_1-C_8 alkyl)-S -, -arylene-S-, -C_1-C_{10} alkylene-arylene-S-, -arylene-C_1-C_{10} alkylene-S-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-S-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-S-, -C_3-C_8 heterocyclo-S-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-S- or -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-S-,

wherein R^{17} is optionally substituted by –$(CH_2)_xNH_2$, –$(CH_2)_xNHR^a$ or –$(CH_2)_xNR^a{}_2$, wherein subscript x is an integer selected from 1-4 and each R^a is independently $C_{1\text{-}6}$ alkyl, or two R^a groups are combined with the nitrogen atom to which they are attached to form an azetidinyl, pyrrolidinyl or piperidinyl;

X is a Releasable Assembly Unit, wherein each Releasable Assembly Unit is capable of releasing free drug upon enzymatic cleavage of the Releasable Assembly Unit, and wherein the Releasable Assembly Unit has the formula of:



wherein Q^{CO} is an optional Covalent Attachment Unit,

Q^{SP} is an optional Spacer Unit,

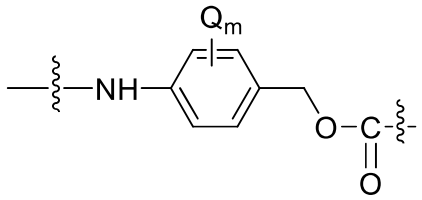
Q^{CL} is a Cleavable Unit,

the asterisk indicates the site of covalent attachment to the Drug Unit, and

the wavy line indicates covalent attachments to L^P or A,

wherein the Cleavable Unit is a peptide Cleavable Unit comprising an amino acid or is a peptide sequence with a cleavable bond to Q^{SP} or D, depending on the presence or absence, respectively, or Q^{SP}, wherein said cleavable bond is capable of enzymatic cleavage by a tumor associated protease for said releasing of free drug,

wherein the Spacer Unit, when present, comprises a para-aminobenyzyl (PAB) moiety that is linked to the amino acid or peptide sequence of the peptide Cleavable Unit via the amino acid nitrogen atom of the PAB moiety, and is connected directly to the Drug Unit via a carbonate, carbamate, or ether functional group that is part of the Spacer Unit, or wherein the Spacer Unit has the formula of:



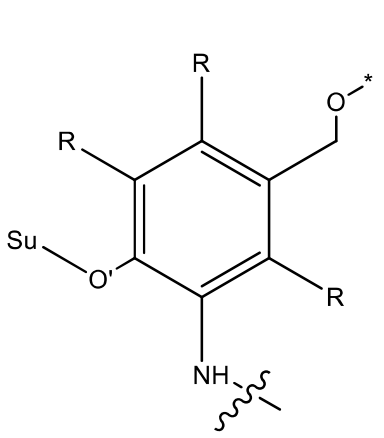
wherein Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano,

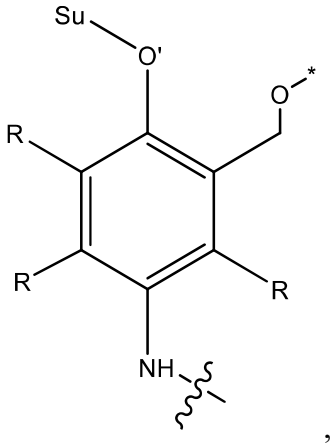
subscript m is an integer from 0 to 4, and

the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to the dipeptide of the peptide Cleavable Unit and the wavy line adjacent to the carbonyl indicates the site of covalent attachment to an oxygen or nitrogen atom of the Drug Unit,

or

wherein the Cleavable Unit has the formula of:



or


,

wherein Su is a sugar moiety,

-O'- is an oxygen glycosidic bond that is capable of enzymatic cleavage by a glycosidase for said free drug release,

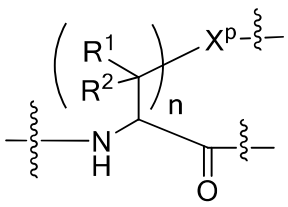
each R is independently selected from the group consisting of hydrogen, halogen, -CN, and $-NO_2$,

the wavy line indicates the site of covalent attachment to L^P or A, depending on the absence or presence of A, either directly or indirectly through the Covalent Attachment Unit, and

the asterisk indicates the site of covalent attachment to the Drug Unit, either directly or indirectly through the Spacer Unit, and

the Spacer Unit, when present, is -C(=O)-;

L^P is a Parallel Connector Unit that connects the Stretcher Unit to the hydrophobic Drug Unit(s) through intermediacy of a Releasable Assembly Unit for each Drug Unit and connects the Polyethylene Glycol in parallel orientation relative to the hydrophobic Drug Unit(s), wherein the Parallel Connector Unit or subunit thereof has the structure of:



wherein subscript n is an integer from 1 to 4,

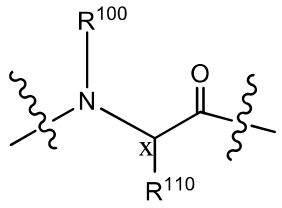
X^P is selected from the group consisting of -O-, -NH-, -S-, -S(=O)-, -C(=O)-, and $-C_2-C_8$ heterocyclo,

R^1 and R^2 are independently selected from the group consisting of -H, -C_1-C_3 alkyl, -phenyl, and -C_2-C_5 heterocycle, and

the wavy lines indicate the sites of covalent attachment to the remainder of the Ligand-Drug Conjugate compound structure,

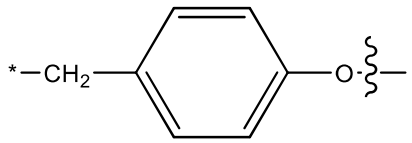
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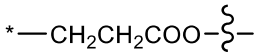
the Parallel Connector Unit or subunit thereof has the formula of:

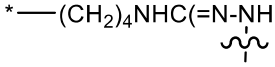


wherein R^{100} is independently selected from the group consisting of -H and -C_1-C_3 alkyl,

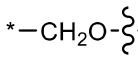
R^{110} is selected from the group consisting of:

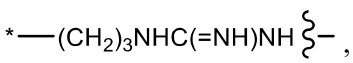


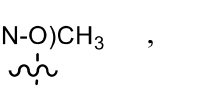
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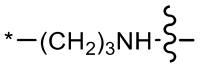
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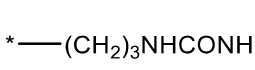


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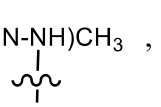
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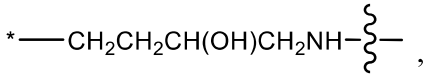


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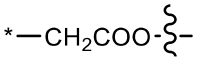
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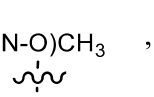


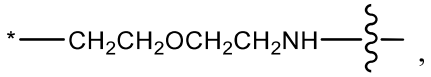
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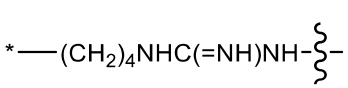
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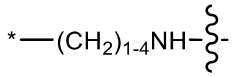


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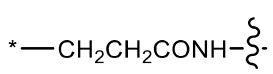
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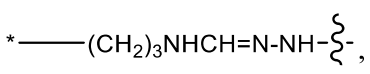


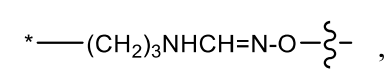
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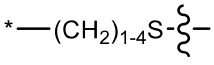

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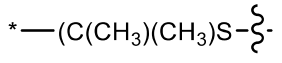


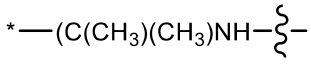
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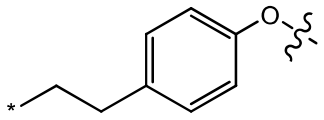
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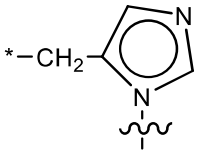


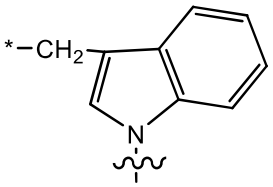
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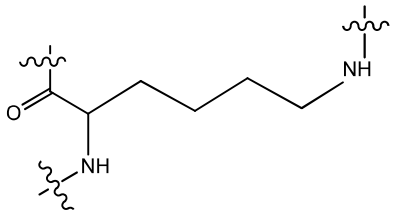
wherein the asterisk indicates the site of covalent attachment to the carbon labeled x and the wavy lines indicate the sites of covalent attachments within the Ligand-Drug Conjugate compound,

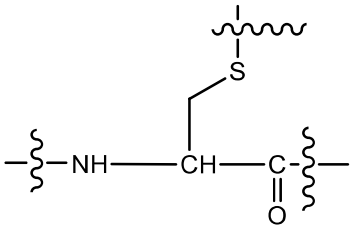
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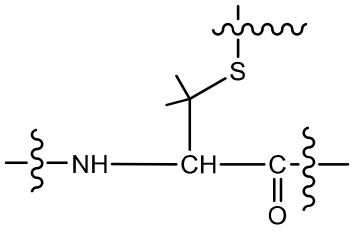
the Parallel Connector Unit or subunit thereof is a trifunctional amino acid residue,

or

has the structure of:



,


, or


,

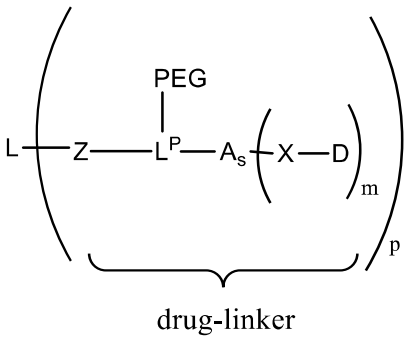
wherein the wavy lines indicate the sites of covalent attachment within the Ligand-Drug Conjugate compound;

A is an optional Branching Unit;

the subscript m is an integer ranging from 1 to 4; and

the subscript s is 0 or 1,with the proviso that when s is 0, m is 1 and when s is 1, m is 2, 3 or 4.

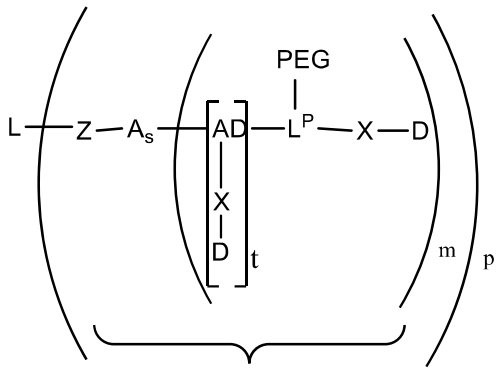
[0035] In principle examples, an LDC of the present disclosure is represented by the structure of Formula I below:



(I)

wherein D is a drug unit, PEG is the polyethylene glycol unit that masks the hydrophobicity of the drug-linker, L^p is the parallel connector unit that allows for a PEG Unit to be in a parallel orientation with respect to X-D, A is a branching unit when m is greater than 1, optionally comprised of subunits, or A is absent when m is 1, X is a Releasable Assembly unit that provides for release of each D from the LDC and Z is an optional spacer unit through which L^p is bonded to L, which is the targeting ligand.

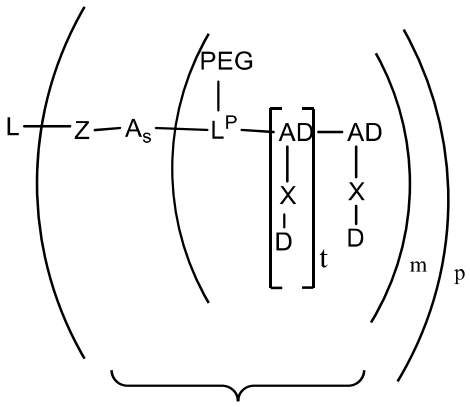
[0036] In other principle examples, an LDC of the present disclosure is represented by the structure of Formula II below:



drug-linker (II)

wherein AD is a drug attachment unit that allows for additional attachment of X-D moieties indicated by t in parallel orientation to the PEG Unit and L, L^p, Z, A, X, D, m, p and s are as defined for Formula I

[0037] In yet other principle examples an LDC of the present disclosure is represented by the structure of Formula III below:



drug-linker (III)

wherein AD, L, L^p, PEG, Z, A, X, D, m, p, s and t are as defined for Formula II.

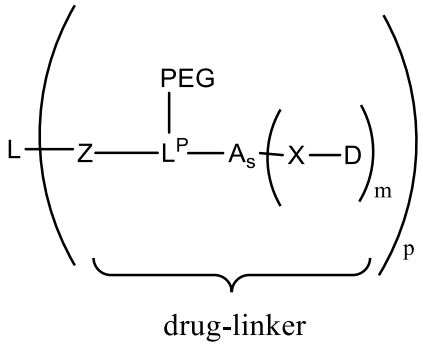
DESCRIPTION OF THE INVENTION

General

[0038] The present invention is based, in part, on the surprising discovery that the orientation of a polyethylene glycol component (PEG Unit) of a Ligand-Drug Conjugate, can have a profound influence on the resulting pharmacokinetics of the conjugate. Specifically, the present

WHAT IS CLAIMED IS:

1. A Ligand-Drug Conjugate compound of formula (I):



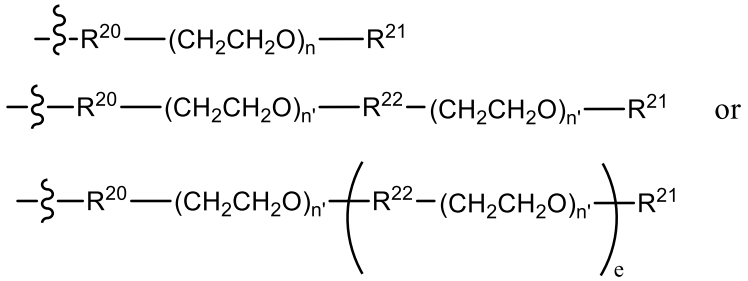
(I)

or a pharmaceutically acceptable salt thereof, wherein,

L is a Ligand Unit, wherein the Ligand Unit is an antibody or antigen-binding fragment thereof;

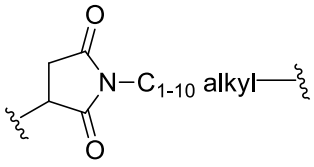
D is a hydrophobic Drug Unit, wherein the Drug Unit corresponds in structure to a hydrophobic cytotoxic, cytostatic, or immunosuppressive agent;

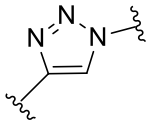
PEG is a Polyethylene Glycol Unit, wherein the PEG Unit has the formula of:



wherein the wavy line indicates the site of attachment of the PEG Unit to L^P,

R^{20} is a PEG Attachment Unit, wherein each R^{20} is –C(O)-, -O-, -S-, -S(O)-, -NH-, -C(O)O-, -C(O)C_{1-10} alkyl, -C(O)C_{1-10} alkyl-O-, -C(O)C_{1-10}alkyl-CO_2-, -C(O)C_{1-10} alkyl-NH-, -C(O)C_{1-10} alkyl-S-, -C(O)C_{1-10} alkyl-C(O)-NH-, -C(O)C_{1-10} alkyl-NH-C(O)-, -C_{1-10} alkyl, -C_{1-10}alkyl-O-, -C_{1-10}alkyl-CO_2-, -C_{1-10}alkyl-NH-, -C_{1-10}alkyl-S-, -C_{1-10}alkyl-C(O)-NH-, -C_{1-10}alkyl-NH-C(O)-, -$CH_2CH_2SO_2$-C_{1-10}alkyl-, -CH_2C(O)-C_{1-10} alkyl-,

=N-(O or N)-C_{1-10}alkyl-O-, =N-(O or N)-C_{1-10}alkyl-NH-, =N-(O or N)-C_{1-10}alkyl-CO_2-, =N-(O or N)-C_{1-10}alkyl-S-, 

, or 

,

R^{21} is a PEG Capping Unit, wherein each R^{21} is independently -C_{1-10} alkyl, -C_{2-10} alkyl-CO_2H, -C_{2-10} alkyl-OH, -C_{2-10} alkyl-NH_2, C_{2-10} alkyl-NH(C_{1-3} alkyl), or C_{2-10} alkyl-N(C_{1-3} alkyl)$_2$,

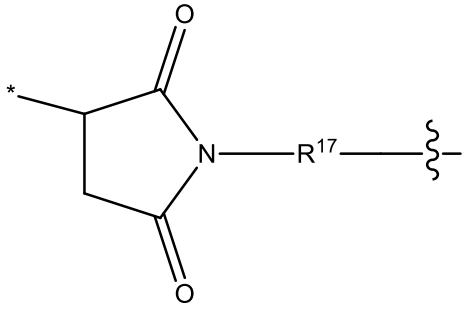
R^{22} is a PEG Coupling Unit, wherein each R^{22} is independently -C_{1-10} alkyl-C(O)-NH-, -C_{1-10} alkyl-NH-C(O)-, -C_{2-10} alkyl-NH-, -C_{2-10} alkyl-O- , -C_{1-10} alkyl-S-, or –C_{2-10} alkyl-NH-,

each n is independently an integer from 8 to 72,

e is an integer from 2 to 5,

and each n' is independently an integer from 6 to 72;

Z is a Stretcher Unit, wherein the Stretcher Unit comprises a succinimide moiety that is connected to a thiol functional group from the antibody or antigen-binding fragment thereof to form a thio-substituted succinimide moiety, or wherein the Stretcher Unit has the structure of:



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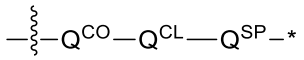
wherein the asterisk indicates covalent attachment of each Z to the Ligand Unit and wavy line adjacent to R^{17} indicates the site of covalent attachment to L^P, and

R^{17} is -C_1-C_{10} alkylene-, -C_1-C_{10} heteroalkylene-, -C_3-C_8 carbocyclo-, -O-(C_1-C_8 alkyl)-, -arylene-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_3-C_8 heterocyclo-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-, or -C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} heteroalkylene-C(=O)-, -C_3-C_8 carbocyclo-C(=O)-, -O-(C_1-C_8 alkyl)-C(=O)-, -arylene-C(=O)-, -C_1-C_{10} alkylene-arylene-C(=O)-, -arylene-C_1-C_{10} alkylene-C(=O)-,

-C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-C(=O)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_3-C_8 heterocyclo-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-C(=O)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-NH-, C_1-C_{10} heteroalkylene-NH-, -C_3-C_8 carbocyclo-NH-, -O-(C_1-C_8 alkyl)-NH-, -arylene-NH-, -C_1-C_{10} alkylene-arylene-NH-, -arylene-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-NH-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-NH-, -C_3-C_8 heterocyclo-NH-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-NH-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-S-, C_1-C_{10} heteroalkylene-S -, -C_3-C_8 carbocyclo-S -, -O-(C_1-C_8 alkyl)-S -, -arylene-S-, -C_1-C_{10} alkylene-arylene-S-, -arylene-C_1-C_{10} alkylene-S-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-S-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-S-, -C_3-C_8 heterocyclo-S-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-S- or -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-S-,

wherein R^{17} is optionally substituted by $–(CH_2)_xNH_2$, $–(CH_2)_xNHR^a$ or $–(CH_2)_xNR^a{}_2$, wherein subscript x is an integer selected from 1-4 and each R^a is independently C_{1-6} alkyl, or two R^a groups are combined with the nitrogen atom to which they are attached to form an azetidinyl, pyrrolidinyl, or piperidinyl;

X is a Releasable Assembly Unit, wherein each Releasable Assembly Unit is capable of releasing free drug upon enzymatic cleavage of the Releasable Assembly Unit, and wherein the Releasable Assembly Unit has the formula of:



wherein Q^{CO} is an optional Covalent Attachment Unit,

Q^{SP} is an optional Spacer Unit,

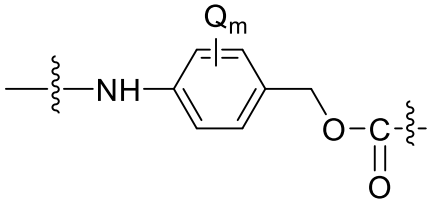
Q^{CL} is a Cleavable Unit,

the asterisk indicates the site of covalent attachment to the Drug Unit and the wavy line indicates covalent attachments to L^P or A,

wherein the Cleavable Unit is a peptide Cleavable Unit comprising an amino acid or is a peptide sequence with a cleavable bond to Q^{SP} or D, depending on the presence or absence, respectively, or Q^{SP}, wherein said cleavable bond is capable of enzymatic cleavage by a tumor associated protease for said releasing of free drug,

wherein the Spacer Unit, when present, comprises a para-aminobenyzyl (PAB) moiety that is linked to the amino acid or peptide sequence of the peptide Cleavable Unit via the amino

acid nitrogen atom of the PAB moiety, and is connected directly to the Drug Unit via a carbonate, carbamate, or ether functional group that is part of the Spacer Unit, or wherein the Spacer Unit has the formula of:



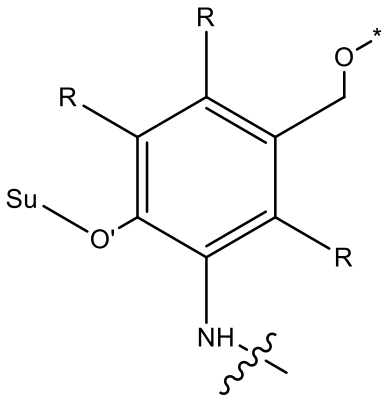
wherein Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano,

subscript m is an integer from 0 to 4, and

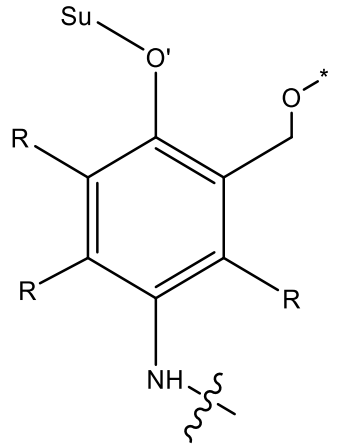
the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to the dipeptide of the peptide Cleavable Unit and the wavy line adjacent to the carbonyl indicates the site of covalent attachment to an oxygen or nitrogen atom of the Drug Unit,

or

wherein the Cleavable Unit has the formula of:



or



,

wherein Su is a sugar moiety,

-O'- is an oxygen glycosidic bond that is capable of enzymatic cleavage by a glycosidase for said free drug release,

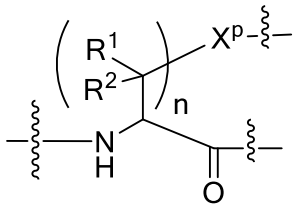
each R is independently selected from the group consisting of hydrogen, halogen, -CN, and -NO_2,

the wavy line indicates the site of covalent attachment to L^P or A, depending on the absence or presence of A, either directly or indirectly through the Covalent Attachment Unit, and

the asterisk indicates the site of covalent attachment to the Drug Unit, either directly or indirectly through the Spacer Unit, and

the Spacer Unit, when present, is -C(=O)-;

L^P is a Parallel Connector Unit that connects the Stretcher Unit to the hydrophobic Drug Unit(s) through intermediacy of a Releasable Assembly Unit for each Drug Unit and connects the Polyethylene Glycol in parallel orientation relative to the hydrophobic Drug Unit(s), wherein the Parallel Connector Unit or subunit thereof has the structure of:



wherein subscript n is an integer from 1 to 4,

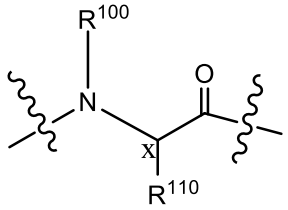
X^P is selected from the group consisting of -O-, -NH-, -S-, -S(=O)-, -C(=O)-, and -C_2-C_8 heterocyclo,

R^1 and R^2 are independently selected from the group consisting of -H, -C_1-C_3 alkyl, -phenyl and -C_2-C_5 heterocycle, and

the wavy lines indicate the sites of covalent attachment to the remainder of the Ligand-Drug Conjugate compound structure,

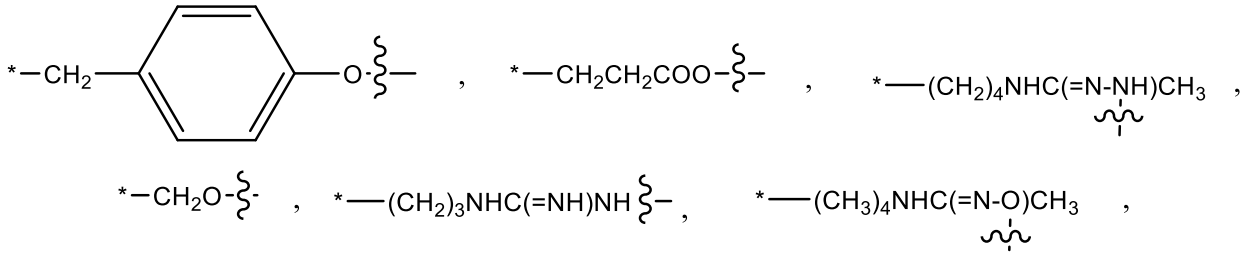
or

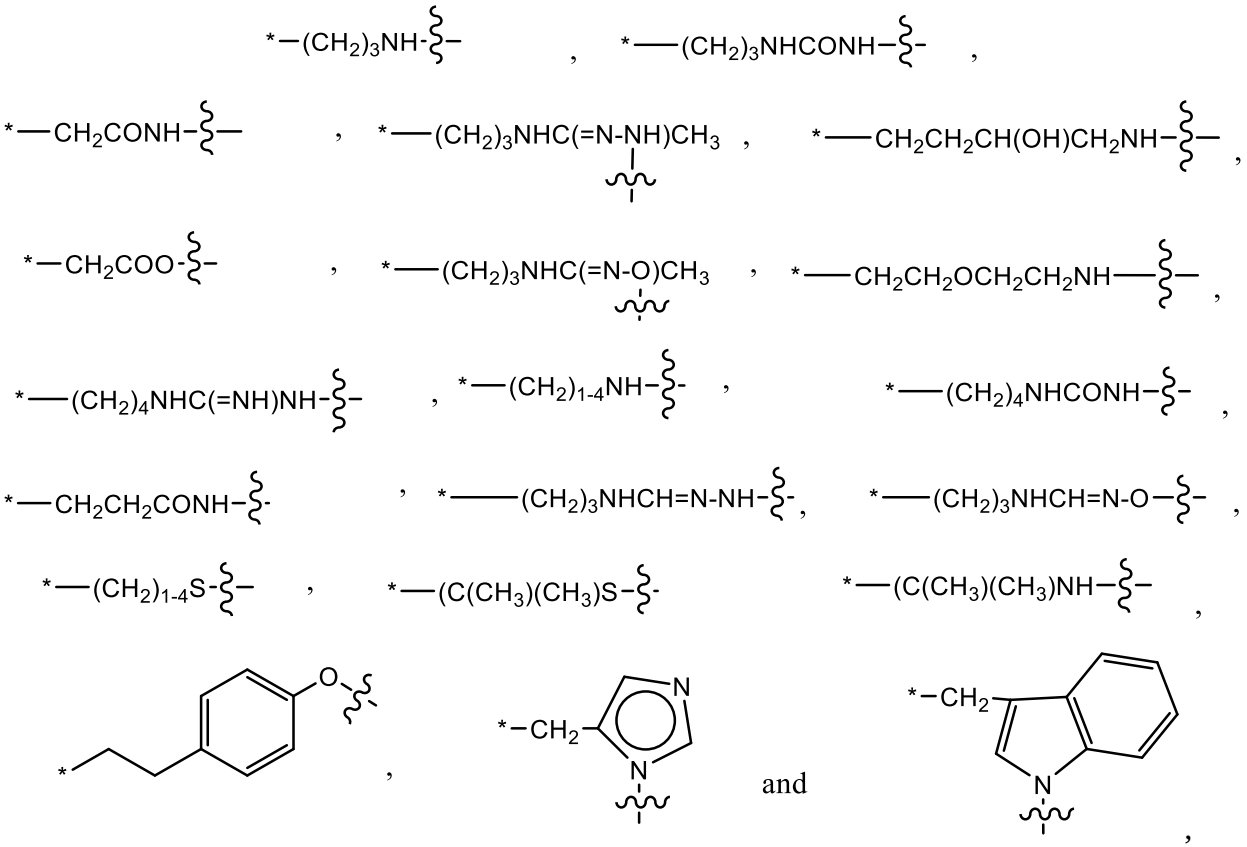
the Parallel Connector Unit or subunit thereof has the formula of:



wherein R^{100} is independently selected from the group consisting of -H and -C_1-C_3 alkyl,

R^{110} is selected from the group consisting of:





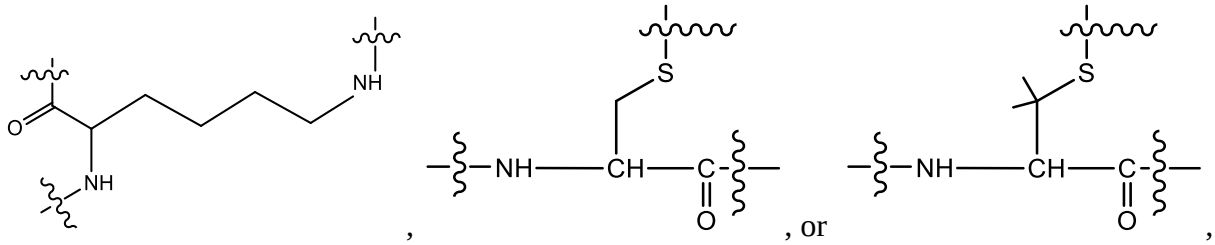
wherein the asterisk indicates the site of covalent attachment to the carbon labeled x and the wavy lines indicate the sites of covalent attachments within the Ligand-Drug Conjugate compound,

or

the Parallel Connector Unit or subunit thereof is a trifunctional amino acid residue,

or

has the structure of:



wherein the wavy lines indicate the sites of covalent attachment within the Ligand-Drug Conjugate compound;

A is an optional Branching Unit;

the subscript p is an integer ranging from 1 to 14;

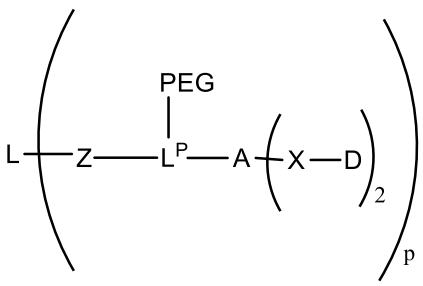
the subscript m is an integer ranging from 1 to 4; and

the subscript s is 0 or 1, with the proviso that when s is 0, m is 1 and when s is 1, m is 2, 3 or 4.

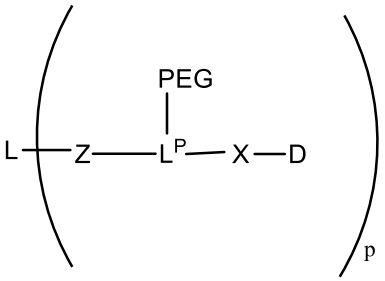
2. The Ligand-Drug Conjugate compound of claim 1, wherein the subscript s is 0.

3. The Ligand-Drug Conjugate compound of claim 2 or 3, wherein the subscript s is 1 and the subscript m is 2, 3 or 4.

4. The Ligand-Drug Conjugate compound of claim 1, wherein the Ligand-Drug Conjugate has the structure represented by formula Ia or Ib:



Ia

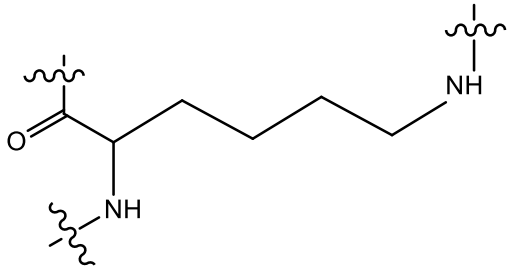


Ib

or a pharmaceutically acceptable salt thereof.

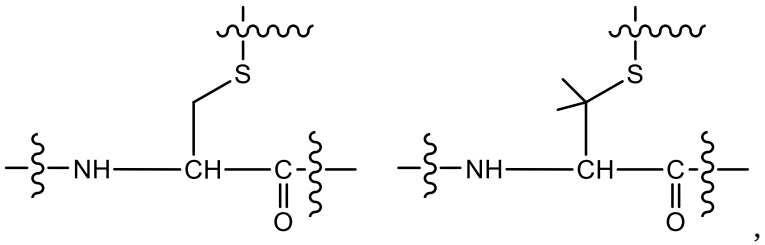
5. The Ligand-Drug Conjugate compound of any one of claims 1 to 4, wherein each Parallel Connector Unit (L^P) comprises an amino acid, amino alcohol, an amino aldehyde or a polyamine.

6. The Ligand-Drug Conjugate compound of claim 5, wherein each Parallel Connector (L^P) Unit corresponds in structure to D/L-lysine as shown in the formula below:



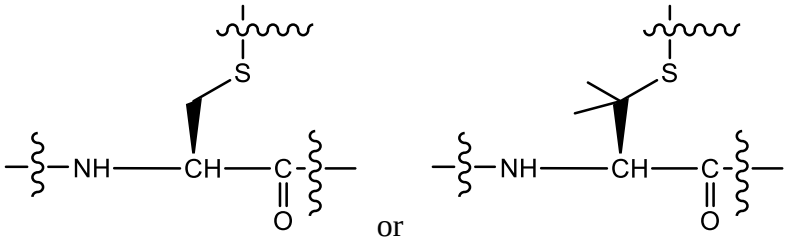
wherein the wavy lines indicates covalent attachment sites of L^P within the Ligand-Drug Conjugate.

7. The Ligand-Drug Conjugate compound of claim 6, wherein each Parallel Connector (L^P) Unit corresponds in structure to D/L-cysteine or D/L-penicillamine as shown in the formula below:



wherein the wavy lines indicates covalent attachment sites of L^P within the Ligand-Drug Conjugate.

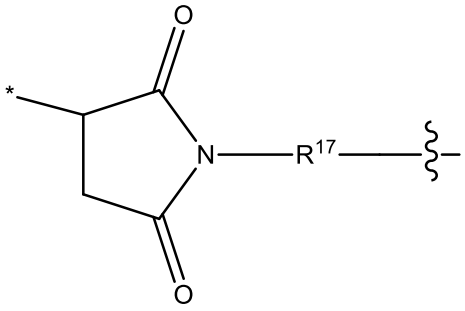
8. The Ligand-Drug Conjugate compound of claim 7, wherein each Parallel Connector (L^P) Unit has the structure of



wherein the wavy line adjacent to the sulfur atom indicates covalent attachment to a Releasable Assembly Unit.

9. The Ligand-Drug Conjugate compound of any one of claims 1 to 8, wherein when A is present, each A is one to 10 amino acids, amino alcohols or amino aldehydes or polyamines or combination thereof covalently bonded to one another.

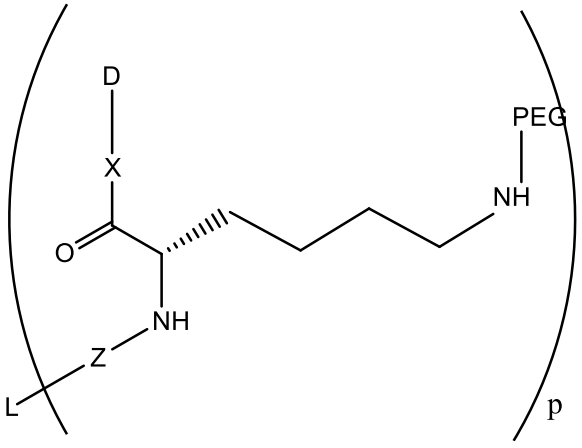
10. The Ligand-Drug Conjugate compound of any one of claims 1 to 9, wherein Z has the structure of



wherein R^{17} is $-(CH_2)_5C(=O)-$, the asterisk indicates covalent attachment of each Z to the Ligand Unit and the wavy line indicates covalent attachment of each Z to the remainder of a Linker-Drug moiety within the Ligand-Drug Conjugate.

11. The Ligand-Drug Conjugate compound of any one of claims 1 to 10, wherein the subscript p is an integer ranging from 6 to 14.

12. The Ligand-Drug Conjugate compound of claim 2, wherein the Ligand-Drug Conjugate is represented by the structure of:



or a pharmaceutically acceptable salt thereof.

13. The Ligand-Drug Conjugate compound of any one of claims 1 to 12, wherein there are from 6 to 32 or from 8 to 32 Drug Units attached to the Ligand Unit.

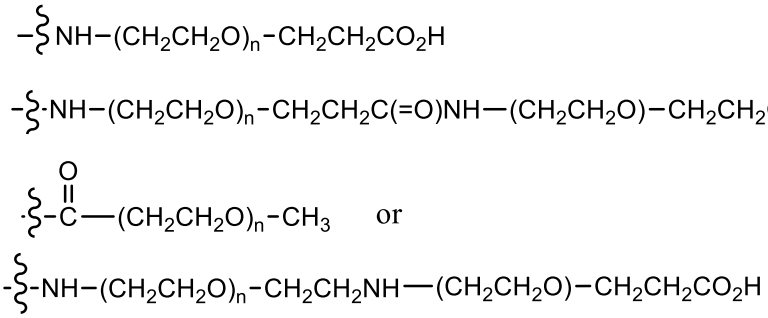
14. The Ligand-Drug Conjugate compound of any one of claims 1 to 13, wherein PEG comprises no more than 36 (OCH_2CH_2) subunits.

15. The Ligand-Drug Conjugate compound of any one of claims 1 to 13, wherein PEG comprises a combined total of from 8 to 72 subunits.

16. The Ligand-Drug Conjugate compound of any one of claims 1 to 15, wherein the PEG unit comprises one or more linear PEG chains.

17. The Ligand-Drug Conjugate compound of any one of claims 1 to 16, wherein R^{20} is -NH- or -C(O)-.

18. The Ligand-Drug Conjugate compound of any one of claims 1 to 17, wherein the PEG Unit has the structure of:



wherein the wavy line indicates site of attachment to the Parallel Connector Unit, and each n is independently selected from an integer ranging from 8 to 72.

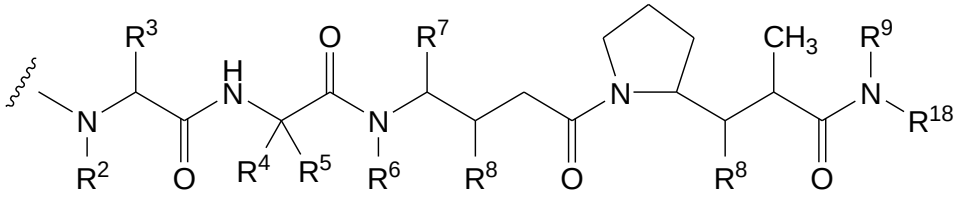
19. The Ligand-Drug Conjugate compound of claim 18, wherein n is independently selected from 8 to 36.

20. The Ligand-Drug Conjugate compound of any one of claims 1 to 19, wherein the PEG Unit has at least 8 -CH_2CH_2O- subunits and no more than 24 subunits -CH_2CH_2O-.

21. The Ligand-Drug Conjugate compound of any one of claims 1 to 20, wherein the Drug Unit is that of a drug having a SlogP value of 2.5 or greater.

22. The Ligand -Drug Conjugate compound of any one of claims 1 to 20, wherein the Drug Unit is an auristatin.

23. The Ligand -Drug Conjugate compound of claim 22, wherein the auristatin Drug Unit is represented by the structure of formula D_E:



D_E

wherein, independently at each location:

R^2 is selected from the group consisting of H and C_1-C_8 alkyl;

R^3 is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle, and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

R^4 is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle, and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

R^5 is selected from the group consisting of H and methyl;

or R^4 and R^5 jointly form a carbocyclic ring and have the formula $-(CR^aR^b)_n-$ wherein R^a and R^b are independently selected from the group consisting of H, C_1-C_8 alkyl, and C_3-C_8 carbocycle and n is selected from the group consisting of 2, 3, 4, 5, and 6;

R^6 is selected from the group consisting of H and C_1-C_8 alkyl;

R^7 is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle, and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

each R^8 is independently selected from the group consisting of H, OH, C_1-C_8 alkyl, C_3-C_8 carbocycle, and O-(C_1-C_8 alkyl);

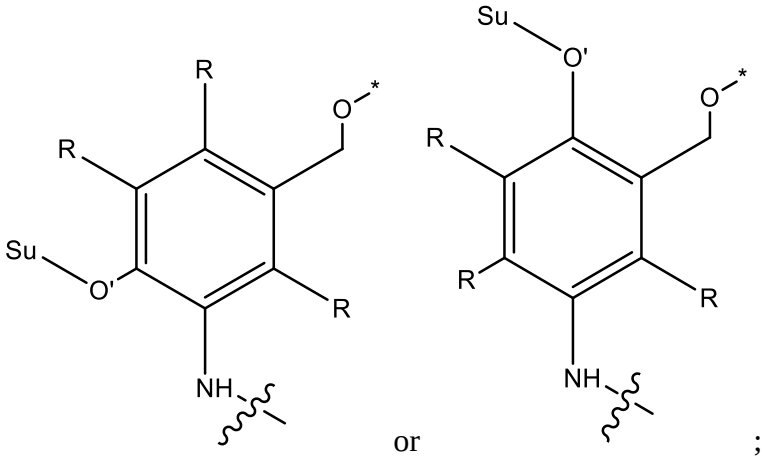
R^9 is selected from the group consisting of H and C_1-C_8 alkyl;

R^{18} is selected from the group consisting of $–C(R^8)_2–C(R^8)_2–$aryl, $–C(R^8)_2–C(R^8)_2–$(C_3-C_8 heterocycle), and $–C(R^8)_2–C(R^8)_2–$(C_3-C_8 carbocycle).

24. The Ligand -Drug Conjugate compound of any one of claims 1 to 23, wherein the Releasable Assembly Unit comprises a sugar moiety linked to a self-immolative group via a glycosidic bond to which the drug unit is bonded so that cleavage of the glycosidic bond by a

glycosidase at the site targeted by the Ligand results in release of free drug from the Ligand-Drug Conjugate.

25. The Ligand -Drug Conjugate compound of claim 24, wherein the Releasable Assembly Unit comprises a glucuronide unit and is represented by the formula:

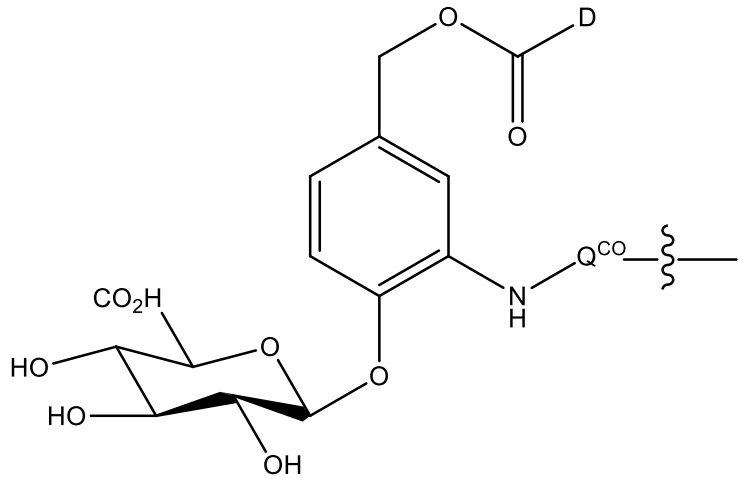


;

wherein Su is the glucuronide moiety, -O'- represents an oxygen glycosidic bond; each R is independently hydrogen, a halogen, -CN, or -NO_2; and wherein the wavy line indicates attachment of the self-immolative group to L^P, AD or A (either directly or indirectly through a Covalent Attachment Unit) and the asterisk indicates attachment of the self-immolative group to the Drug Unit (either directly or indirectly via a Spacer Unit).

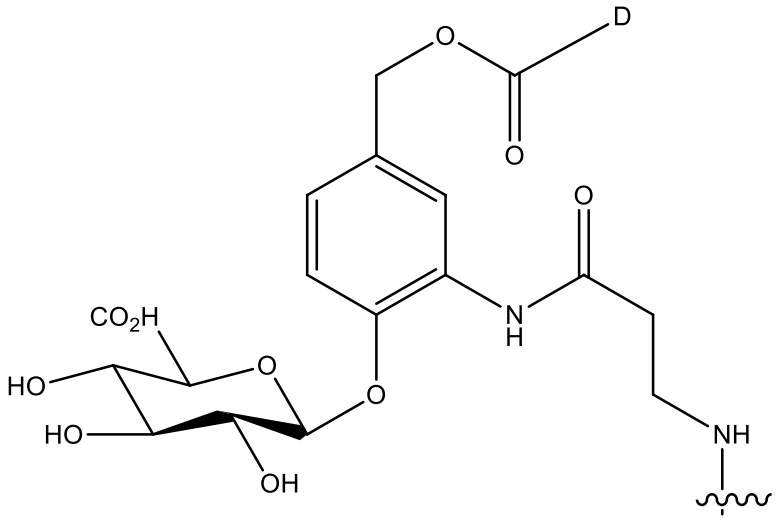
26. The Ligand-Drug Conjugate compound of any one of claims 1 to 23, wherein the Releasable Assembly Unit comprises a peptide cleavable by cathepsin B.

27. The Ligand-Drug Conjugate compound of any one of claims 1 to 25, wherein –X-D has the structure of:



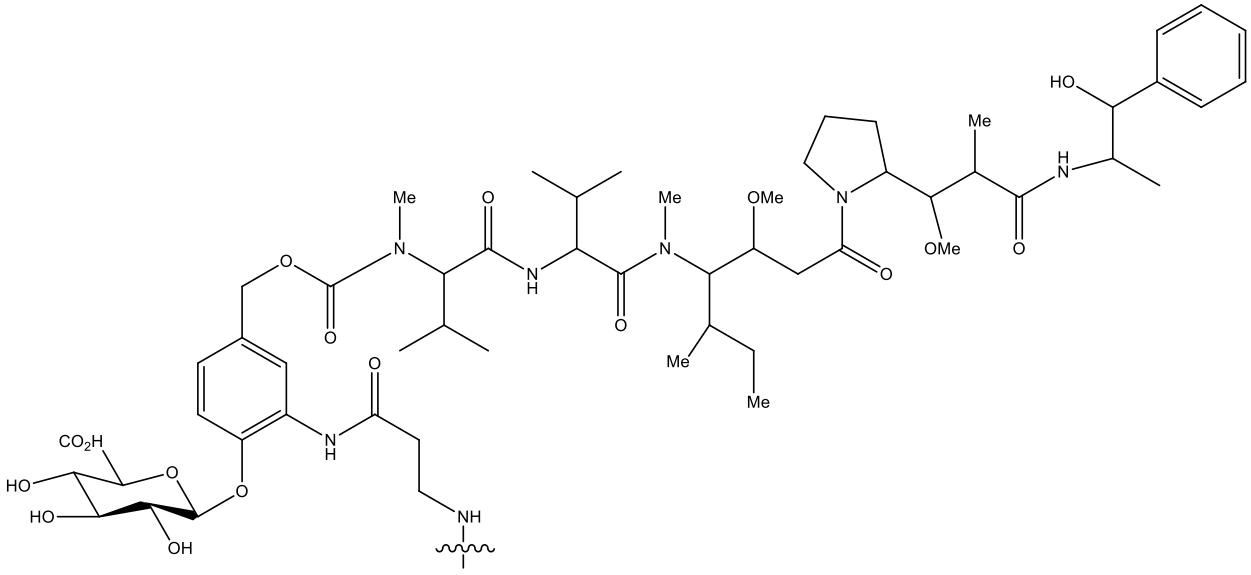
wherein Q^{CO} is an optional Covalent Attachment Unit and the wavy line indicates covalent attachment to the remainder of a Drug Linker moiety of the Ligand-Drug Conjugate.

28. The Ligand -Drug Conjugate compound of claim 27, wherein –X-D is

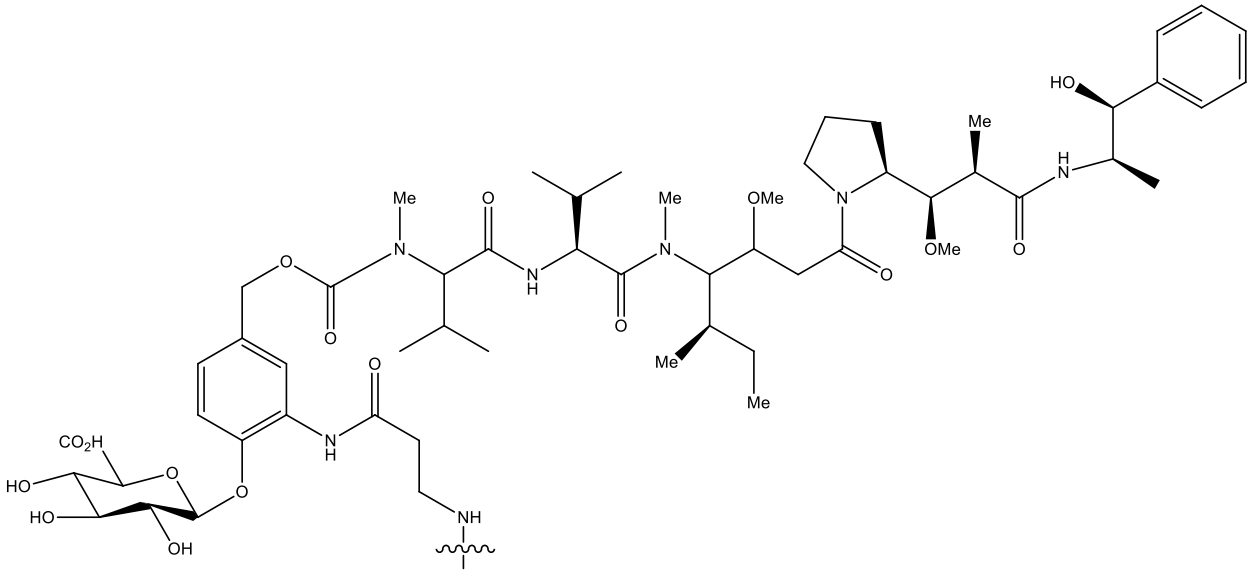


wherein the wavy line indicates covalent to the remainder of a Drug Linker moiety of the Ligand-Drug Conjugate.

29. The Ligand-Drug Conjugate compound of any one of claims 1 to 28, wherein –X-D has the structure of:



or



wherein the wavy line indicates covalent attachment to the to the remainder of a Drug Linker moiety of the Ligand-Drug Conjugate.

30. The Ligand-Drug Conjugate compound of any one of claims 1 to 29, wherein the Ligand Unit is a monoclonal antibody.

31. The Ligand-Drug Conjugate compound of any one of claims 1 to 30, wherein the Ligand is an antibody and the antibody is conjugated to each Stretcher Unit (Z) via a sulfur atom of a cysteine residue of the antibody.

32. The Ligand-Drug Conjugate compound of claim 31, wherein the cysteine residue is naturally occurring and is from an interchain disulfide.

33. The Ligand-Drug Conjugate compound of claim 31, wherein the cysteine residue is non-naturally occurring and is from a cysteine introduced into the antibody.

34. The Ligand-Drug Conjugate compound of claim 33, wherein the introduced cysteine is at residue 239 according to the EU index.

35. The Ligand-Drug Conjugate compound of any one of claims 1 to 34, wherein there are 6 to 14 Drug Units attached to the Ligand Unit.

36. The Ligand-Drug Conjugate compound of any one of claims 1 to 35, wherein the Ligand Unit is an antibody, the subscript p is 8, and the antibody is conjugated to Stretcher Units (Z) through the sulfur atoms of the interchain disulfides of the antibody.

37. The Ligand-Drug Conjugate compound of any one of claims 1 to 35, wherein the Ligand is an antibody, the subscript p is an integer ranging from 10 to 14 or 10 to 12, and the antibody is conjugated to each Stretcher Unit both through sulfur atoms from the interchain disulfides of the antibody and cysteine residues introduced into the antibody.

38. The Ligand-Drug Conjugate compound of claim 37, wherein the cysteine residue is at position 239 according to the EU index.

39. The Ligand-Drug Conjugate compound of any one of claims 1 to 38, wherein the Ligand Unit has a molecular weight of at least about 80 Kd.

40. The Ligand Drug Conjugate compound of any of claims 1 to 39, wherein the Parallel Connector Unit has (a) a mass of no more than about 500 daltons, preferably no more than about 200 daltons.

41. The Ligand Drug Conjugate compound of any of claims 1 to 40, wherein the Stretcher Unit has a mass of no more than about 1000 daltons, preferably no more than about 200 daltons.

42. The Ligand-Drug Conjugate compound of any one claims 1 to 41, wherein when the Branching Unit is present, the Branching Unit has a mass of no more than about 1000 daltons, preferably no more than about 500 daltons.

43. The Ligand-Drug Conjugate compound of any one of claims 1 to 42, wherein the Releasable Assembly Unit has a mass of no more than about 5000 daltons, preferably a mass of from 100 daltons, or from 200 daltons, or from 300 daltons to 1000 daltons.

44. The Ligand-Drug Conjugate compound of any one of claims 1 to 43, wherein, apart from the PEG Unit, there are no more than 4 other polyethylene glycol subunits present in the Ligand-Drug Conjugate.

45. The Ligand-Drug Conjugate compound of any one of claims 1 to 44, wherein there are no more than 50 intervening atoms between the Ligand Unit and the Drug Unit.

46. The Ligand-Drug Conjugate compound of any one of claims 1 to 45, wherein there are no more than 40, no more than 35, no more than 30, or no more than 25 intervening atoms between the Ligand Unit and the Cleavable Unit of the Releasable Assembly Unit.

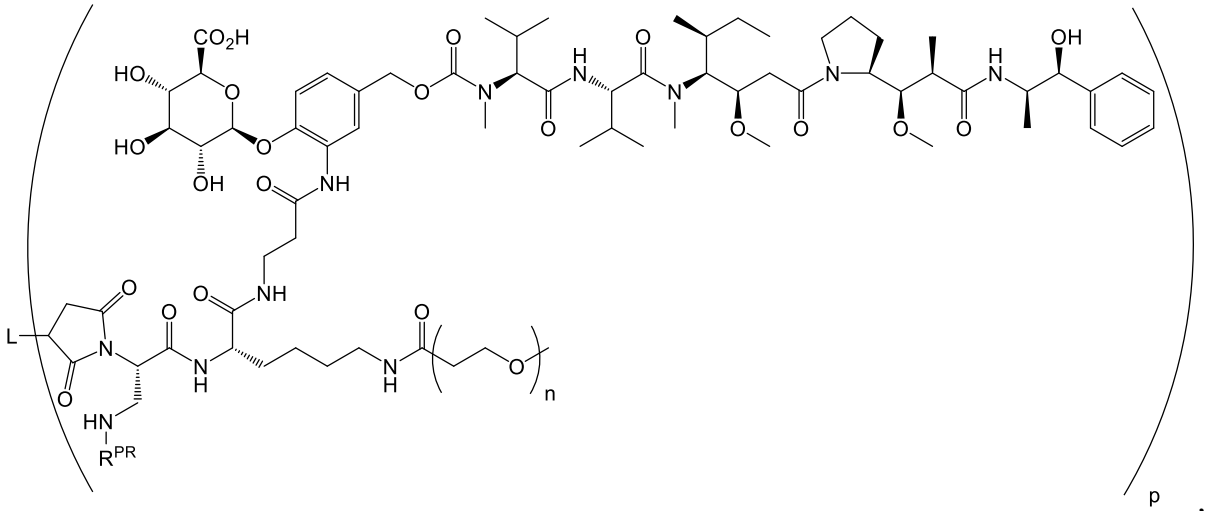
47. The Ligand-Drug Conjugate compound of any one of claims 1 to 46, wherein there are fewer intervening atoms between the Ligand and the Drug Unit than there are atoms in the PEG Unit.

48. The Ligand-Drug Conjugate compound of any one of claims 1 to 47, wherein there are fewer intervening atoms between the Ligand and the Cleavable Unit of the Releasable Assembly Unit than there are atoms in the PEG Unit.

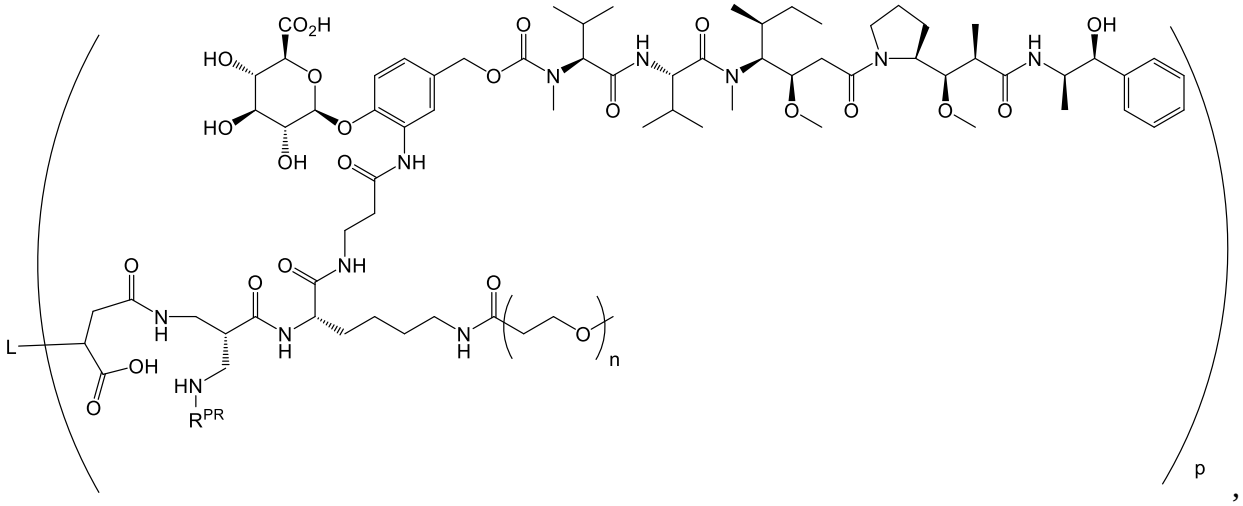
49. The Ligand-Drug Conjugate compound of any one of claims 1 to 48, wherein there are fewer intervening atoms between the Ligand and the Drug Unit than there are intervening atoms between the distal end of the PEG Unit and the Parallel Connector Unit.

50. The Ligand-Drug Conjugate compound of any one of claims 1 to 49, wherein there are fewer intervening atoms between the Ligand and the Cleavable Unit of the Releasable Assembly Unit than there are intervening atoms between the distal end of the PEG Unit and the Parallel Connector Unit.

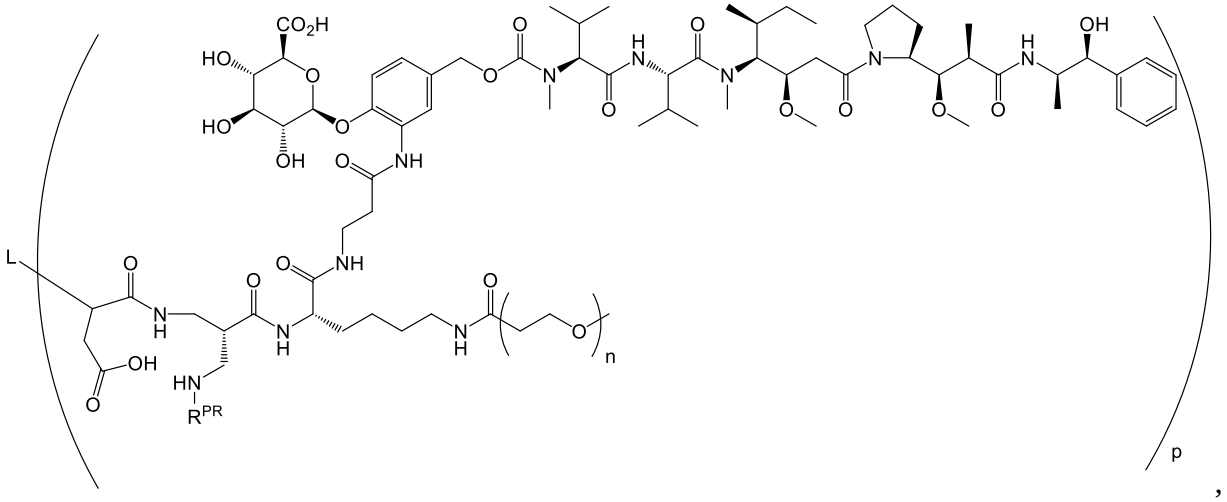
51. The Ligand-Drug Conjugate compound of claim 1, wherein the compound has the structure of:



,



,

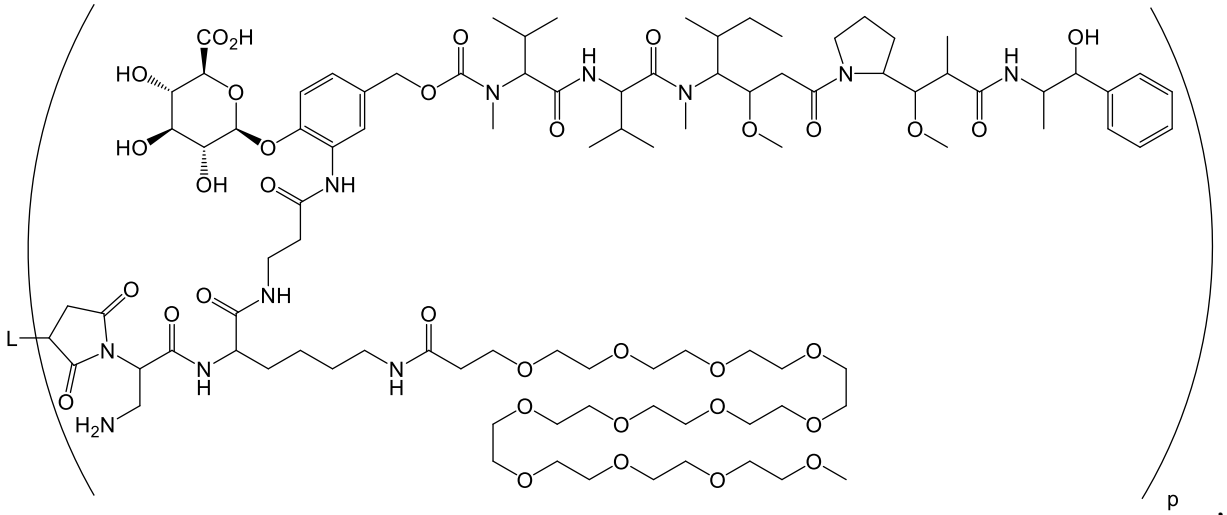


or a pharmaceutically acceptable salt thereof, wherein

R^{PR} is hydrogen or a protecting group; and

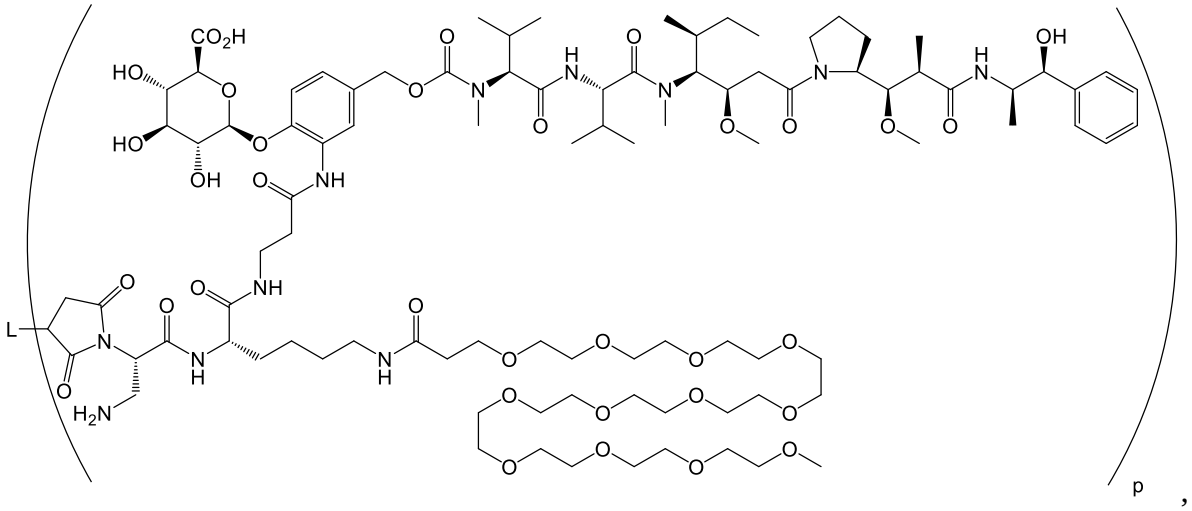
subscript n is 8, 10, 12, or 24.

52. The Ligand-Drug Conjugate compound of claim 1, wherein the compound has the structure of:



or a pharmaceutically acceptable salt thereof.

53. The Ligand-Drug Conjugate compound of claim 1, wherein the compound has the structure of:



or a pharmaceutically acceptable salt thereof.

54. A pharmaceutical composition comprising a population of Ligand-Drug Conjugate compounds, or pharmaceutically acceptable salts thereof, of any one of claims 1 to 53, and a pharmaceutically acceptable carrier, wherein the average p value of the Ligand-Drug Conjugate compounds in the composition is from 4 to 14.

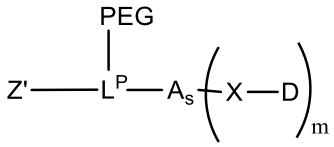
55. The pharmaceutical composition of claim 54, wherein the average p value of the Ligand-Drug Conjugate compounds in the compositions is from 6 to 14.

56. The pharmaceutical composition of claim 54, wherein the average p value of the Ligand-Drug Conjugate compounds in the compositions is from 8 to 14.

57. The pharmaceutical composition of claim 54, wherein the average p value of the Ligand-Drug Conjugate compounds in the compositions is from 8 to 12.

58. The pharmaceutical composition of claim 56, wherein the average p value of the Ligand-Drug Conjugate compounds in the composition is about 8.

59. A Drug-Linker Compound wherein the Drug-Linker Compound is represented by the structure of formula IV:

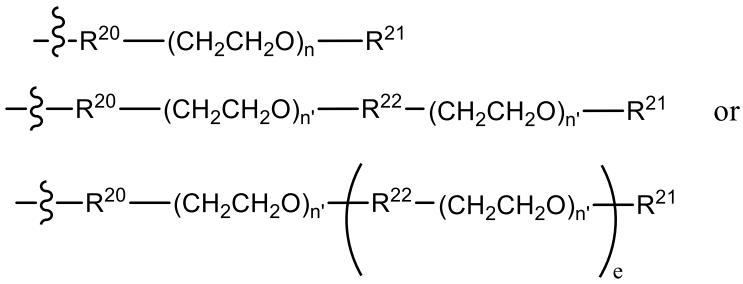


(IV)

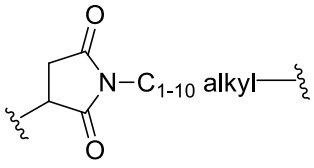
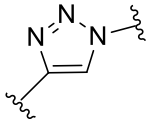
or a pharmaceutically acceptable salt thereof, wherein

D is a hydrophobic Drug Unit, wherein the Drug Unit corresponds in structure to a hydrophobic cytotoxic, cytostatic, or immunosuppressive agent;

PEG is a Polyethylene Glycol Unit, wherein the PEG Unit has the formula of:



wherein the wavy line indicates the site of attachment of the PEG Unit to L^P,

R^{20} is a PEG Attachment Unit, wherein each R^{20} is –C(O)-, -O-, -S-, -S(O)-, -NH-, -C(O)O-, -C(O)C_{1-10} alkyl, -C(O)C_{1-10} alkyl-O-, -C(O)C_{1-10}alkyl-CO_2-, -C(O)C_{1-10} alkyl-NH-, -C(O)C_{1-10} alkyl-S-, -C(O)C_{1-10} alkyl-C(O)-NH-, -C(O)C_{1-10} alkyl-NH-C(O)-, -C_{1-10} alkyl, -C_{1-10}alkyl-O-, -C_{1-10}alkyl-CO_2-, -C_{1-10}alkyl-NH-, -C_{1-10}alkyl-S-, -C_{1-10}alkyl-C(O)-NH-, -C_{1-10}alkyl-NH-C(O)-, -$CH_2CH_2SO_2$-C_{1-10}alkyl-, -CH_2C(O)-C_{1-10} alkyl-, =N-(O or N)-C_{1-10}alkyl-O-, =N-(O or N)-C_{1-10}alkyl-NH-, =N-(O or N)-C_{1-10}alkyl-CO_2-, =N-(O or N)-C_{1-10}alkyl-S-,  , or  ,

R^{21} is a PEG Capping Unit, wherein each R^{21} is independently -C_{1-10} alkyl, -C_{2-10} alkyl-CO_2H, -C_{2-10} alkyl-OH, -C_{2-10} alkyl-NH_2, C_{2-10} alkyl-NH(C_{1-3} alkyl), or C_{2-10} alkyl-N(C_{1-3} alkyl)$_2$,

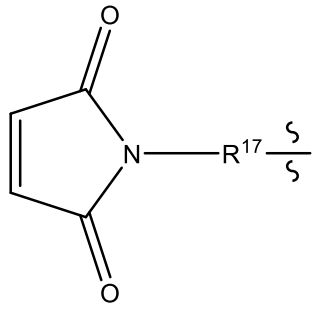
R^{22} is a PEG Coupling Unit, wherein each R^{22} is independently -C_{1-10} alkyl-C(O)-NH-, -C_{1-10} alkyl-NH-C(O)-, -C_{2-10} alkyl-NH-, -C_{2-10} alkyl-O- , -C_{1-10} alkyl-S-, or –C_{2-10} alkyl-NH-,

each n is independently an integer from 8 to 72,

e is an integer from 2 to 5,

and each n' is independently an integer from 6 to 72;

Z' is a Stretcher Unit, wherein the Stretcher Unit comprises a maleimide moiety capable of reacting with a thiol functional group from an antibody or antigen-binding fragment thereof to form a thio-substituted succinimide moiety, or wherein the Stretcher Unit has the structure of:



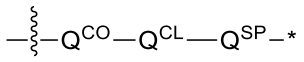
,

wherein the asterisk indicates covalent attachment of Z' to the Ligand Unit and wavy line adjacent to R^{17} indicates the site of covalent attachment to L^P, and

R^{17} is -C_1-C_{10} alkylene-, -C_1-C_{10} heteroalkylene-, -C_3-C_8 carbocyclo-, -O-(C_1-C_8 alkyl)-, -arylene-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_3-C_8 heterocyclo-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-, or -C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} heteroalkylene-C(=O)-, -C_3-C_8 carbocyclo-C(=O)-, -O-(C_1-C_8 alkyl)-C(=O)-, -arylene-C(=O)-, -C_1-C_{10} alkylene-arylene-C(=O)-, -arylene-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-C(=O)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_3-C_8 heterocyclo-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-C(=O)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-NH-, C_1-C_{10} heteroalkylene-NH-, -C_3-C_8 carbocyclo-NH-, -O-(C_1-C_8 alkyl)-NH-, -arylene-NH-, -C_1-C_{10} alkylene-arylene-NH-, -arylene-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-NH-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-NH-, -C_3-C_8 heterocyclo-NH-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-NH-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-S-, C_1-C_{10} heteroalkylene-S -, -C_3-C_8 carbocyclo-S -, -O-(C_1-C_8 alkyl)-S -, -arylene-S-, -C_1-C_{10} alkylene-arylene-S-, -arylene-C_1-C_{10} alkylene-S-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-S-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-S-, -C_3-C_8 heterocyclo-S-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-S- or -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-S-,

wherein R^{17} is optionally substituted by $–(CH_2)_xNH_2$, $–(CH_2)_xNHR^a$ or $–(CH_2)_xNR^a{}_2$, wherein subscript x is an integer selected from 1-4 and each R^a is independently C_{1-6} alkyl, or two R^a groups are combined with the nitrogen atom to which they are attached to form an azetidinyl, pyrrolidinyl or piperidinyl;

X is a Releasable Assembly Unit, wherein each Releasable Assembly Unit is capable of releasing free drug upon enzymatic cleavage of the Releasable Assembly Unit, and wherein the Releasable Assembly Unit has the formula of:



wherein Q^{CO} is an optional Covalent Attachment Unit,

Q^{SP} is an optional Spacer Unit,

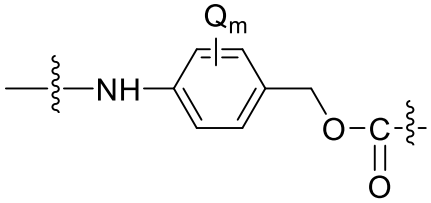
Q^{CL} is a Cleavable Unit,

the asterisk indicates the site of covalent attachment to the Drug Unit, and

the wavy line indicates covalent attachments to L^P or A,

wherein the Cleavable Unit is a peptide Cleavable Unit comprising an amino acid or is a peptide sequence with a cleavable bond to Q^{SP} or D, depending on the presence or absence, respectively, or Q^{SP}, wherein said cleavable bond is capable of enzymatic cleavage by a tumor associated protease for said releasing of free drug,

wherein the Spacer Unit, when present, comprises a para-aminobenyzyl (PAB) moiety that is linked to the amino acid or peptide sequence of the peptide Cleavable Unit via the amino acid nitrogen atom of the PAB moiety, and is connected directly to the Drug Unit via a carbonate, carbamate, or ether functional group that is part of the Spacer Unit, or wherein the Spacer Unit has the formula of:



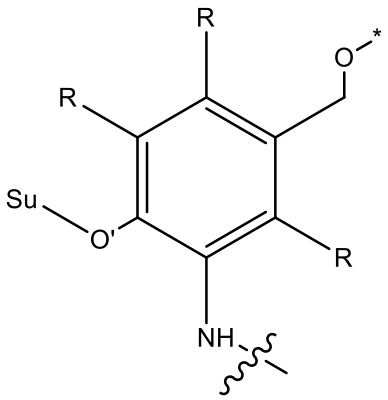
wherein Q is $-C_1$-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano,

subscript m is an integer from 0 to 4, and

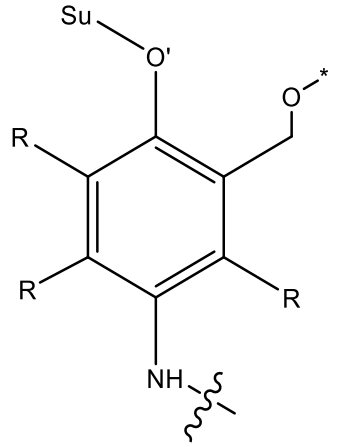
the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to the dipeptide of the peptide Cleavable Unit and the wavy line adjacent to the carbonyl indicates the site of covalent attachment to an oxygen or nitrogen atom of the Drug Unit,

or

wherein the Cleavable Unit has the formula of:



or



,

wherein Su is a sugar moiety,

-O'- is an oxygen glycosidic bond that is capable of enzymatic cleavage by a glycosidase for said free drug release,

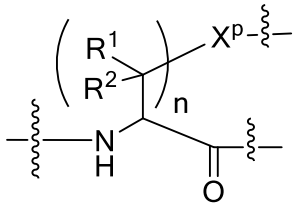
each R is independently selected from the group consisting of hydrogen, halogen, -CN, and $-NO_2$,

the wavy line indicates the site of covalent attachment to L^P or A, depending on the absence or presence of A, either directly or indirectly through the Covalent Attachment Unit, and

the asterisk indicates the site of covalent attachment to the Drug Unit, either directly or indirectly through the Spacer Unit, and

the Spacer Unit, when present, is -C(=O)-;

L^P is a Parallel Connector Unit that connects the Stretcher Unit to the hydrophobic Drug Unit(s) through intermediacy of a Releasable Assembly Unit for each Drug Unit and connects the Polyethylene Glycol in parallel orientation relative to the hydrophobic Drug Unit(s), wherein the Parallel Connector Unit or subunit thereof has the structure of:



wherein subscript n is an integer from 1 to 4,

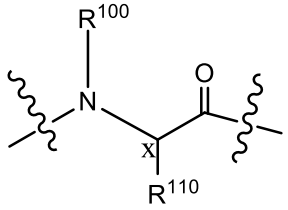
X^P is selected from the group consisting of -O-, -NH-, -S-, -S(=O)-, -C(=O)-, and -C_2-C_8 heterocyclo,

R^1 and R^2 are independently selected from the group consisting of -H, -C_1-C_3 alkyl, -phenyl, and -C_2-C_5 heterocycle, and

the wavy lines indicate the sites of covalent attachment to the remainder of the Ligand-Drug Conjugate compound structure,

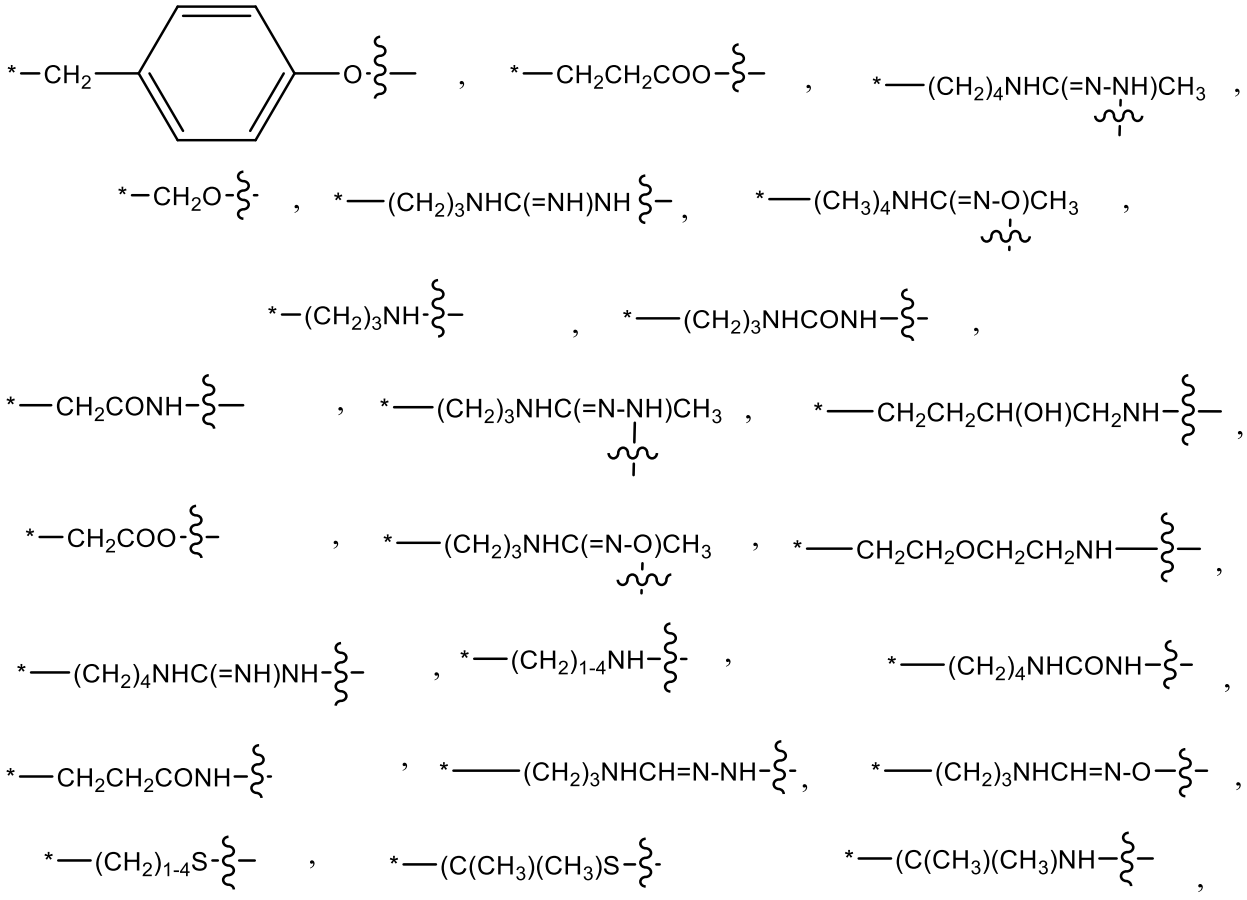
or

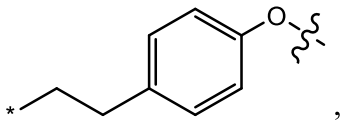
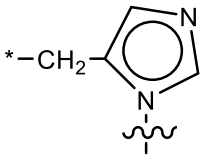
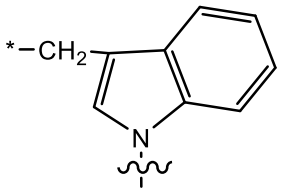
the Parallel Connector Unit or subunit thereof has the formula of:



wherein R^{100} is independently selected from the group consisting of -H and -C_1-C_3 alkyl,

R^{110} is selected from the group consisting of:




,  and ,

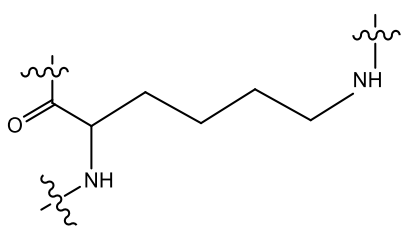
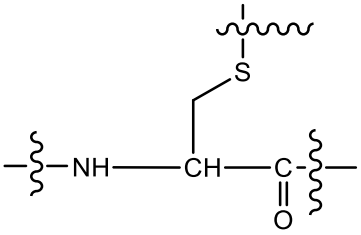
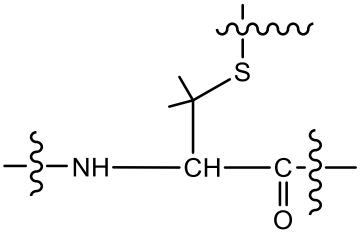
wherein the asterisk indicates the site of covalent attachment to the carbon labeled x and the wavy lines indicate the sites of covalent attachments within the Ligand-Drug Conjugate compound,

or

the Parallel Connector Unit or subunit thereof is a trifunctional amino acid residue,

or

has the structure of:


, , or ,

wherein the wavy lines indicate the sites of covalent attachment within the Ligand-Drug Conjugate compound;

A is an optional Branching Unit;

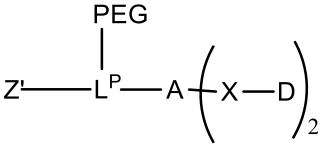
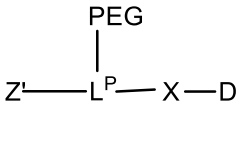
the subscript m is an integer ranging from 1 to 4; and

the subscript s is 0 or 1, with the proviso that when s is 0, m is 1 and when s is 1, m is 2, 3 or 4.

60. The Drug-Linker Compound of claim 59, wherein s is zero (i.e., A is absent).

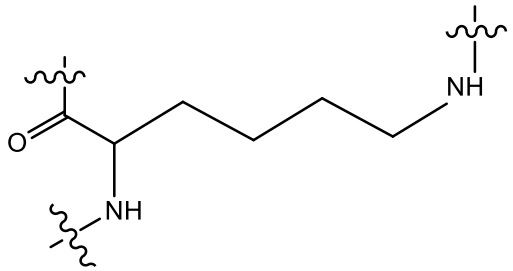
61. The Drug-Linker Compound of claim 59, wherein s is 1 and m is 2 to 4.

62. The Drug-Linker Compound of claim 59, wherein the Drug-Linker has the structure represented by formula IVa or IVb:

 IVa  IVb

or a pharmaceutically acceptable salt thereof.

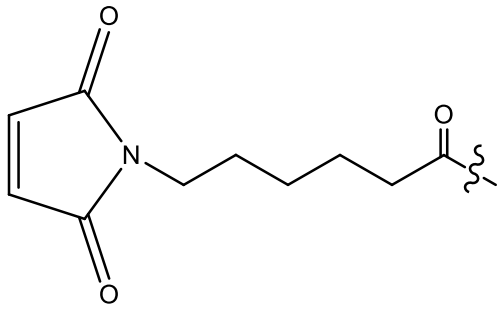
63. The Drug-Linker Compound of claim 59, wherein each L^P corresponds in structure to D/L lysine as shown in the formula below:



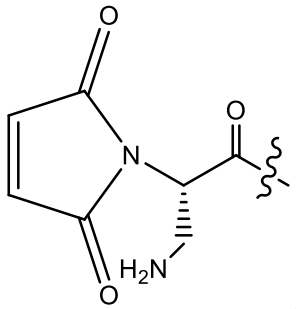
.

64. The Drug-Linker Compound of claim any one of claims 59 to 63, wherein when A is present, A is from 1 to 10 amino acids, amino alcohols, amino aldehyde, polyamines, or combinations thereof.

65. The Drug-Linker Compound of any one of claims 59 to 64, wherein Z' has the structure of

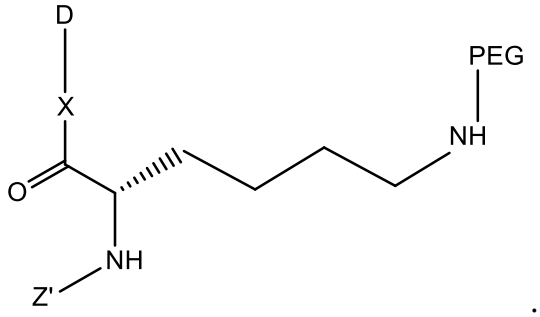


or



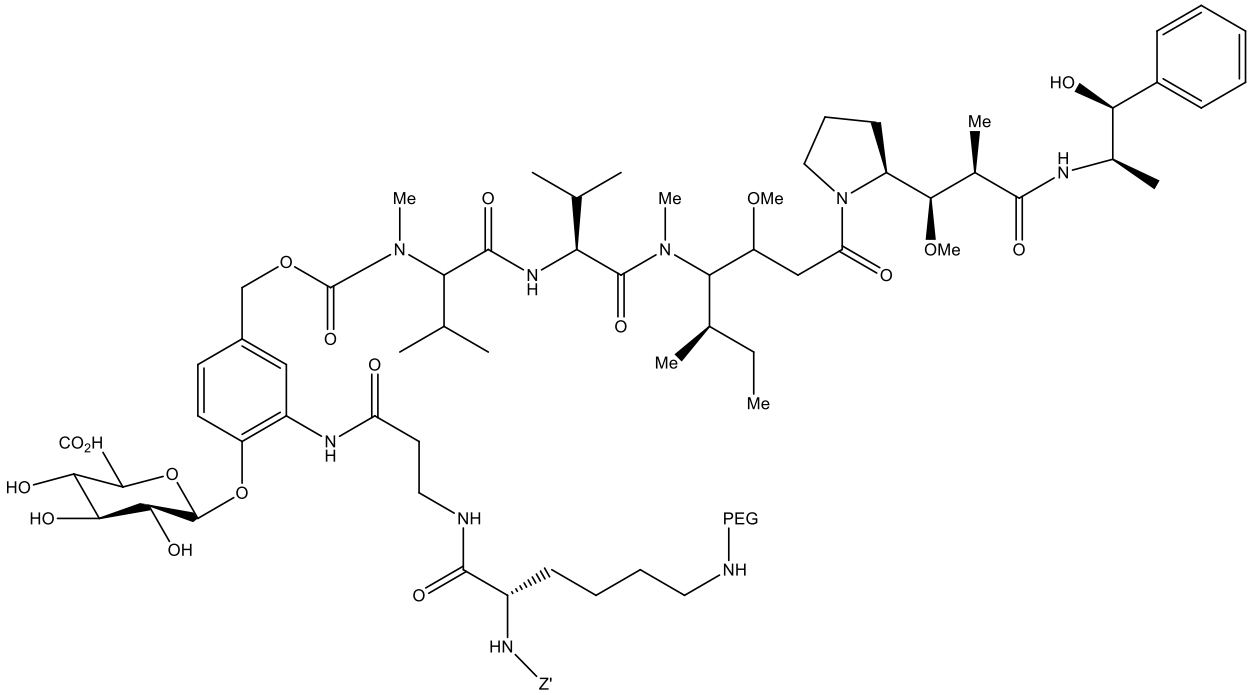
, optionally protected by an amine protecting group, wherein the wavy line indicates covalent attachment to the remainder of the Drug-Linker structure.

66. The Drug-Linker Compound of claim 59, wherein the Drug-Linker compound has the structure of:

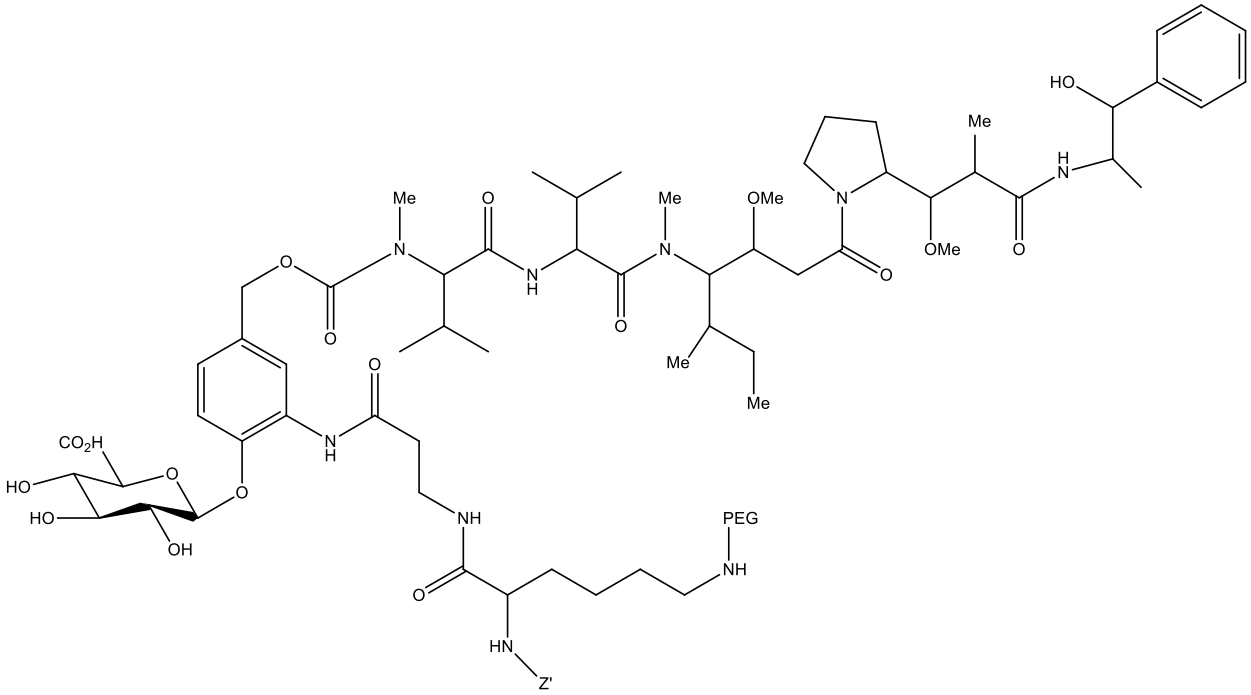


or a pharmaceutically acceptable salt thereof.

67. The Drug-Linker Compound of claim 59, wherein the Drug-Linker Compound has the structure of:

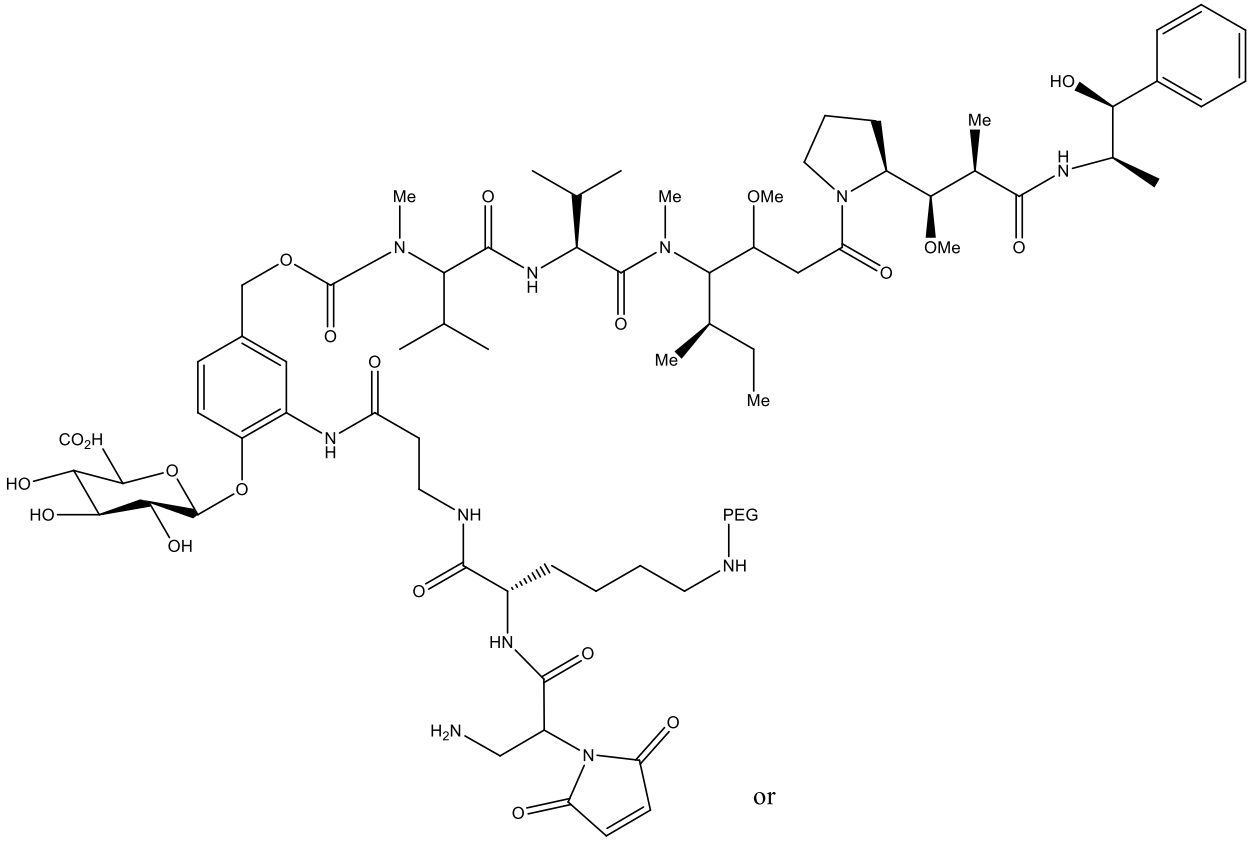


or

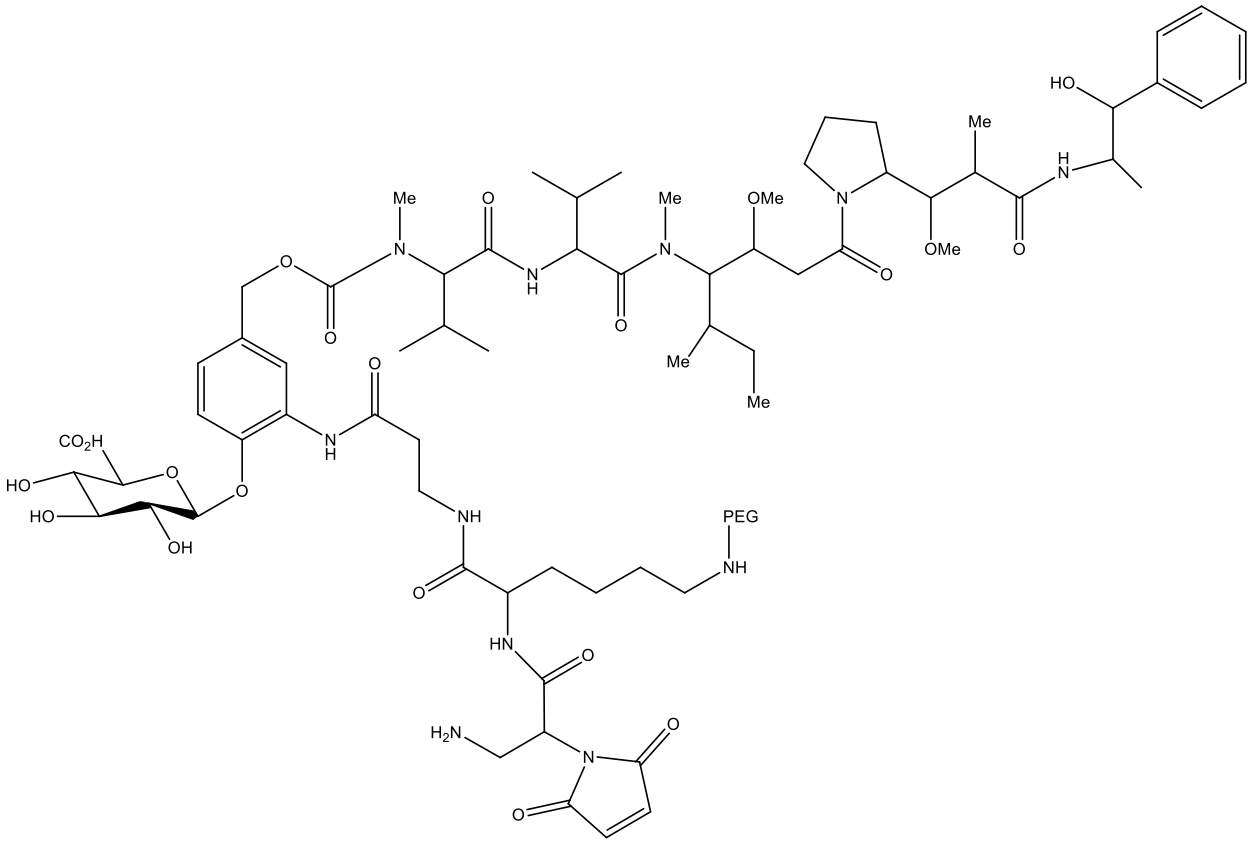


or a pharmaceutically acceptable salt thereof.

68. The Drug-Linker Compound of claim 59, wherein the Drug-Linker Compound has the structure of:

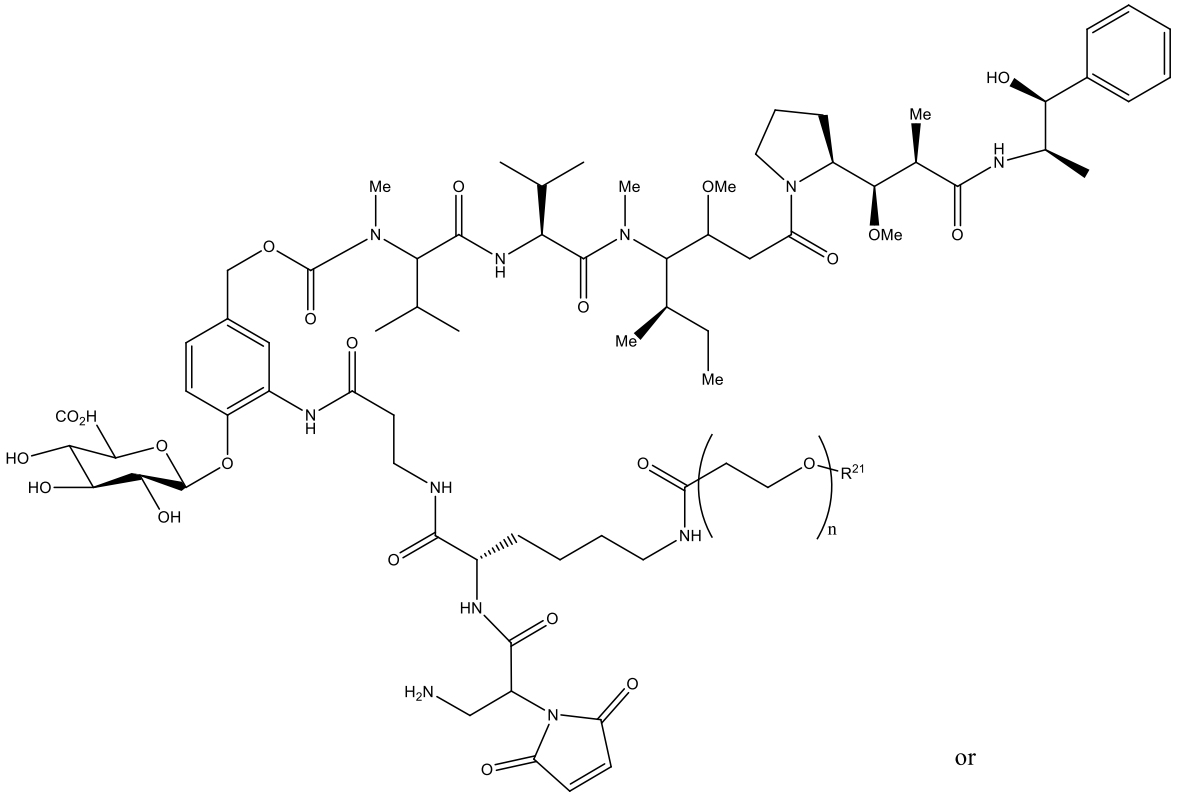


or

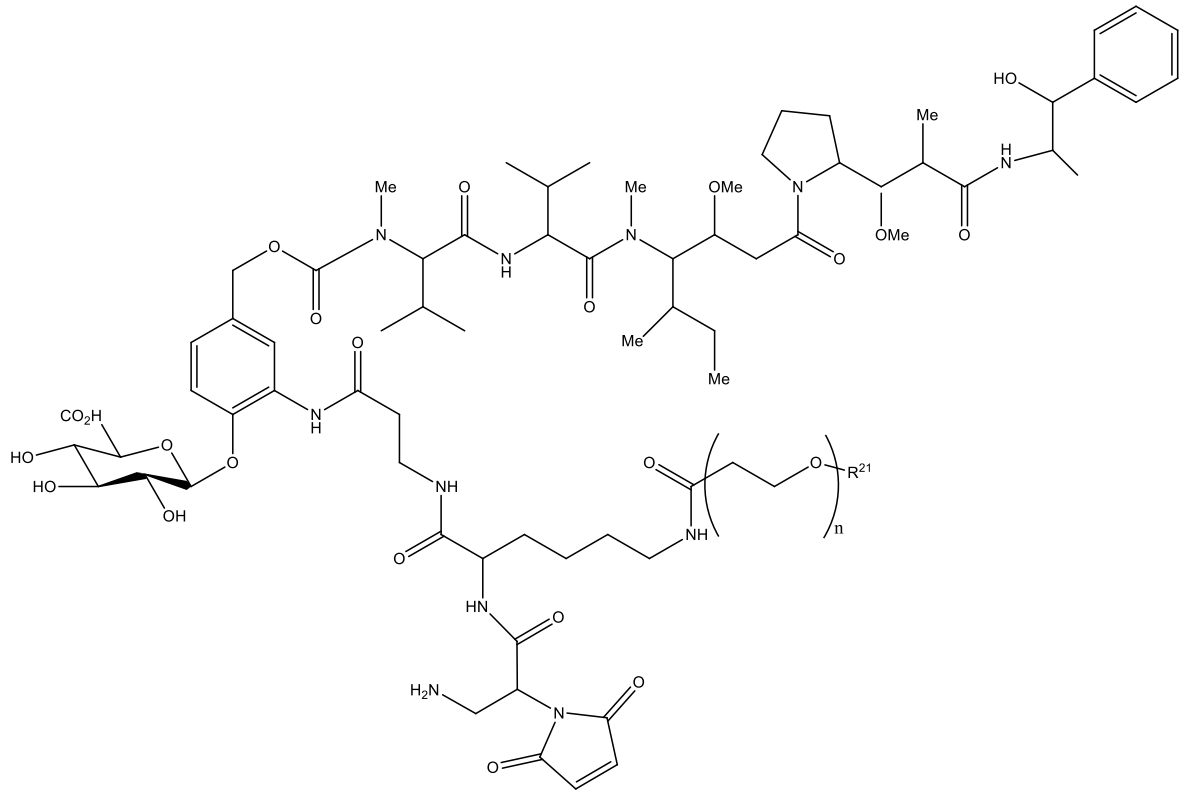


or a pharmaceutically acceptable salt thereof.

69. The Drug-Linker Compound of claim 59, wherein the Drug-Linker Compound has the structure of:

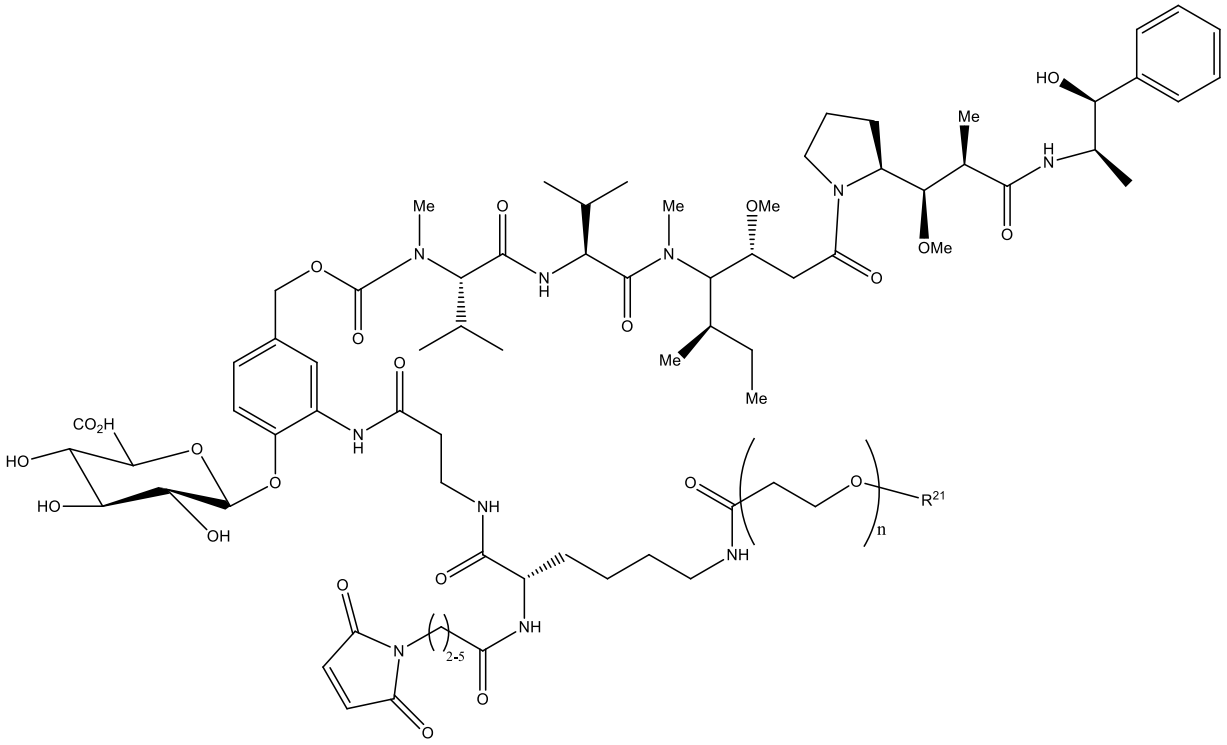


or

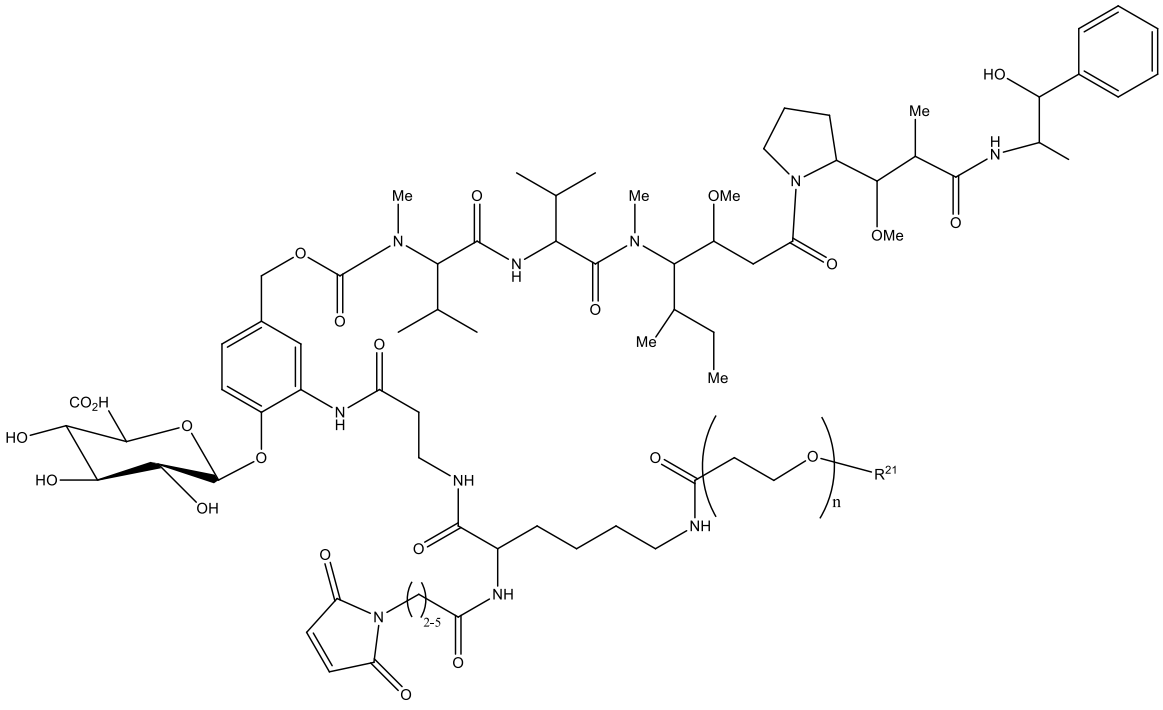


or a pharmaceutically acceptable salt thereof, wherein R^{21} is a PEG Capping Unit and n is an integer ranging from 6 to 72, 8 to 72, or 8 to 24.

70. The Drug-Linker Compound of claim 59, wherein the Drug-Linker Compound has the structure of:



or

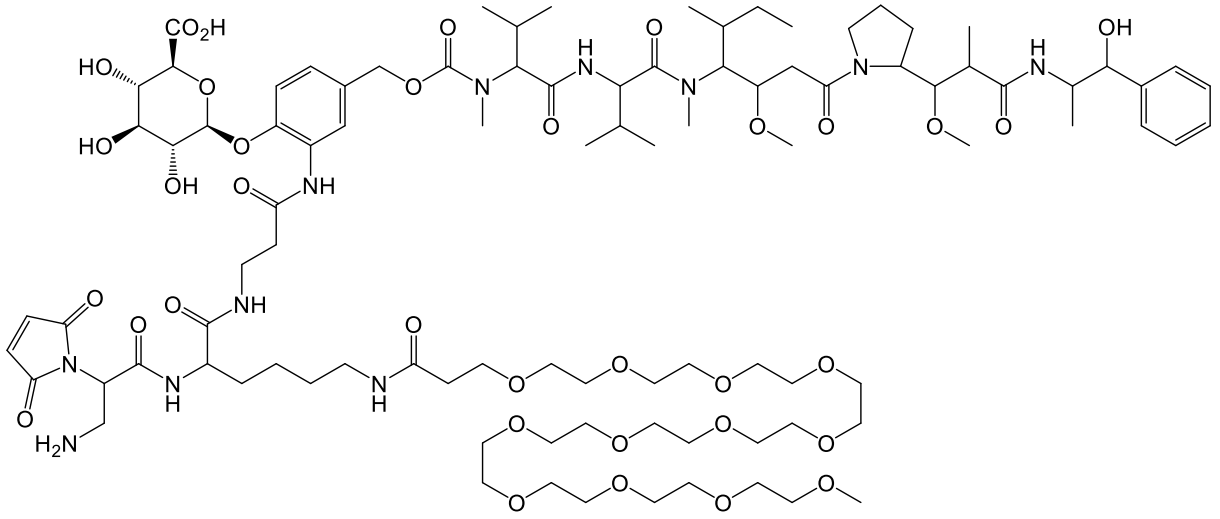


or a pharmaceutically acceptable salt thereof, wherein R^{21} is a PEG Capping Unit and n is 6 to 72.

71. The Drug-Linker Compound of claim 69 or 70, wherein n is 8, 12, or 24.

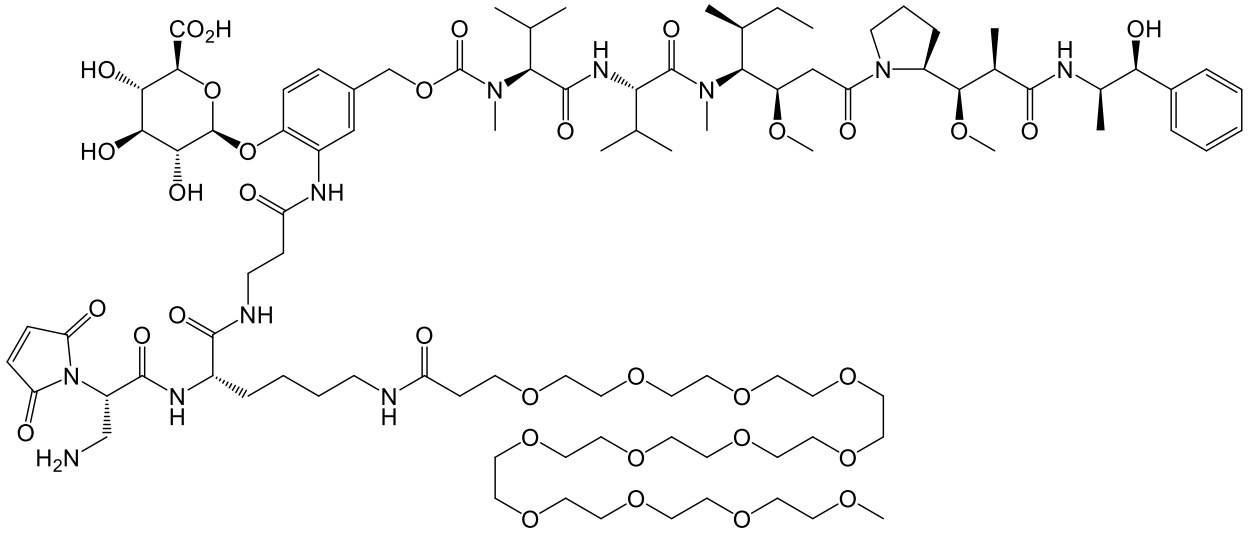
72. The Drug-Linker Compound of any one of claims 69-71, wherein R^{21} is methyl, ethyl or propyl.

73. The Drug Linker Compound of claim 59, wherein the Compound has the structure of:



or a pharmaceutically acceptable salt thereof.

74. The Drug Linker Compound of claim 59, wherein the Compound has the structure of:



or a pharmaceutically acceptable salt thereof.

75. The Ligand-Drug Conjugate compound of any one of claims 1 to 53, wherein the ligand is a monoclonal antibody that specifically binds to CD19, CD20, CD30 (preferably chimeric or humanized AC10 antibody), CD33, CD70, alpha-v-beta-6, or Liv-1 antigen.