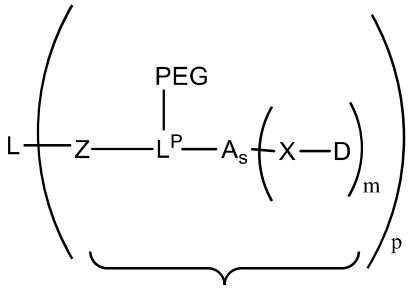
BRIEF SUMMARY ~~OF THE INVENTION~~

[0034] The ~~invention~~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):



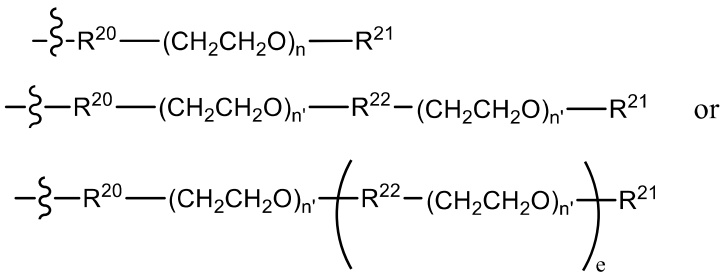
(I)

or a pharmaceutically acceptable salt thereof, wherein,

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

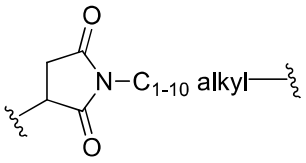
D is a hydrophobic Drug Unit, wherein the Drug Unit corresponds in structure to a hydrophobic cytotoxic, cytostatic, or immunosuppressive agent;

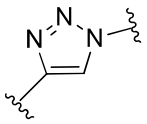
PEG is a Polyethylene Glycol Unit, wherein the PEG Unit has the formula of:



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)$_2$,

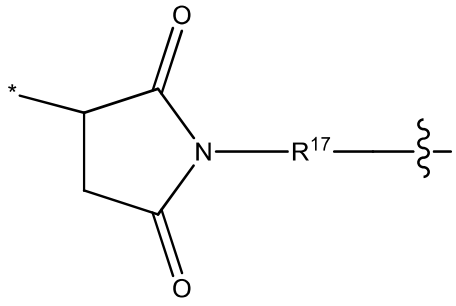
R^{22} is a PEG Coupling Unit, wherein each R^{22} is independently -C_{1-10} alkyl-C(O)-NH-, -C_{1-10} alkyl-NH-C(O)-, -C_{2-10} alkyl-NH-, -C_{2-10} alkyl-O- , -C_{1-10} alkyl-S-, or –C_{2-10} alkyl-NH-,

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:



,

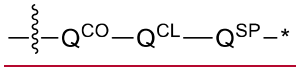
wherein the asterisk indicates covalent attachment of each Z to the Ligand Unit and wavy line adjacent to R^{17} indicates the site of covalent attachment to L^P, and

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,

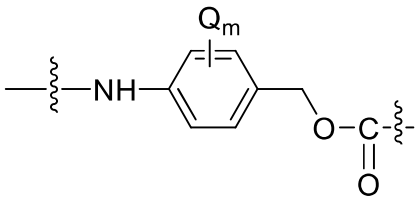
Q^{CL} is a Cleavable Unit,

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:



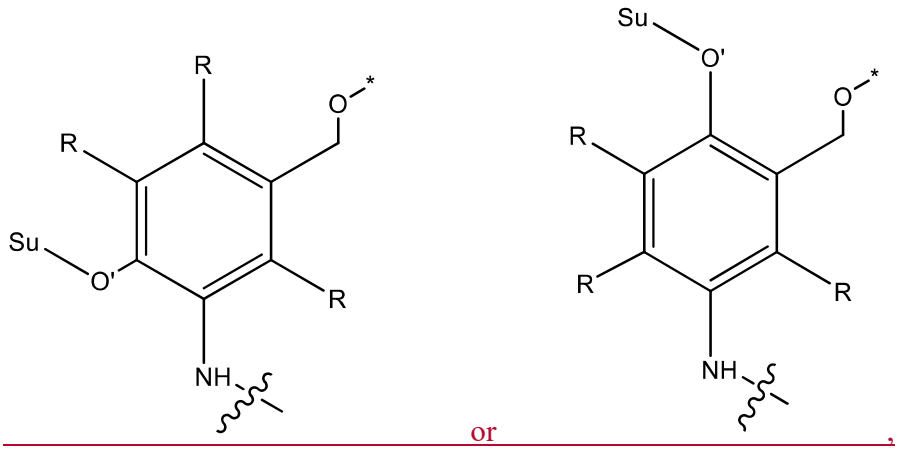
wherein Q is $-C_1$-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano,

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:



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,

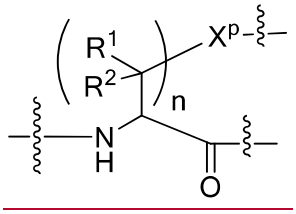
each R is independently selected from the group consisting of hydrogen, halogen, -CN, and $-NO_2$,

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,

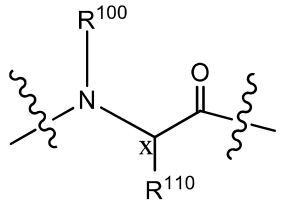
X^P is selected from the group consisting of -O-, -NH-, -S-, -S(=O)-, -C(=O)-, and $-C_2$-C_8 heterocyclo,

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,

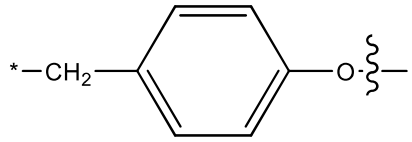
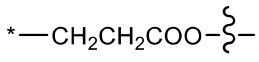
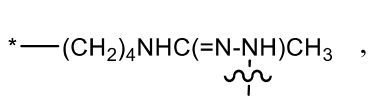
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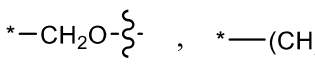
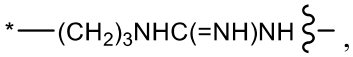
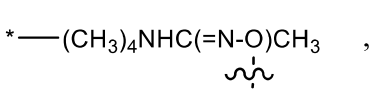
the Parallel Connector Unit or subunit thereof has the formula of:

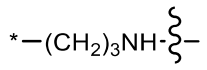


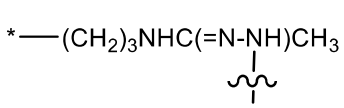
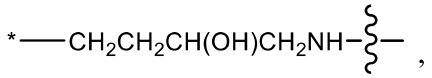
wherein R^{100} is independently selected from the group consisting of -H and $-C_1$-C_3 alkyl,

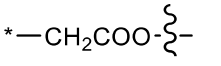
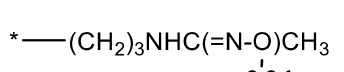
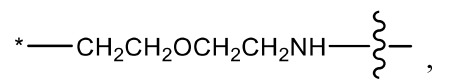
R^{110} is selected from the group consisting of:

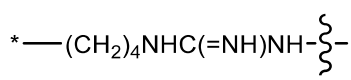
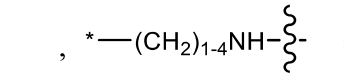
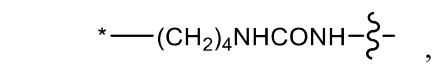

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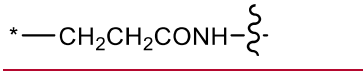
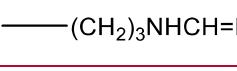
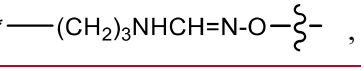

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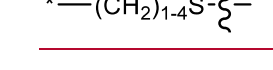
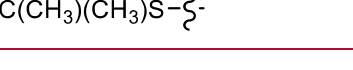
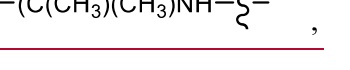

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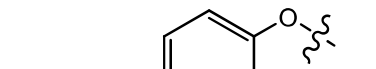
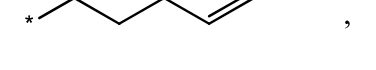
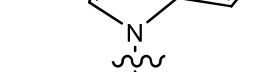

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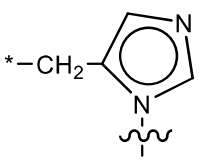

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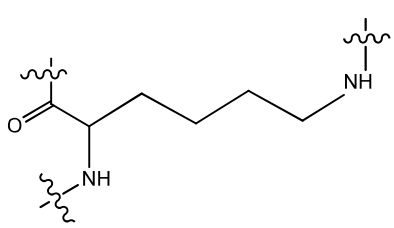
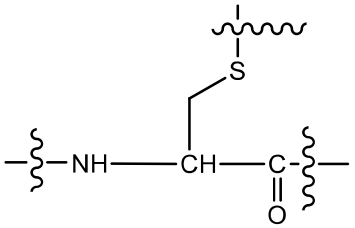
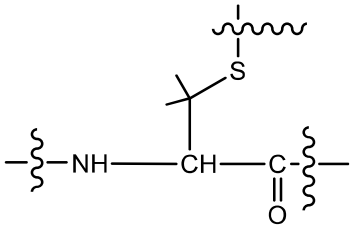
wherein the asterisk indicates the site of covalent attachment to the carbon labeled x and the wavy lines indicate the sites of covalent attachments within the Ligand-Drug Conjugate compound,

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;

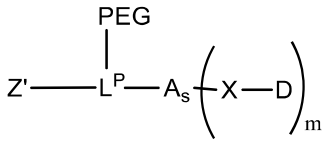
the subscript p is an integer ranging from 1 to 14;

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:

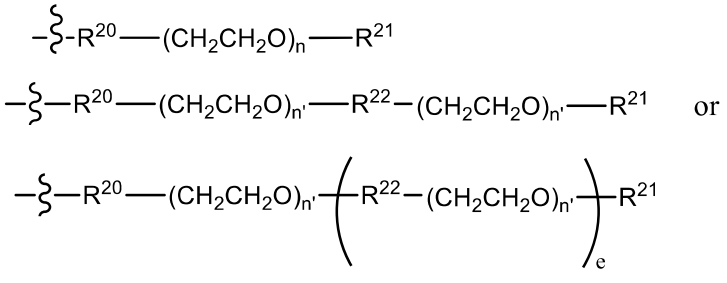


(IV)

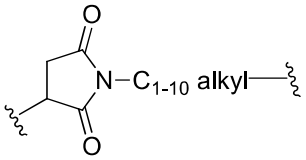
or a pharmaceutically acceptable salt thereof, wherein

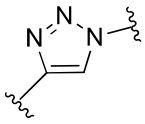
D is a hydrophobic Drug Unit, wherein the Drug Unit corresponds in structure to a hydrophobic cytotoxic, cytostatic, or immunosuppressive agent;

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



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)$_2$,

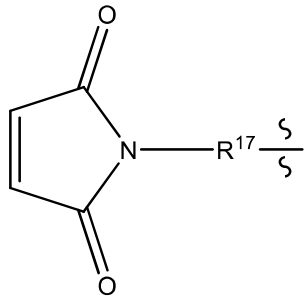
R^{22} is a PEG Coupling Unit, wherein each R^{22} is independently -C_{1-10} alkyl-C(O)-NH-, -C_{1-10} alkyl-NH-C(O)-, -C_{2-10} alkyl-NH-, -C_{2-10} alkyl-O- , -C_{1-10} alkyl-S-, or –C_{2-10} alkyl-NH-,

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:



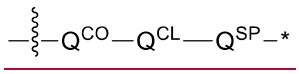
,

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,

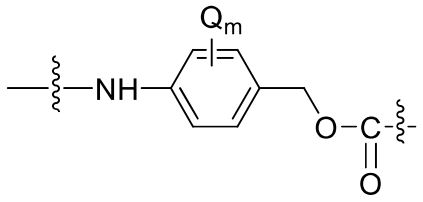
Q^{CL} is a Cleavable Unit,

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:



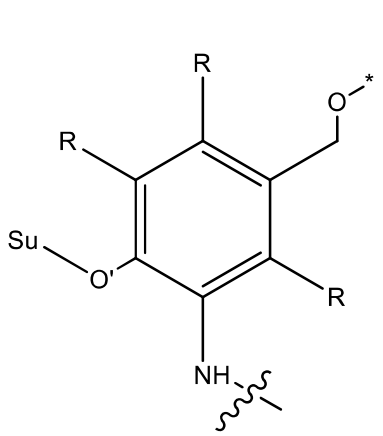
wherein Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano,

subscript m is an integer from 0 to 4, and

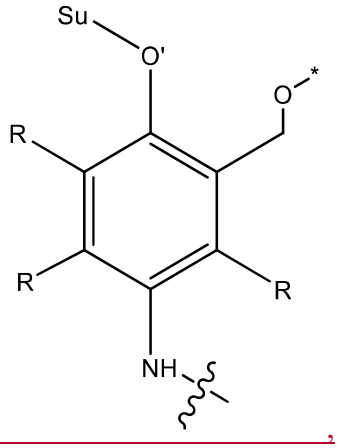
the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to the dipeptide of the peptide Cleavable Unit and the wavy line adjacent to the carbonyl indicates the site of covalent attachment to an oxygen or nitrogen atom of the Drug Unit,

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,

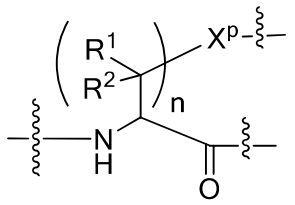
each R is independently selected from the group consisting of hydrogen, halogen, -CN, and $-NO_2$,

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,

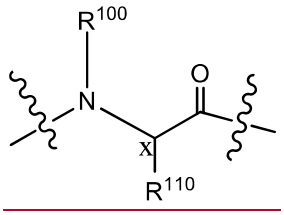
X^P is selected from the group consisting of -O-, -NH-, -S-, -S(=O)-, -C(=O)-, and $-C_2$-C_8 heterocyclo,

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,

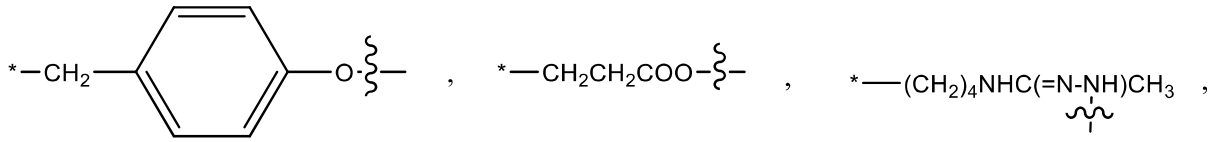
or

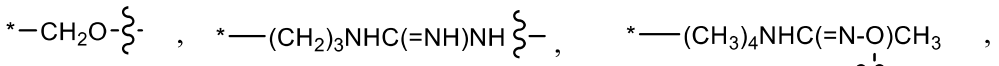
the Parallel Connector Unit or subunit thereof has the formula of:

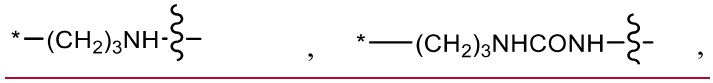


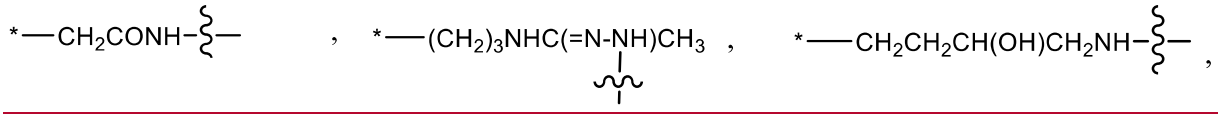
wherein R^{100} is independently selected from the group consisting of -H and -C_1-C_3 alkyl,

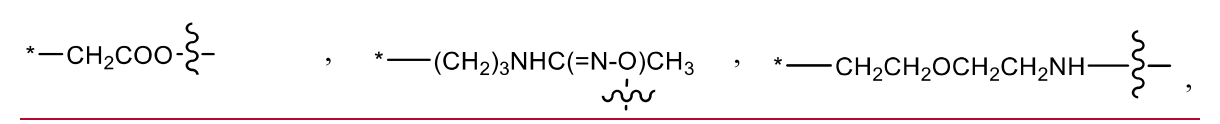
R^{110} is selected from the group consisting of:

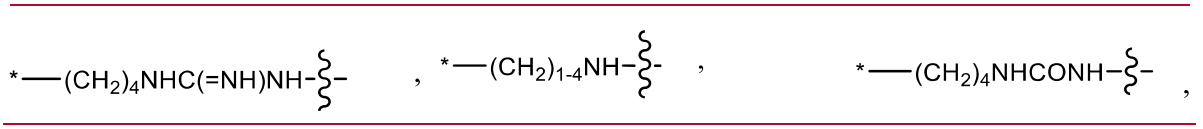


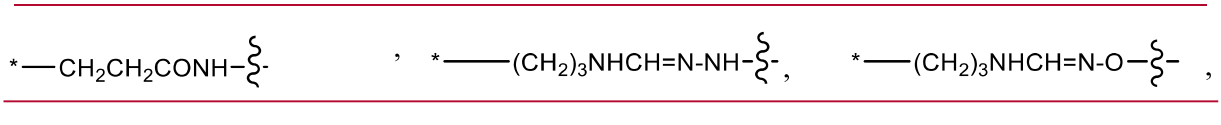


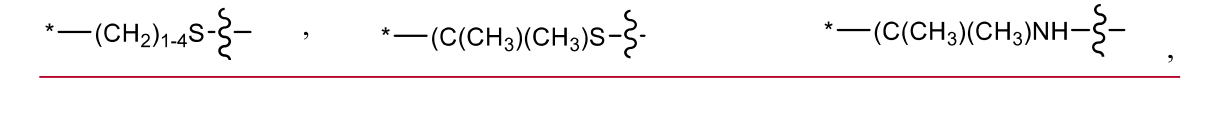




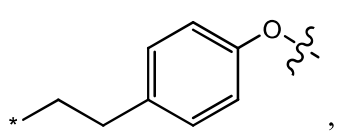
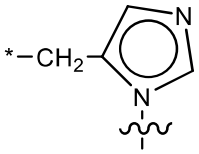
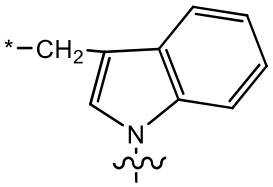












and


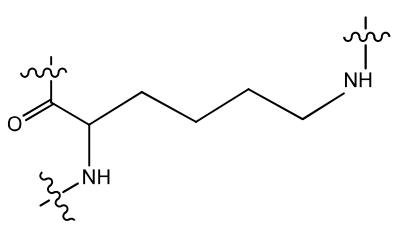
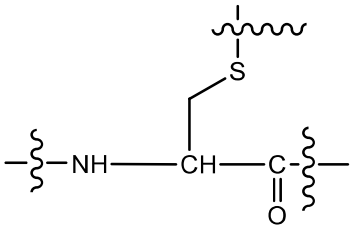
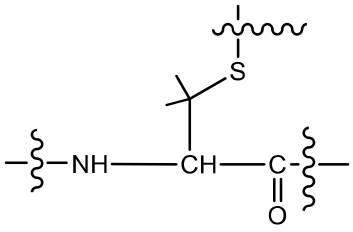
wherein the asterisk indicates the site of covalent attachment to the carbon labeled x and the wavy lines indicate the sites of covalent attachments within the Ligand-Drug Conjugate compound,

or

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

or

has the structure of:



, or


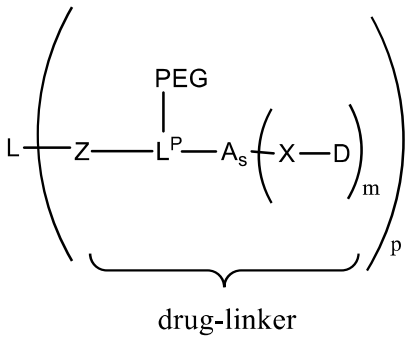
wherein the wavy lines indicate the sites of covalent attachment within the Ligand-Drug Conjugate compound;

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.

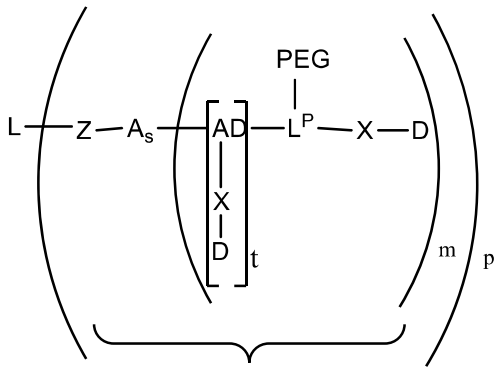
[0035] In principle ~~embodiment~~examples, an LDC of the present ~~invention~~disclosure is represented by the structure of Formula I below:



(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.

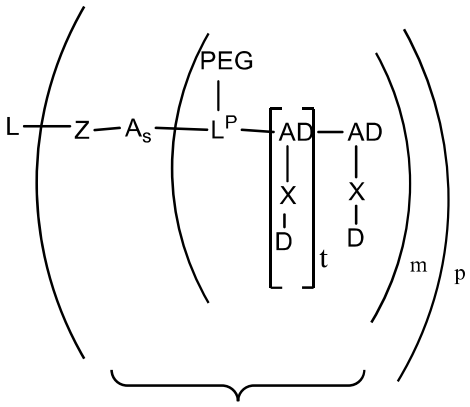
[0036] In other principle ~~embodiment~~examples, an LDC of the present ~~invention~~disclosure is represented by the structure of Formula II below:



(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 ~~embodiment~~examples an LDC of the present ~~invention~~disclosure is represented by the structure of Formula III below:



(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

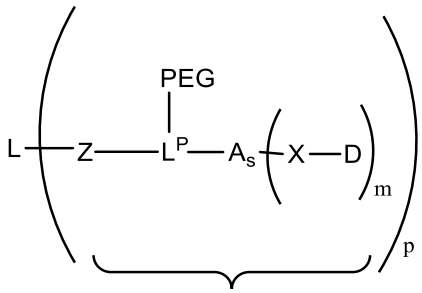
General

[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

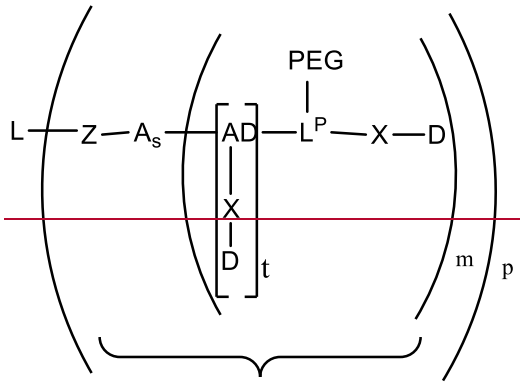
WHAT IS CLAIMED IS:

~~**1.** A Ligand-Drug Conjugate compound wherein the Ligand-Drug conjugate compound is comprised of a Ligand Unit and one or more Linker-Drug moieties covalently bonded to the Ligand Unit, wherein each Linker-Drug moiety is comprised of a Parallel Connector Unit that connects the Ligand Unit to one or more Drug Units through intermediacy of a Releasable Assembly Unit for each Drug Unit, and connects a Polyethylene Glycol Unit in parallel orientation relative to the Drug Units of each Linker-Drug moiety, wherein the Releasable Assembly units are capable of releasing free drug in proximity to a target site targeted by the Ligand Unit, wherein the Linker-Drug moieties provide for loading of one to thirty-two Drug Units onto the Ligand-Drug Conjugate.~~

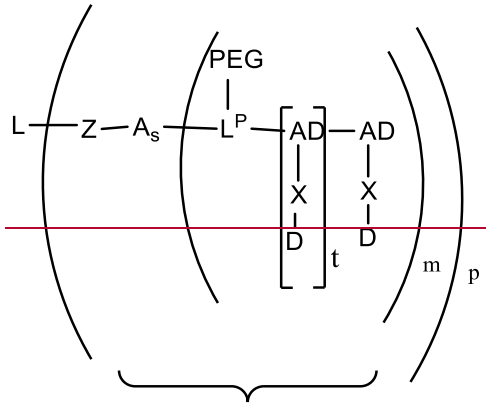
21. ~~The~~A Ligand-Drug Conjugate compound of ~~claim 1 wherein the Ligand-Drug has the structure represented by~~ formula (I)~~, (II), or (III)~~:



drug-linker (I)



drug-linker ~~(II)~~



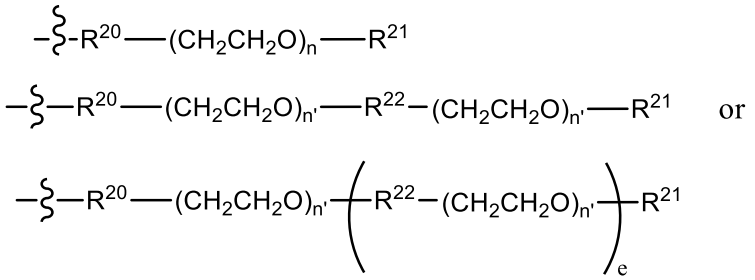
~~(III)~~

or a pharmaceutically acceptable salt thereof, wherein,

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

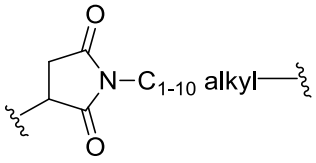
D is a hydrophobic Drug Unit, wherein the Drug Unit corresponds in structure to a hydrophobic cytotoxic, cytostatic, or immunosuppressive agent;

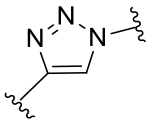
PEG is a Polyethylene Glycol Unit, wherein the PEG Unit has the formula of:



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)$_2$,

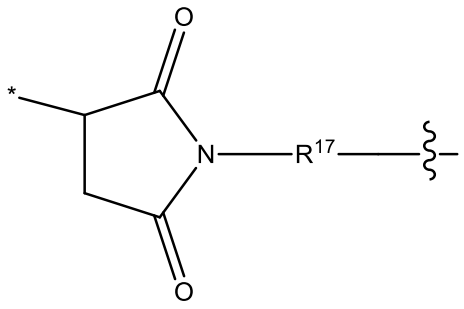
R^{22} is a PEG Coupling Unit, wherein each R^{22} is independently -C_{1-10} alkyl-C(O)-NH-, -C_{1-10} alkyl-NH-C(O)-, -C_{2-10} alkyl-NH-, -C_{2-10} alkyl-O- , -C_{1-10} alkyl-S-, or –C_{2-10} alkyl-NH-,

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:



,

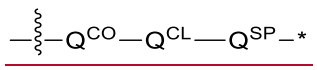
wherein the asterisk indicates covalent attachment of each Z to the Ligand Unit and wavy line adjacent to R^{17} indicates the site of covalent attachment to L^P, and

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,

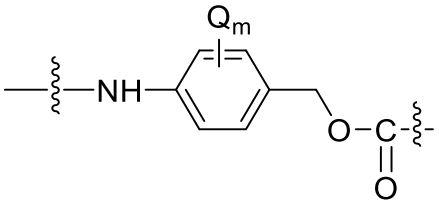
Q^{CL} is a Cleavable Unit,

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:



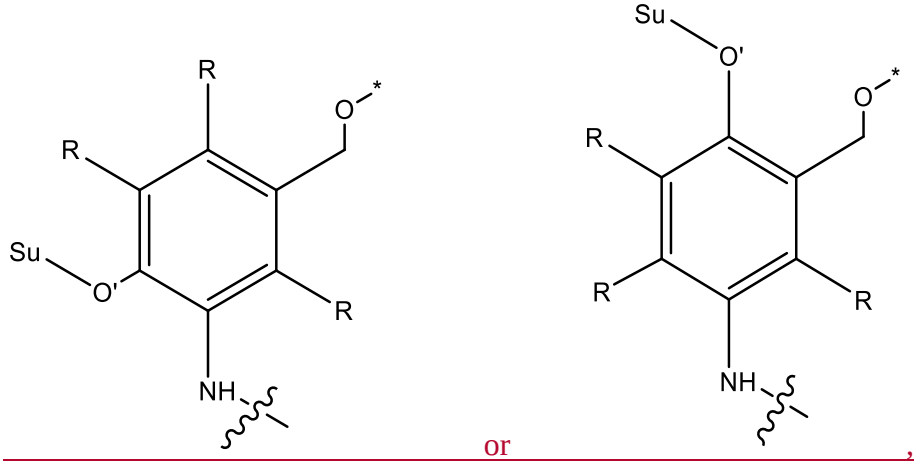
wherein Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano,

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:



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,

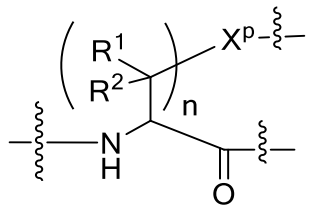
each R is independently selected from the group consisting of hydrogen, halogen, -CN, and -NO_2,

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,

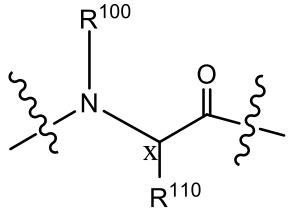
X^P is selected from the group consisting of -O-, -NH-, -S-, -S(=O)-, -C(=O)-, and -C_2-C_8 heterocyclo,

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,

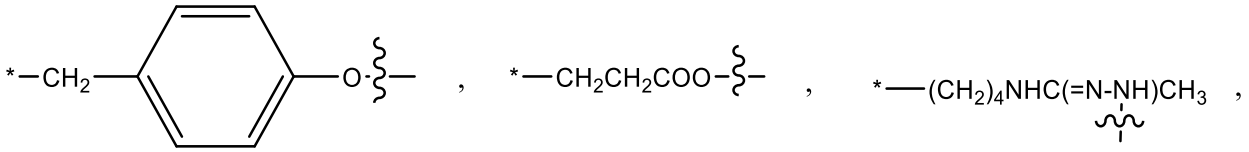
or

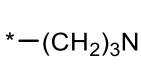
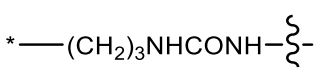
the Parallel Connector Unit or subunit thereof has the formula of:

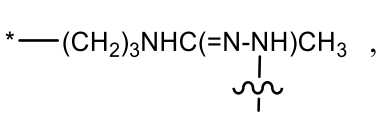
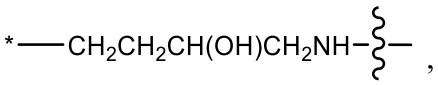


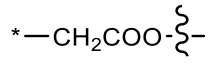
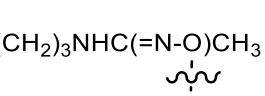
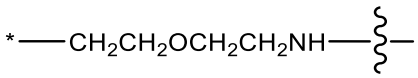
wherein R^{100} is independently selected from the group consisting of -H and -C_1-C_3 alkyl,

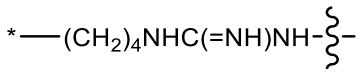
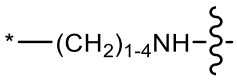
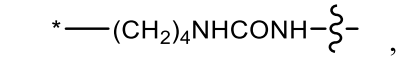
R^{110} is selected from the group consisting of:

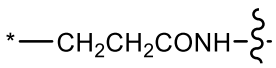
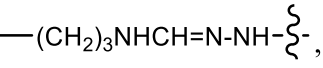
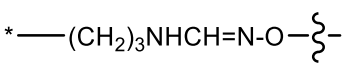


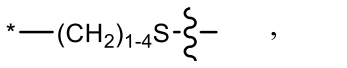
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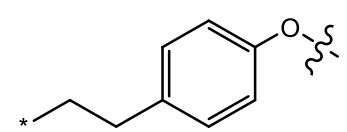
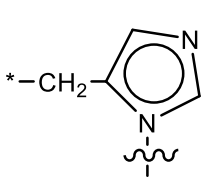
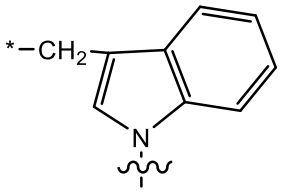
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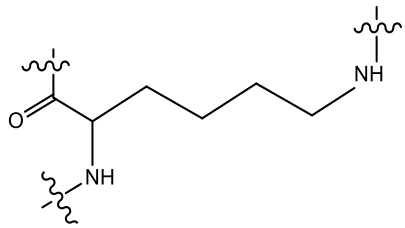
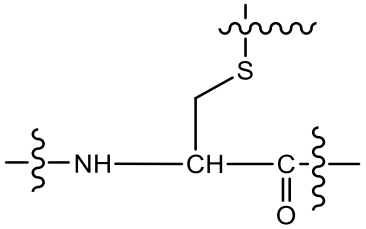
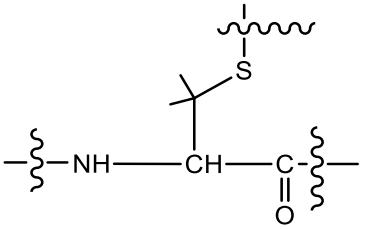
wherein the asterisk indicates the site of covalent attachment to the carbon labeled x and the wavy lines indicate the sites of covalent attachments within the Ligand-Drug Conjugate compound,

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;

~~AD is a Drug Attachment Unit;~~

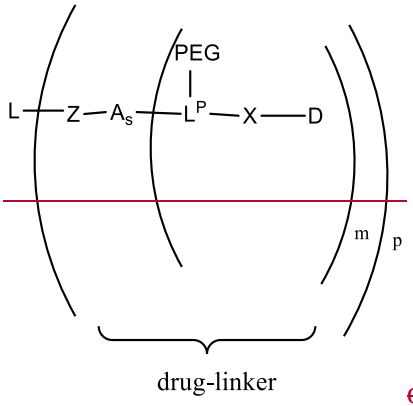
the subscript p is an integer ranging from 1 to 14~~, preferably 2 to 12 (preferably 6 to 14, 6 to 12, 8 to 14 or 8 to 12)~~;

~~the subscript t is 0 to 8, preferably 0, 1, 2 or 3;~~

the subscript m is an integer ranging from 1 to 4~~, preferably 1 or 2~~; 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.

~~**3**. The Ligand-Drug Conjugate compound of claim 2 wherein the Ligand-Drug Conjugate is represented by the structure:~~

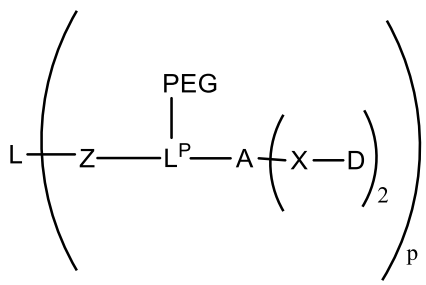


~~or a pharmaceutically acceptable salt thereof.~~

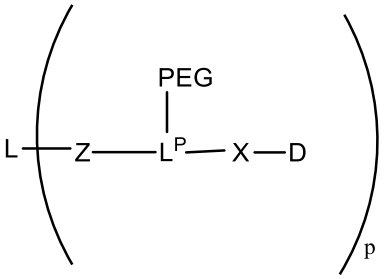
~~4~~2. The Ligand-Drug Conjugate compound of claim ~~2 or 3~~1, wherein the subscript s is 0.

~~5~~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.

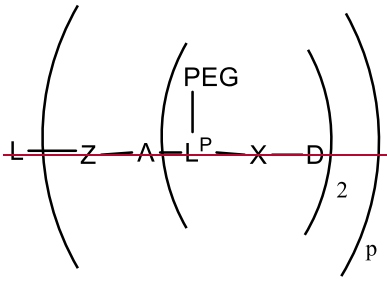
~~6~~4. The Ligand-Drug Conjugate compound of claim ~~2~~1, wherein the Ligand-Drug Conjugate has the structure represented by formula Ia or Ib:~~, Ib, IIa, IIb, IIb, IIIa, or IIIb:~~



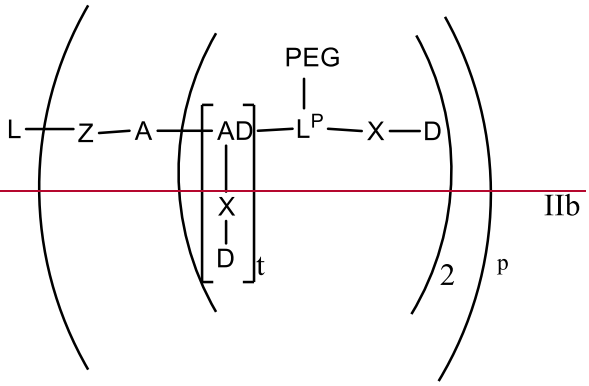
Ia



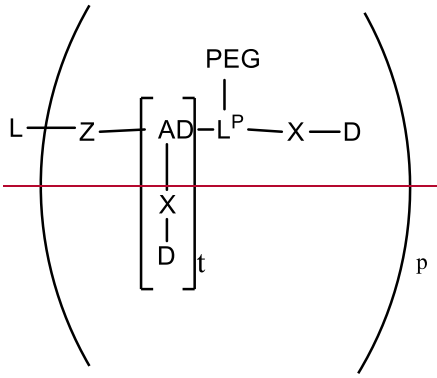
Ib



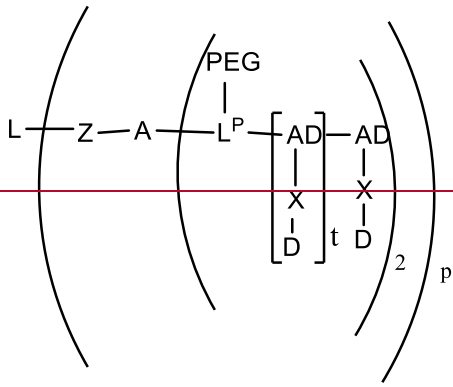
IIa



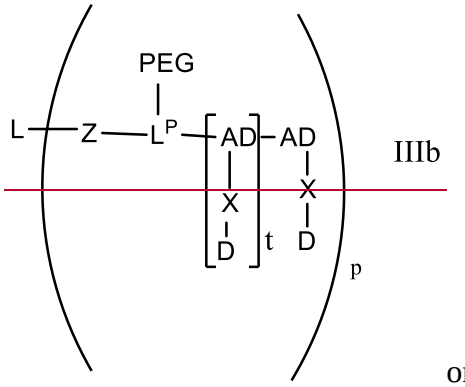
IIb



IIc



IIIa

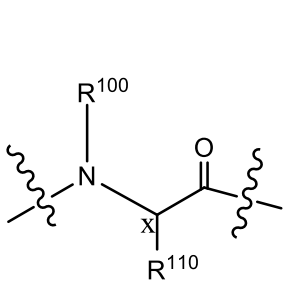


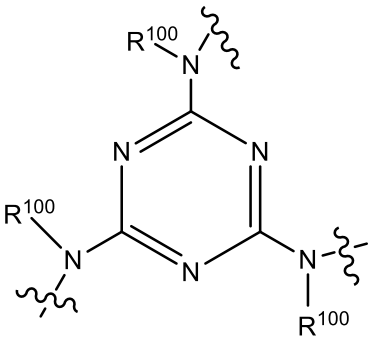
IIIb

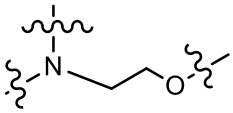
or a pharmaceutically acceptable salt thereof.

~~75~~**75**. The Ligand-Drug Conjugate compound of any one of claims 1 to ~~64~~**64**, wherein each Parallel Connector Unit (L^P) comprises an amino acid, amino alcohol, an amino aldehyde or a polyamine.

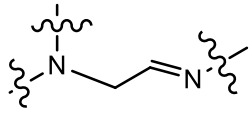
8. The Ligand-Drug Conjugate compound of any one of claims 1 to 6 wherein each Parallel Connector (L^P) Unit independently has the structure of:

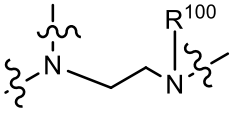


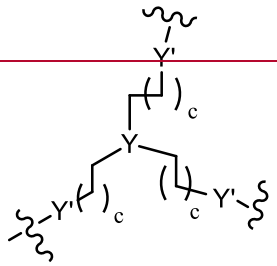
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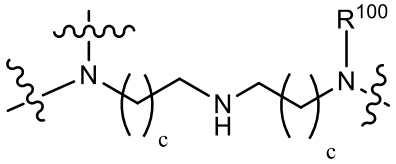
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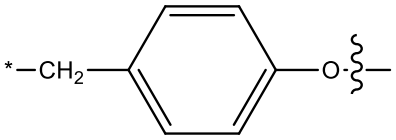
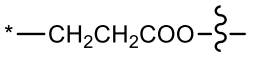
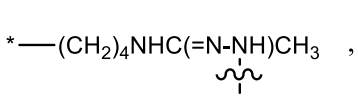
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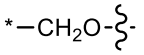
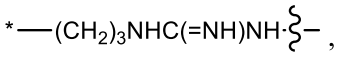
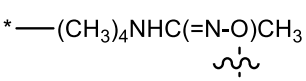
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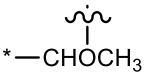
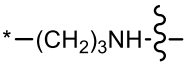
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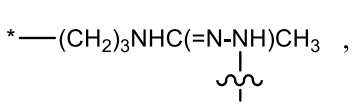
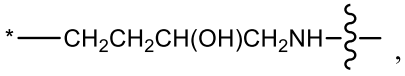


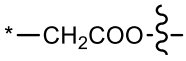
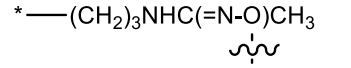
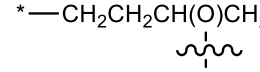
wherein the wavy lines indicates covalent attachment sites of L^P within the Ligand-Drug Conjugate; and wherein R^{110} is:

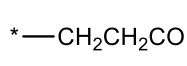
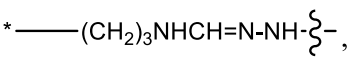
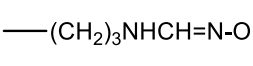

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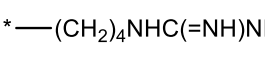
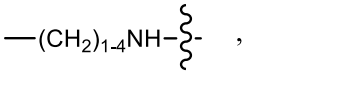
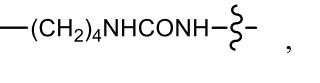

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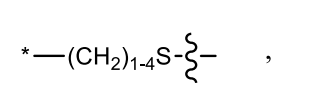
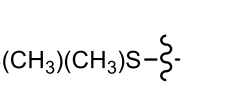
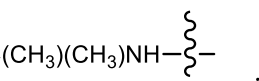

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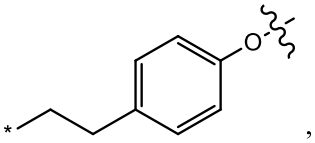
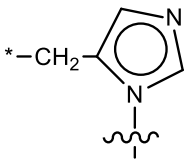
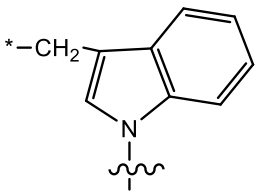

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~~wherein the asterisk indicates covalent attachment of the R^{110} moiety to the carbon labeled x and the wavy line in the R^{110} moiety indicates one of the three attachment sites of L^p within the Ligand-Drug moiety;~~

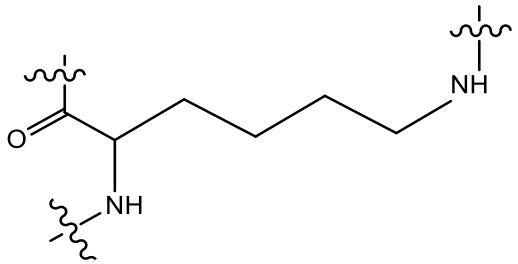
~~each R^{100} is independently selected from hydrogen or C_1-C_3 alkyl, preferably H or CH_3;~~

~~Y is independently selected from N or CH;~~

~~each Y' is independently selected from NH, O, or S; and~~

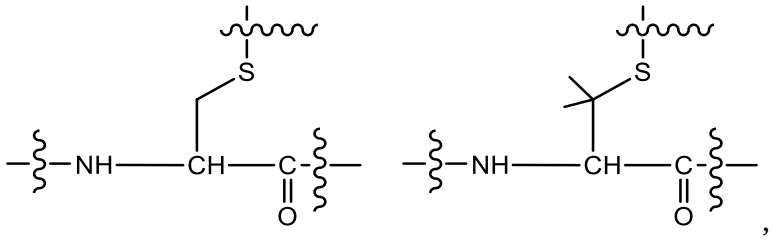
~~the subscript c is independently selected from an integer ranging from 1 to 10, preferably 1, 2, or 3.~~

~~96~~. The Ligand-Drug Conjugate compound of claim ~~7~~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.

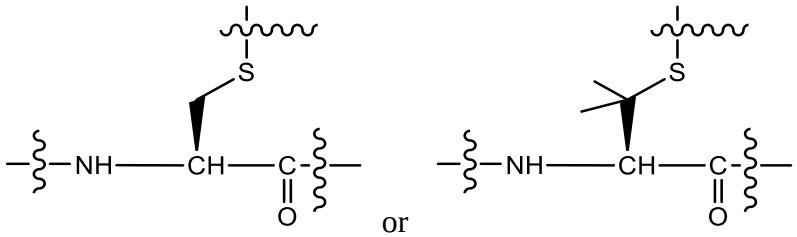
~~10~~7. The Ligand-Drug Conjugate compound of claim ~~7~~ 6, wherein each Parallel Connector (L^P) Unit corresponds in structure to D/L-cysteine or D/L-penicillamine as shown in the formula below:



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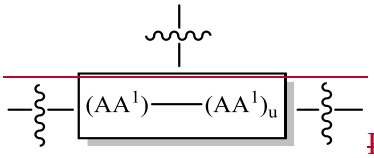
wherein the wavy lines indicates covalent attachment sites of L^P within the Ligand-Drug Conjugate.

~~11~~8. The Ligand-Drug Conjugate compound of claim ~~10~~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.

~~**12**. The Ligand-Drug Conjugate compound of any one of claims 2 - 6 wherein the structure of each Parallel Connector (L^P) Unit is independently represented by Formula A:~~



~~Formula A~~

~~wherein~~

~~AA^1 is independently selected from an amino acid, optionally substituted C_{1-20} heteroalkylene (preferably optionally substituted C_{1-12} heteroalkylene), optionally substituted C_{3-8} heterocyclo, optionally substituted C_{6-14} arylene, or optionally substituted C_3-C_8 carbocyclo;~~

~~and the subscript u is an integer independently selected from 0 to 4; wherein at least one AA^1 of each L^P Unit has a functionalized side chain that provides for an attachment site to a PEG, AD, A or Z unit or an X-D moiety,~~

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

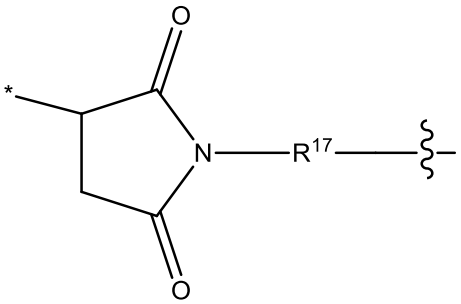
~~**13**. The Ligand-Drug Conjugate compound of claim 12 wherein each AA^1 of each Parallel Connector Unit (L^P) is an an independently selected amino acid or is an optionally substituted C_{1-20} heteroalkylene, optionally substituted C_{3-8} heterocyclo, optionally substituted C_{6-14} arylene, or optionally substituted C_3-C_8 carbocyclo, provided that no more than 2 of AA^1 is~~

~~optionally substituted C_{1-20} heteroalkylene, optionally substituted C_{3-8} heterocyclo, optionally substituted C_{6-14} arylene, or optionally substituted C_3-C_8 carbocyclo.~~

~~14~~9. The Ligand-Drug Conjugate compound of any one of ~~claims 2 - 13~~ 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.

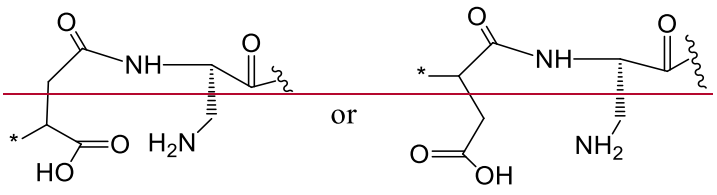
~~15. The Ligand-Drug Conjugate compound of any one of claims 2 - 14 wherein when AD is present, each AD is one to 10 independently selected amino acids or amino alcohols or amino aldehydes or polyamines or combination thereof covalently bonded to one another.~~

~~16~~10. The Ligand-Drug Conjugate compound of any one of claims ~~2 - 15~~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.

~~17. The Ligand-Drug Conjugate compound of any one of claims 2 - 15 wherein Z has the structure of~~

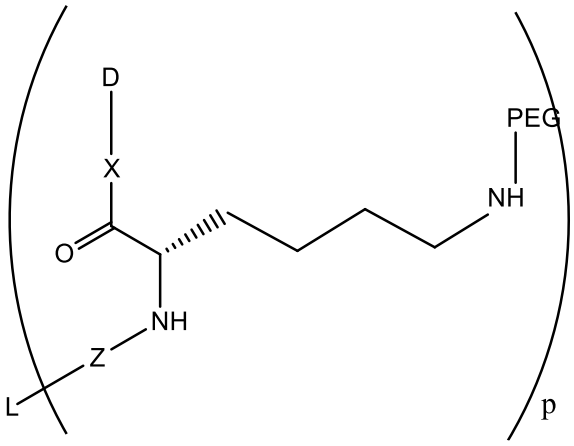


~~wherein the asterisk indicates attachment of each Z to the Ligand Unit and the wavy line indicates covalent attachment of each Z to the remainder of a Linker-Drug moiety within the Ligand-Drug Conjugate.~~

~~**18**. The Ligand-Drug Conjugate compound of any one of claims 2 - 17 wherein the subscript t is 0, 1 or 2.~~

~~**19**~~**11**. The Ligand-Drug Conjugate compound of any one of claims ~~2 - 18~~ 1 to 10, wherein the subscript p is an integer ranging from 6 to 14.

~~**20**~~**12**. The Ligand-Drug Conjugate compound of claim 2, ~~16, or 17~~ wherein the Ligand-Drug Conjugate is represented by the structure of:



or a pharmaceutically acceptable salt thereof.

~~**21**~~**13**. The Ligand-Drug Conjugate compound of any one of claims ~~1 - 18~~ 1 to 12, wherein there are from 6 to 32 or from 8 to 32 Drug Units attached to the Ligand Unit.

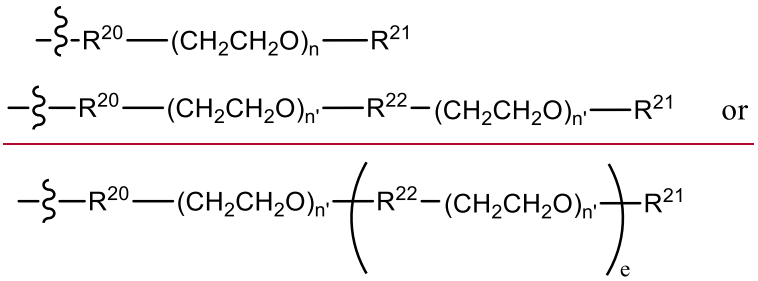
~~**22**~~**14**. ~~A~~ The Ligand-Drug Conjugate compound of any one of claims 1 to ~~21~~13, wherein PEG comprises ~~no more than about 72 (OCH_2CH_2) subunits, preferably~~ no more than ~~about~~ 36 (OCH_2CH_2) subunits.

~~**23**~~**15**. ~~A~~ The Ligand-Drug Conjugate compound of any one of claims 1 to ~~23~~13, wherein PEG comprises a combined total of from 8 to 72~~, 8 to 60, 8 to 48, 8 to 36 or 8 to 24~~

~~(OCH_2CH_2) subunits, from 10 to 72, 10 to 60, 10 to 48, 10 to 36 or 10 to 24 (OCH_2CH_2)~~ ~~subunits, or from 12 to 72, 12 to 60, 12 to 48, 12 to 36 or 12 to 24 (OCH_2CH_2)~~ subunits.

~~24~~**16**. The Ligand-Drug Conjugate compound of any one of claims ~~1 – 23~~1 to 15, wherein the PEG unit comprises one or more linear PEG chains.

~~**25**. The Ligand-Drug Conjugate compound of any one of claims 1 - 21 wherein the PEG Unit has the structure of:~~



~~wherein the wavy line indicates site of attachment the PEG Unit to the Parallel Connector Unit,~~

~~R^{20} is a PEG Attachment Unit,~~

~~R^{21} is a PEG Capping Unit;~~

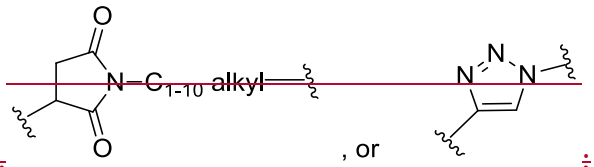
~~R^{22} is an PEG Coupling Unit~~

~~n is independently selected from 4 to 72, preferably 6 to 72, 8 to 72, 10 to 72 or 12 to 72;~~

~~e is 2 to 5~~

~~each n' is independently selected from 1 to 72, provided that there are at least 4, preferably at least 6, at least 8, at least 10, or at least 12 PEG (OCH_2CH_2) subunits in the PEG Unit.~~

~~**26**. The Ligand-Drug Conjugate compound of claim 25 wherein~~

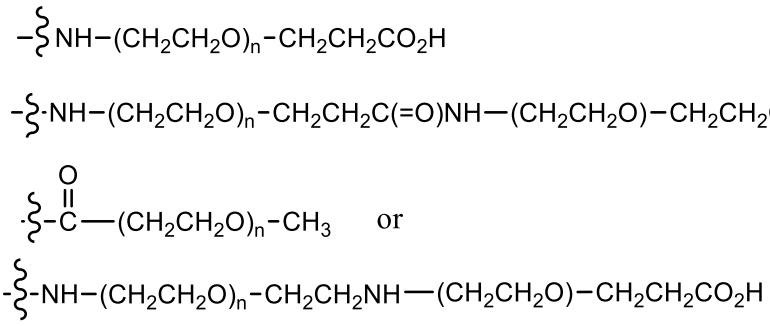
~~R^{20} is is -C(O)-, -O-, -S-, -S(O)-, -NH-, -C(O)O-, -C(O)C_{1-10}alkyl, -C(O)C_{1-10}alkyl-O-, -C(O)C_{1-10}alkyl-CO_2-, -C(O)C_{1-10}alkyl-NH-, -C(O)C_{1-10}alkyl-S-, -C(O)C_{1-10}alkyl-C(O)-NH-, -C(O)C_{1-10}alkyl-NH-C(O)-, -C_{1-10}alkyl, -C_{1-10}alkyl-O-, -C_{1-10}alkyl-CO_2-, -C_{1-10}alkyl-NH-, -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~~ ~~;~~

~~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)$_2$; and~~

~~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-.~~

~~27~~17. The Ligand-Drug Conjugate compound of ~~claim 26~~ any one of claims 1 to 16, wherein R^{20} is -NH- or -C(O)-.

~~28~~18. The Ligand-Drug Conjugate compound of ~~claim 25~~ 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 ~~4~~8 to 72.

~~29~~19. The Ligand-Drug Conjugate compound of claim ~~28~~18, wherein n is independently selected from ~~6 to 24 or from~~ 8 to ~~24~~36.

~~30. The Ligand-Drug Conjugate compound of any one of claims 1 29 wherein the PEG Unit has at least 6 CH_2CH_2O subunits.~~

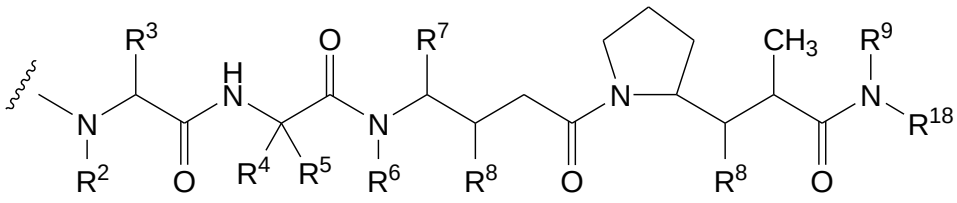
~~31~~20. The Ligand-Drug Conjugate compound of any one of claims ~~1 30~~ 1 to 19, wherein the PEG Unit has at least 8 -CH_2CH_2O- subunits and no more than ~~about 36~~ 24 subunits -CH_2CH_2O-.

~~32. The Ligand-Drug Conjugate compound of any one of the preceding claims wherein the Drug Unit is hydrophobic.~~

~~33~~21. The Ligand-Drug Conjugate compound of ~~claim 32~~ 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.

~~34~~22. The Ligand -Drug Conjugate compound of any one of claims 1 to 20, ~~claim 32~~ wherein the Drug Unit is an auristatin.

~~35~~23. The Ligand -Drug Conjugate compound of claim ~~34~~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);

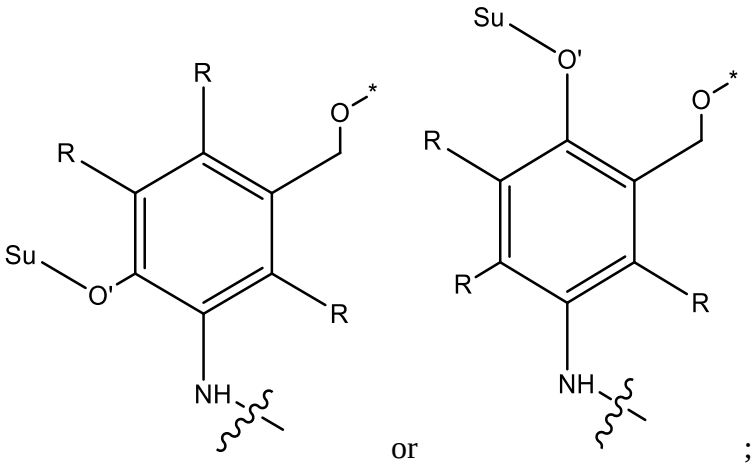
each R^8 is independently selected from the group consisting of H, OH, C_1-C_8 alkyl, C_3-C_8 carbocycle, and O-(C_1-C_8 alkyl);

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).

~~36~~24. The Ligand -Drug Conjugate compound of any one of claims ~~1 35~~ 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.

~~37~~25. The Ligand -Drug Conjugate compound of claim ~~36~~24, wherein the Releasable Assembly Unit comprises a glucuronide unit and is represented by the formula:

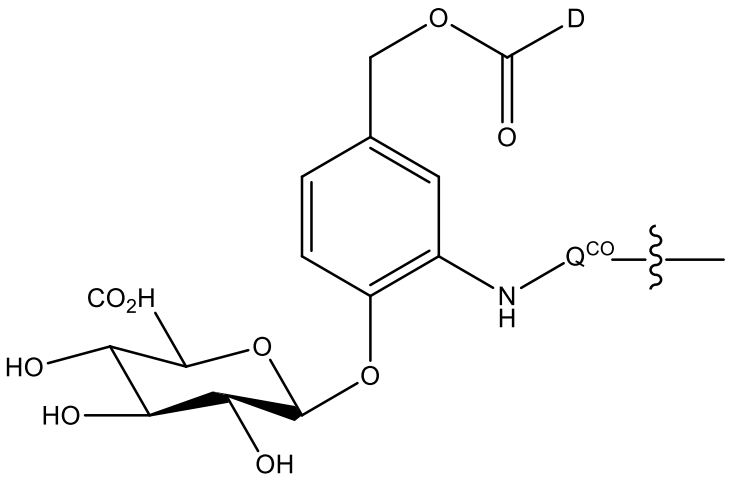


or ;

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).

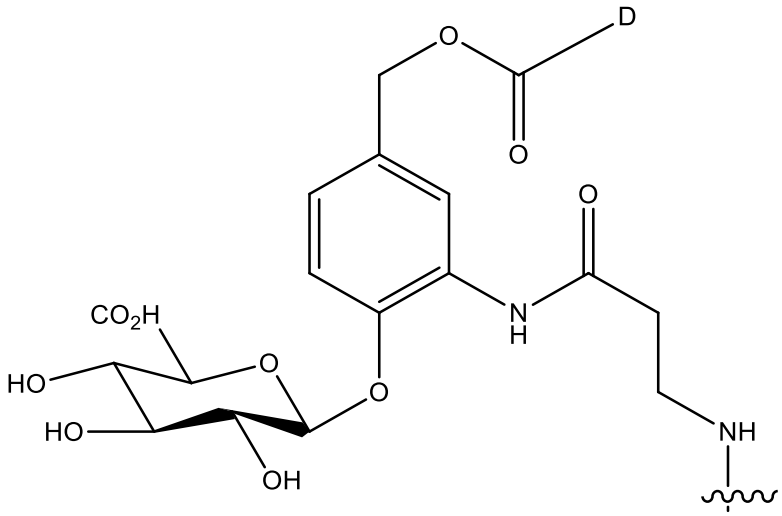
~~38~~26. The Ligand-Drug Conjugate compound of any one of claims ~~1—35~~1 to 23, wherein the Releasable Assembly Unit comprises a peptide cleavable by cathepsin B.

~~39~~27. The Ligand-Drug Conjugate compound of any one of claims ~~1—35~~1 to 25, wherein –X-D has the structure of:



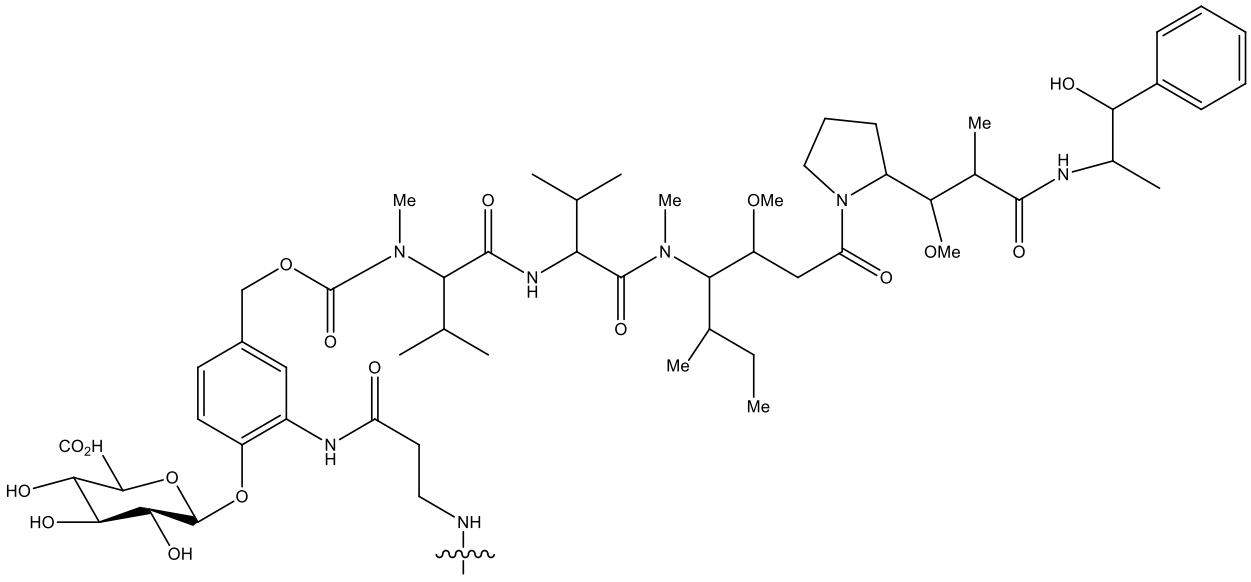
wherein Q^{CO} is an optional Covalent Attachment Unit ~~Unit~~ and the wavy line indicates covalent attachment to the remainder of a Drug Linker moiety of the Ligand-Drug Conjugate.

~~40~~28. The Ligand -Drug Conjugate compound of claim ~~39~~27, wherein –X-D is

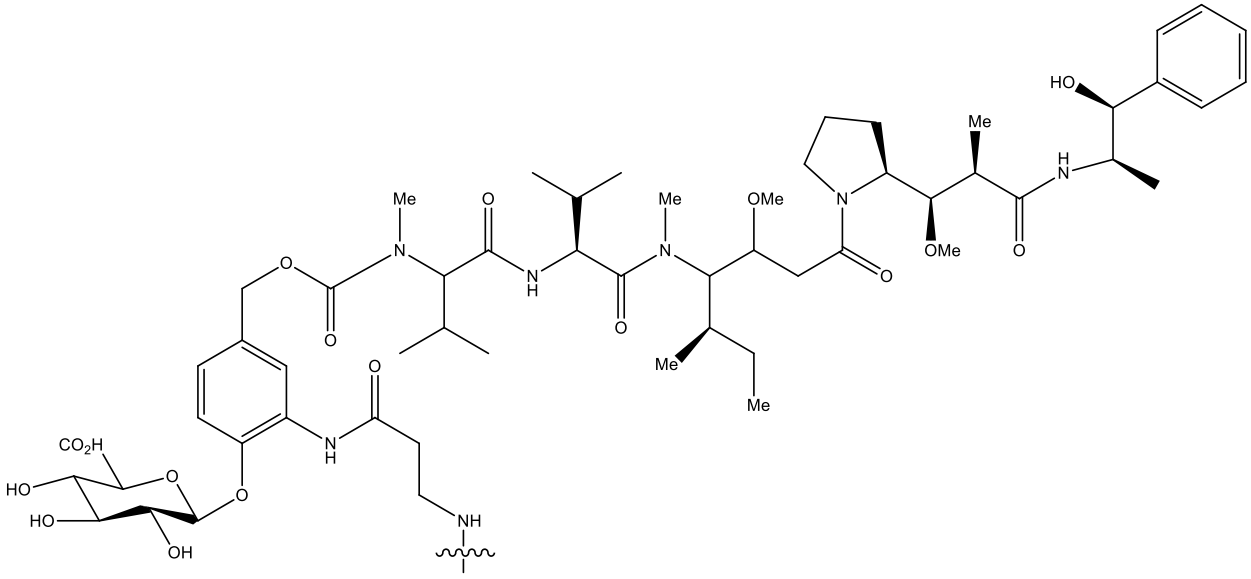


wherein the wavy line indicates covalent to the remainder of a Drug Linker moiety of the Ligand-Drug Conjugate.

~~41~~29. The Ligand-Drug Conjugate compound of any one of claims ~~1 35~~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.

~~42~~30. The Ligand-Drug Conjugate compound of any one of claims 1 to 29, ~~1-41~~ wherein the Ligand Unit is a monoclonal antibody.

~~43~~31. The Ligand-Drug Conjugate compound of any one of claims 1 to 30, ~~1—42~~ 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.

~~44~~32. The Ligand-Drug Conjugate compound of claim ~~43~~31, wherein the cysteine residue is naturally occurring and is from an interchain disulfide.

~~45~~33. The Ligand-Drug Conjugate compound of claim ~~43~~31, wherein the cysteine residue is non-naturally occurring and is from a cysteine introduced into the antibody.

~~46~~34. The Ligand-Drug Conjugate compound of claim ~~45~~33, wherein the introduced cysteine is at residue 239 according to the EU index.

~~47~~35. The Ligand-Drug Conjugate compound of any one of ~~the preceding~~ claims 1 to 34, wherein there are 6 to 14 Drug Units attached to the Ligand Unit.

~~48~~36. The Ligand-Drug Conjugate compound of any one of claims ~~2 – 47~~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.

~~49~~37. The Ligand-Drug Conjugate compound of any one of claims ~~2 – 47~~ 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.

~~50~~38. The Ligand-Drug Conjugate compound of claim ~~49~~37, wherein the cysteine residue is at position 239 according to the EU index.

~~51~~39. ~~A~~ The Ligand-Drug Conjugate compound of any one of claims 1 to ~~50~~38, wherein the Ligand Unit has a molecular weight of at least about 80 Kd.

~~52~~40. The Ligand Drug Conjugate compound of any of claims ~~2 – 51~~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.

~~53~~41. The Ligand Drug Conjugate compound of any of claims ~~2 – 52~~ 1 to 40, wherein the Stretcher Unit has a mass of no more than about 1000 daltons, preferably no more than about 200 daltons.

~~54~~42. ~~A~~ The Ligand-Drug Conjugate compound of any one claims ~~2 to 53~~ 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.

~~55. A Ligand-Drug Conjugate compound of any one of claims 2 to 54 wherein when the Drug Attachment Unit is present, the Drug Attachment Unit has a mass of no more than about 1000 daltons, preferably no more than about 500 daltons.~~

~~56~~**43**. ~~A~~ The Ligand-Drug Conjugate compound of any one of claims ~~2 to 55~~1 to 42, wherein the Releasable Assembly Unit has a mass of no more than about 5000 daltons, preferably a mass of from ~~about~~ 100 daltons, or from ~~about~~ 200 daltons, or from ~~about~~ 300 daltons to ~~about~~ 1000 daltons.

~~57~~**44**. The~~A~~ Ligand-Drug Conjugate compound of any one of ~~the preceding~~ claims 1 to 43, wherein, apart from the PEG Unit, there are no more than 4~~, no more than 3, no more than 2 or no more than 1~~ other polyethylene glycol subunits present in the Ligand-Drug Conjugate.

~~58~~**45**. The~~A~~ Ligand-Drug Conjugate compound of any ~~of the preceding claims~~ one of claims 1 to 44, wherein there are no more than 50~~, no more than 45, 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 Drug Unit.

~~59~~**46**. The~~A~~ Ligand-Drug Conjugate compound of any ~~of the preceding claims~~ 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.

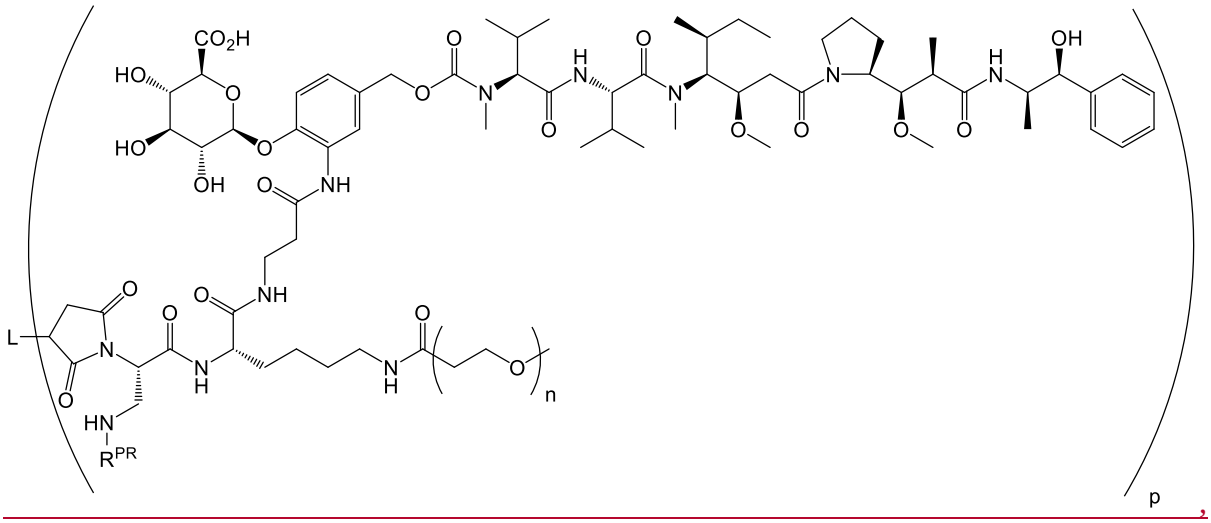
~~60~~**47**. The~~A~~ Ligand-Drug Conjugate compound of any ~~of the preceding claims~~ one of claims 1 to 46, wherein there are fewer intervening atoms between the Ligand and the Drug Unit than there are atoms in the PEG Unit.

~~61~~**48**. The~~A~~ Ligand-Drug Conjugate compound of any ~~of the preceding claims~~ 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.

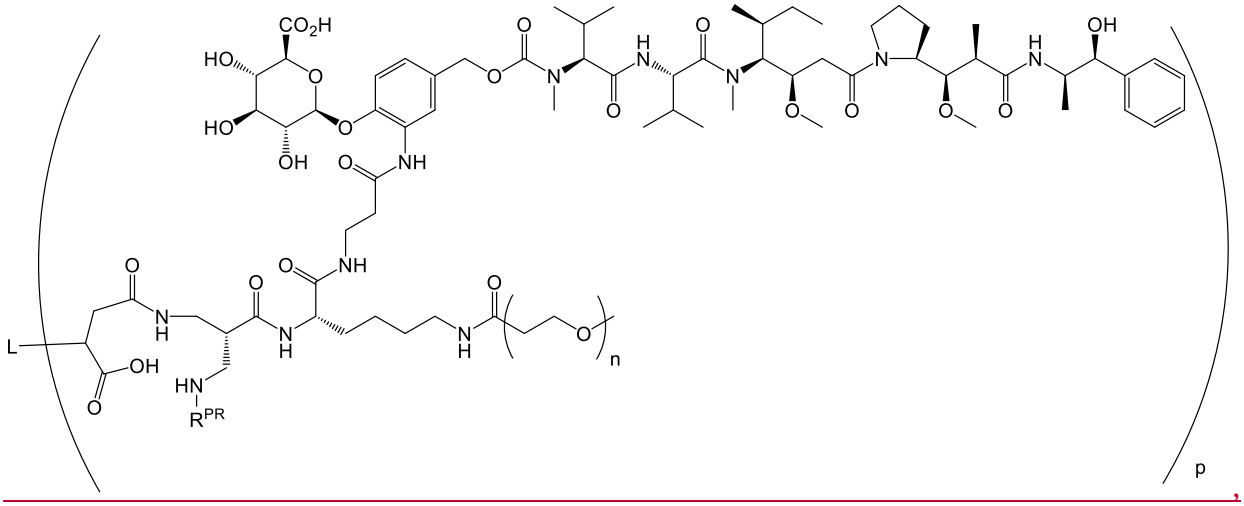
~~62~~**49**. The~~A~~ Ligand-Drug Conjugate compound of any ~~of the preceding claims~~ one of claims 1 to 48, wherein there are fewer intervening atoms between the Ligand and the Drug Unit than there are intervening atoms between the distal end of the PEG Unit and the Parallel Connector Unit.

~~63~~**50**. The~~A~~ Ligand-Drug Conjugate compound of any ~~of the preceding claims~~ 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.

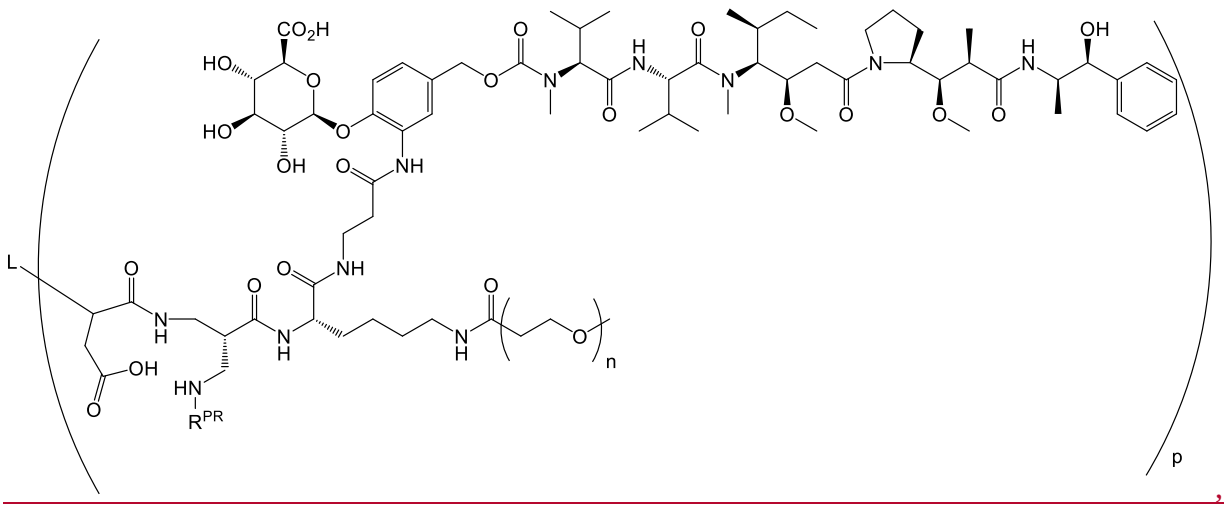
51. The Ligand-Drug Conjugate compound of claim 1, wherein the compound has the structure of:



,



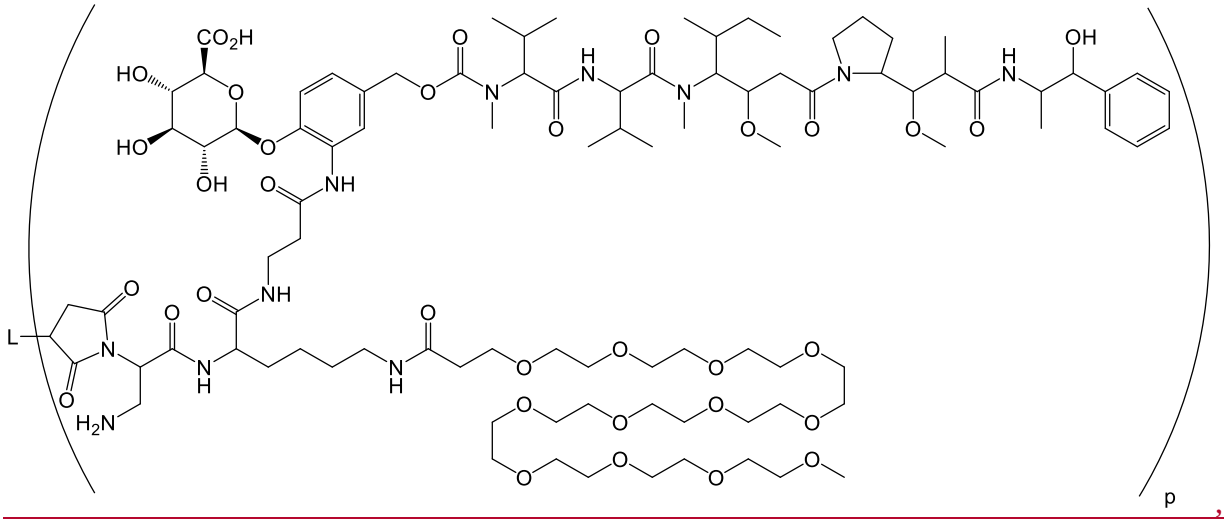
,



or a pharmaceutically acceptable salt thereof, wherein

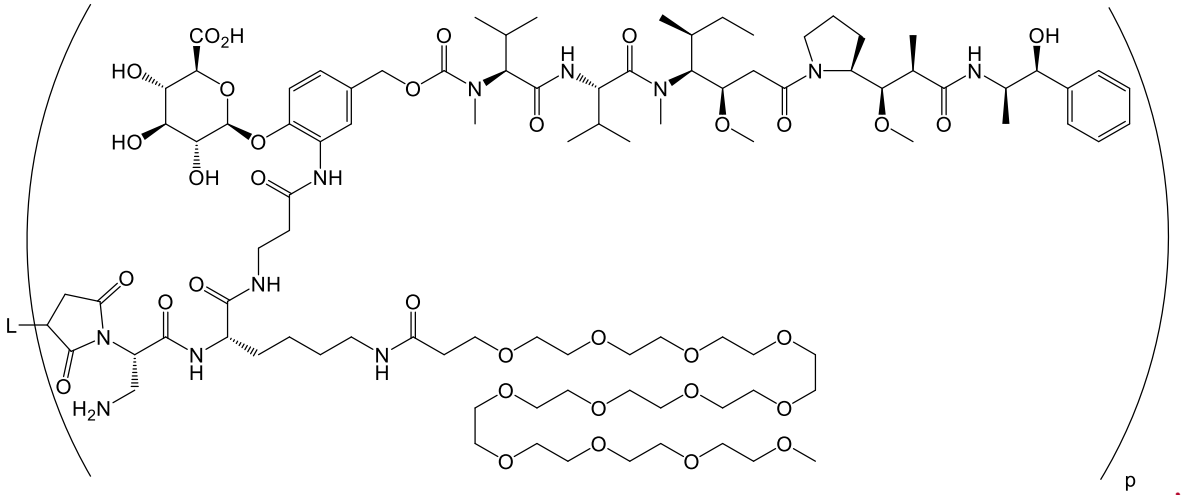
R^{PR} is hydrogen or a protecting group; and

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.

~~64~~54. A pharmaceutical composition comprising a population of Ligand-Drug Conjugate compounds, or pharmaceutically acceptable salts thereof, of any one of claims ~~1-63~~ 1 to 53, ~~wherein the average number of drug-linker moieties per Ligand Unit in the composition ranges from about 4 to about 14~~; and a pharmaceutically acceptable carrier, wherein the average p value of the Ligand-Drug Conjugate compounds in the composition is from 4 to 14.

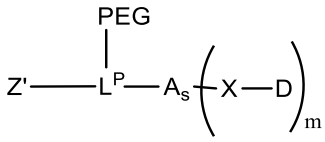
~~65~~55. The pharmaceutical composition of claim ~~64~~54, wherein the average ~~number of drug-linker moieties per Ligand Unit in the composition ranges~~ p value of the Ligand-Drug Conjugate compounds in the compositions is from ~~about~~ 6 to ~~about~~ 14.

~~66~~56. The pharmaceutical composition of claim ~~64~~54, wherein the average ~~number of drug-linker moieties per Ligand Unit in the composition ranges~~ p value of the Ligand-Drug Conjugate compounds in the compositions is from ~~about~~ 8 to ~~about~~ 14.

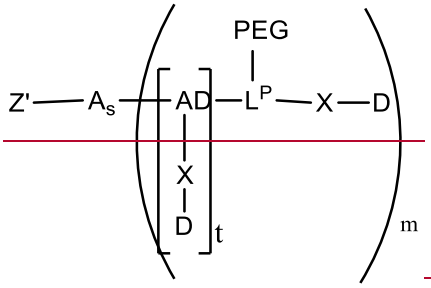
~~67~~57. The pharmaceutical composition of claim ~~64~~54, wherein the average ~~number of molecules of drug-linkers per Ligand in the composition ranges~~ p value of the Ligand-Drug Conjugate compounds in the compositions is from ~~about~~ 8 to ~~about~~ 12.

~~68~~58. The pharmaceutical composition of claim ~~66~~56, wherein the average ~~number of molecules of drug-linkers per Ligand in the~~ p value of the Ligand-Drug Conjugate compounds in the composition is about 8.

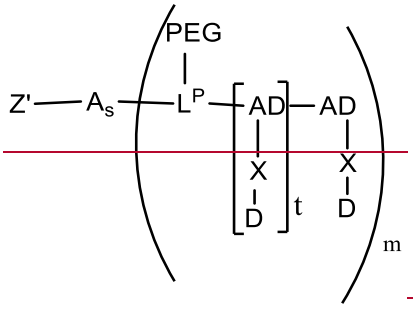
~~69~~59. A Drug-Linker Compound wherein the Drug-Linker ~~c~~Compound is represented by the structure of formula IV~~, V, or VI~~:



(IV)



~~(V)~~

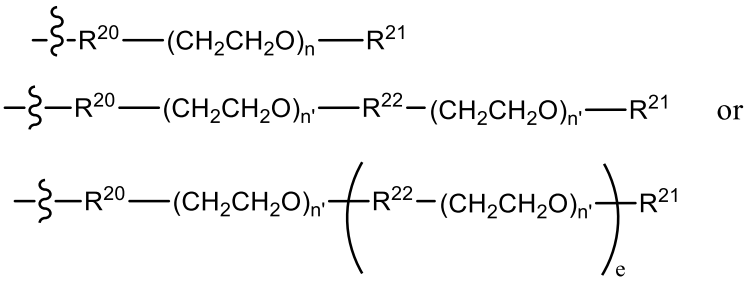


~~(VI)~~

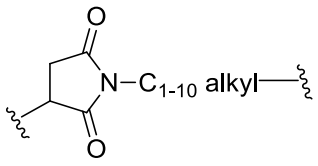
or a pharmaceutically acceptable salt thereof, wherein

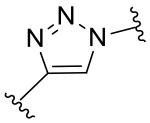
D is a hydrophobic Drug Unit, wherein the Drug Unit corresponds in structure to a hydrophobic cytotoxic, cytostatic, or immunosuppressive agent;

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)$_2$,

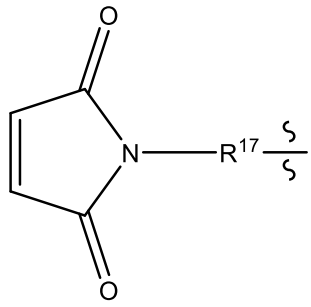
R^{22} is a PEG Coupling Unit, wherein each R^{22} is independently -C_{1-10} alkyl-C(O)-NH-, -C_{1-10} alkyl-NH-C(O)-, -C_{2-10} alkyl-NH-, -C_{2-10} alkyl-O- , -C_{1-10} alkyl-S-, or –C_{2-10} alkyl-NH-,

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

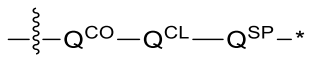
R^{17} is -C_1-C_{10} alkylene-, -C_1-C_{10} heteroalkylene-, -C_3-C_8 carbocyclo-, -O-(C_1-C_8 alkyl)-, -arylene-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-,

-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;

~~capable of forming a covalent attachment to a Ligand Unit;~~

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,

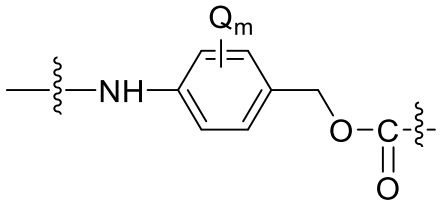
Q^{CL} is a Cleavable Unit,

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:



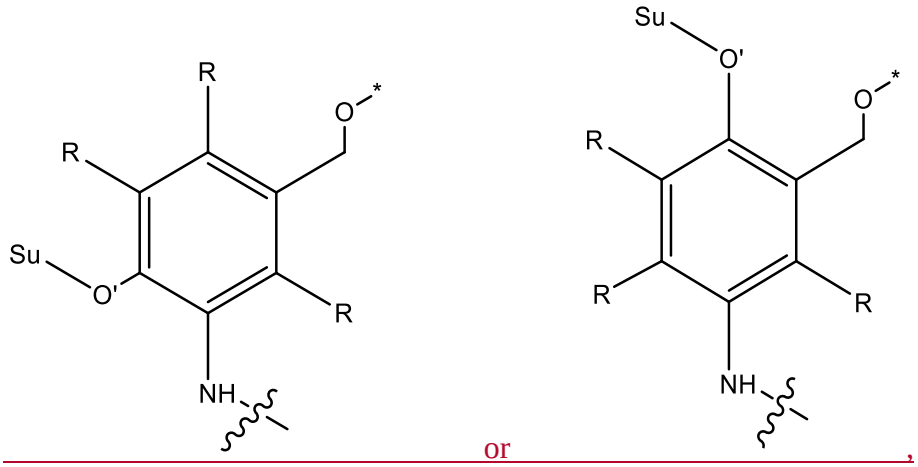
wherein Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano,

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:



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,

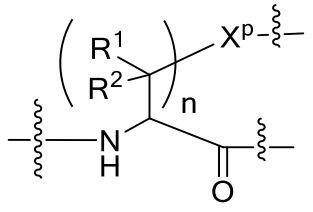
each R is independently selected from the group consisting of hydrogen, halogen, -CN, and $-NO_2$,

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,

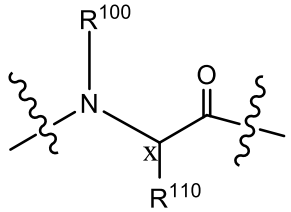
X^P is selected from the group consisting of -O-, -NH-, -S-, -S(=O)-, -C(=O)-, and $-C_2$-C_8 heterocyclo,

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,

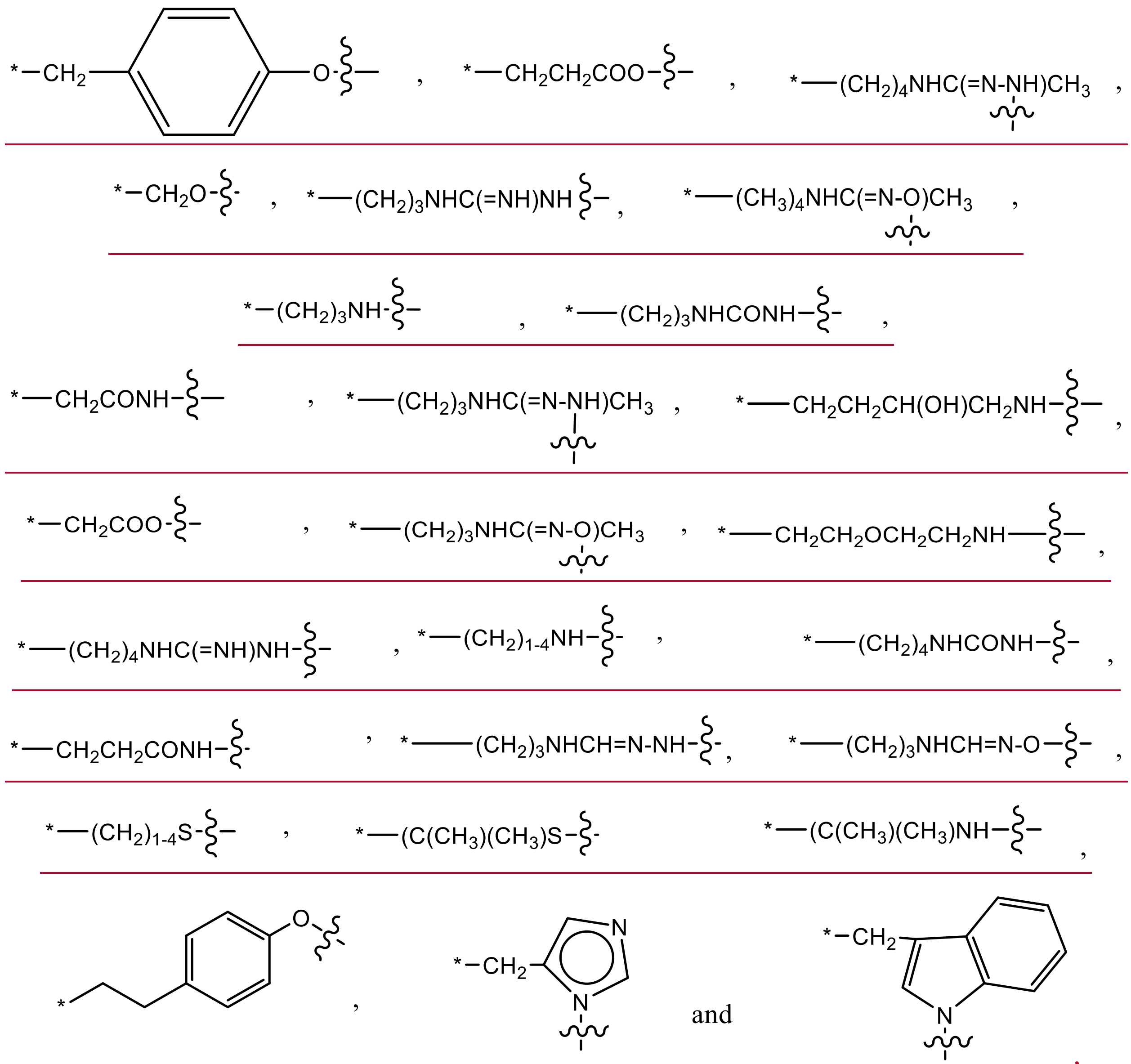
or

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:



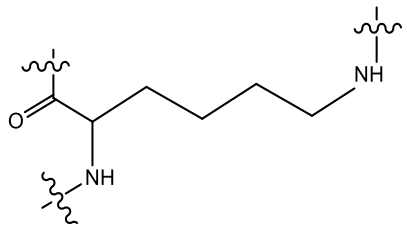
wherein the asterisk indicates the site of covalent attachment to the carbon labeled x and the wavy lines indicate the sites of covalent attachments within the Ligand-Drug Conjugate compound,

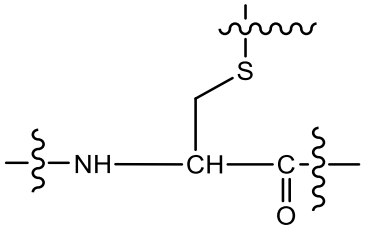
or

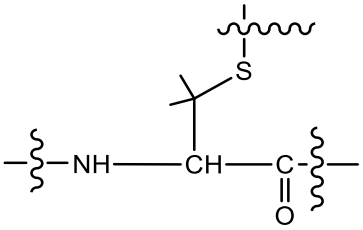
the Parallel Connector Unit or subunit thereof is a trifunctional amino acid residue,

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;

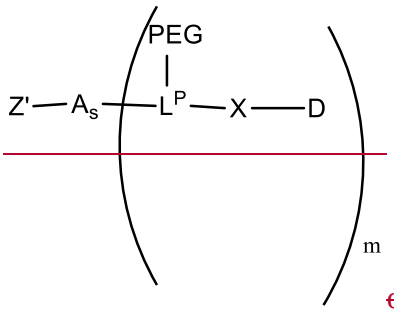
~~AD is a Drug Attachment Unit;~~

~~the subscript t is an integer and is 0 to 8, preferably 0, 1, 2, or 3;~~

the subscript m is an integer ranging from 1 to 4~~, preferably 1 or 2~~; 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.

~~**70**. The Drug-Linker Compound of claim 69 wherein the Drug-Linker Compound has the structure of :~~

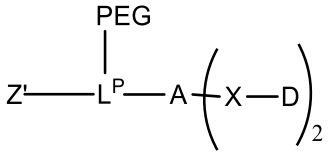


~~or a pharmaceutically acceptable salt thereof.~~

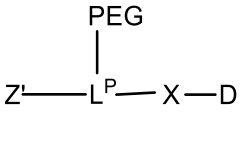
~~71~~**60**. The Drug-Linker Compound of claim ~~69 or 70~~59, wherein s is zero (i.e., A is absent).

~~72~~**61**. The Drug-Linker Compound of claim ~~69 or 70 or 71~~ 59, wherein s is 1 and m is 2 to 4.

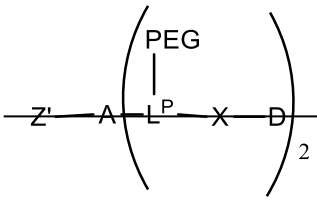
~~73~~62. The Drug-Linker Compound of claim ~~69~~59, wherein the Drug-Linker has the structure represented by formula IVa or IVb:~~, IVb, Va, Vb, Vc, VIa or VIb:~~



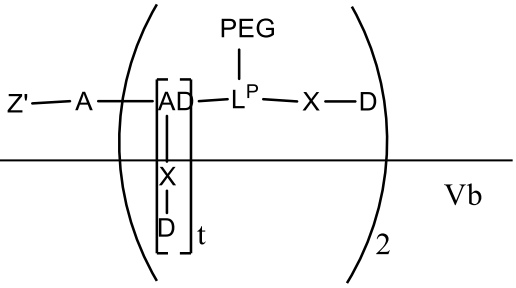
IVa



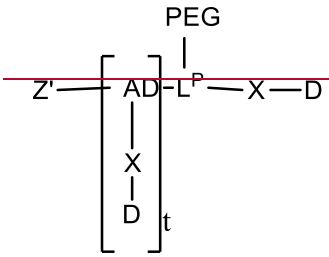
IVb



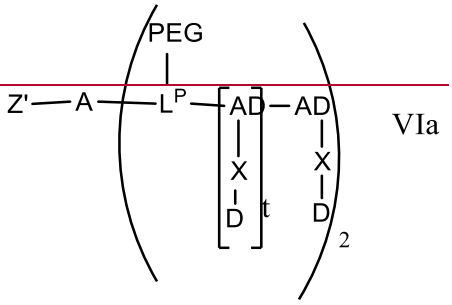
Va



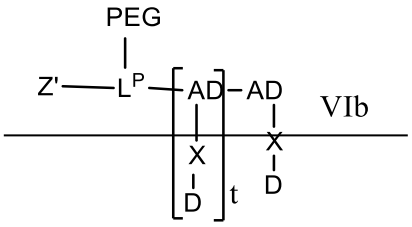
Vb



Vc



VIa



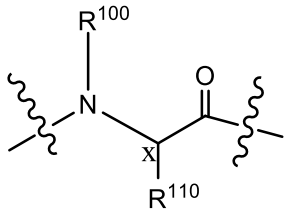
VIb

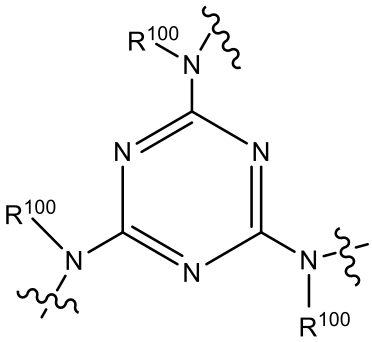
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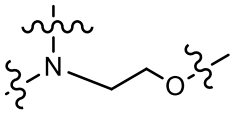
or a pharmaceutically acceptable salt thereof.

~~74. A Drug-Linker Compound of any one of claims 69 to 73 wherein L^P is an amino acid, amino alcohol, amino aldehyde or polyamine.~~

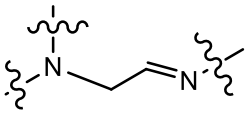
~~75. The Drug-Linker Compound of any one of claims 69 to 73 wherein each L^P independently has the structure of:~~

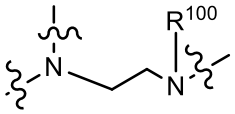


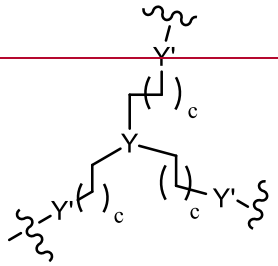
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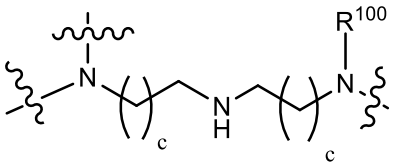
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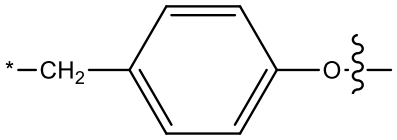
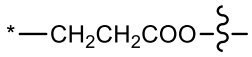
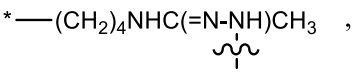
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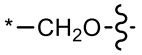
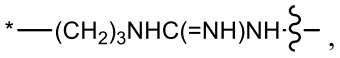
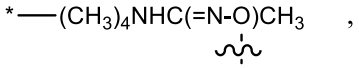
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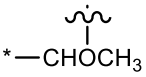
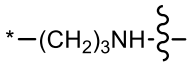
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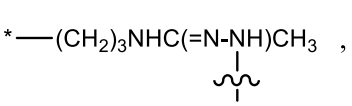
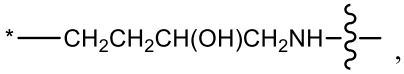


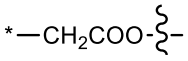
~~wherein the wavy line indicates the covalent attachment sites within the compound wherein R^{110} has the structure of~~

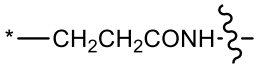
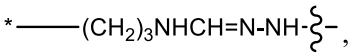
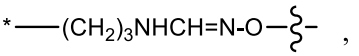

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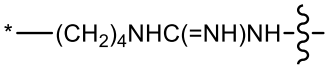
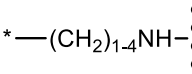
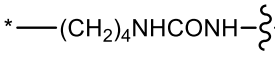

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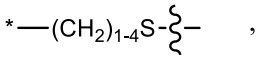
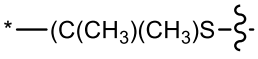
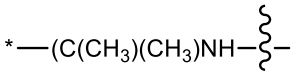

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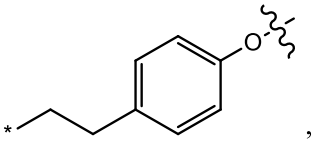
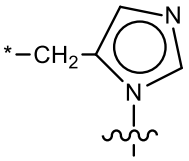
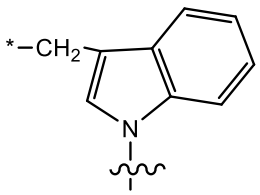

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~~wherein the asterisk indicates attachment of the R^{110} moiety to the carbon labeled x and the wavy line in the R^{110} moiety indicates one of the three attachment sites of L^P within the Ligand-Drug conjugate;~~

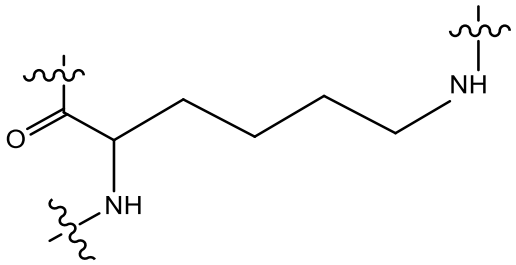
~~wherein each R^{100} is independently selected from hydrogen or C_1-C_3 alkyl, preferably hydrogen or CH_3;~~

~~Y is independently selected from N or CH;~~

~~each Y' is independently selected from NH, O, or S, and~~

~~the subscript c is independently selected from an integer ranging from 1 to 10, preferably 1, 2, or 3.~~

~~76~~**63**. The Drug-Linker Compound of claim ~~74~~59, wherein each L^P corresponds in structure to D/L lysine as shown in the formula below:

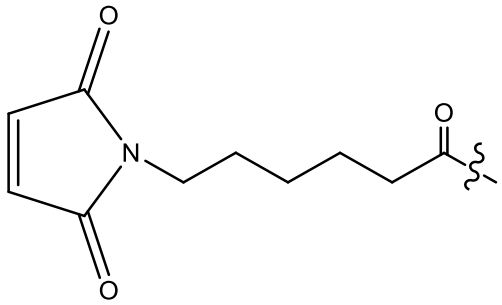


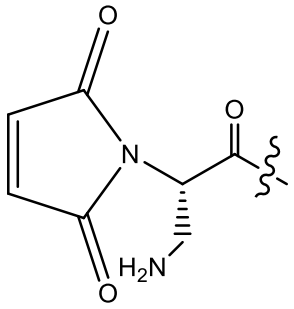
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~~77~~**64**. The Drug-Linker Compound of claim any one of claims ~~70 - 76~~59 to 63, wherein when A is present, A is from 1 to 10 amino acids, amino alcohols, amino aldehyde, polyamines, or combinations thereof.

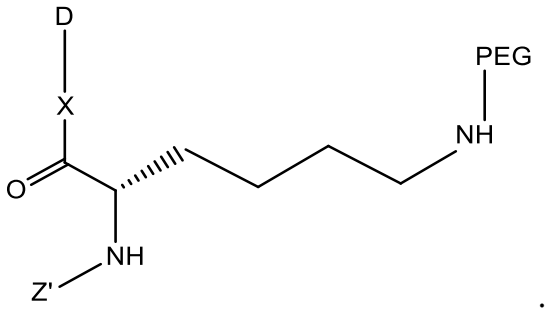
~~**78**. A Drug-Linker Compound of any one of claims 70 - 77 wherein when AD is present, AD is from 1 to 10 amino acids, amino alcohols, amino aldehyde, polyamines, or combinations thereof.~~

~~79~~**65**. The Drug-Linker Compound of any one of claims ~~69 - 78~~59 to 64, wherein Z' has the structure of



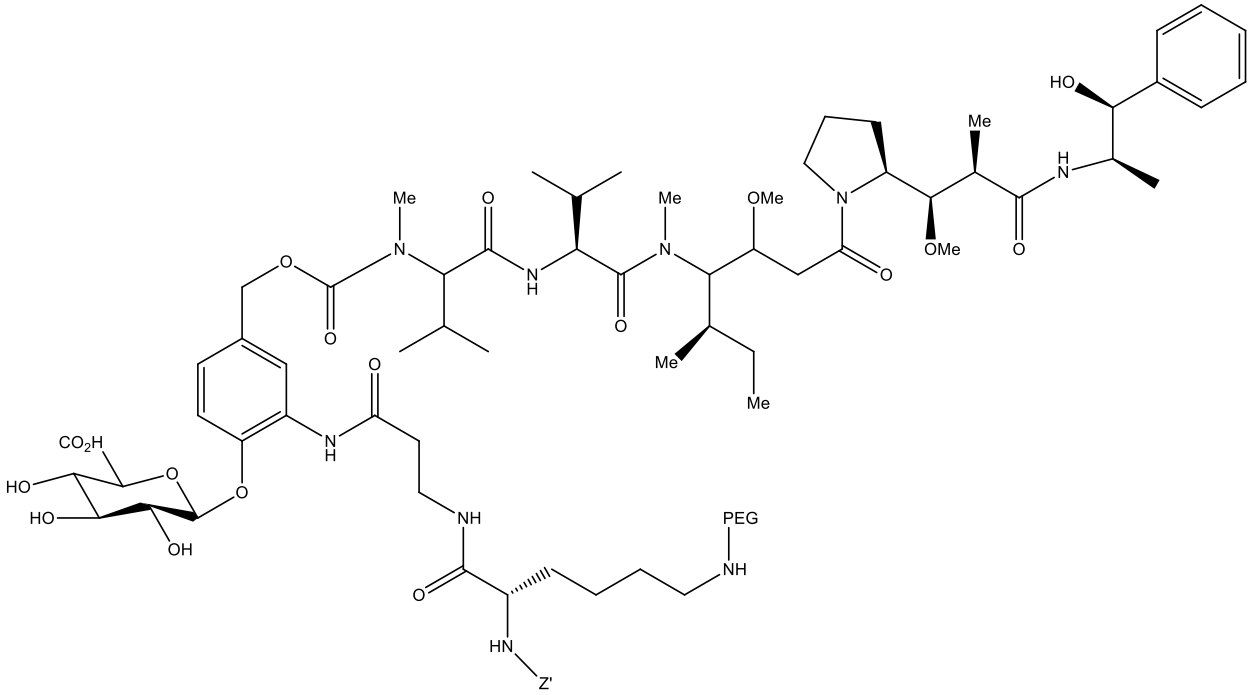
or  , optionally protected by an amine protecting group, wherein the wavy line indicates covalent attachment to the remainder of the Drug-Linker structure.

~~80~~66. The Drug-Linker Compound of claim ~~69~~59, wherein the Drug-Linker compound has the structure of:

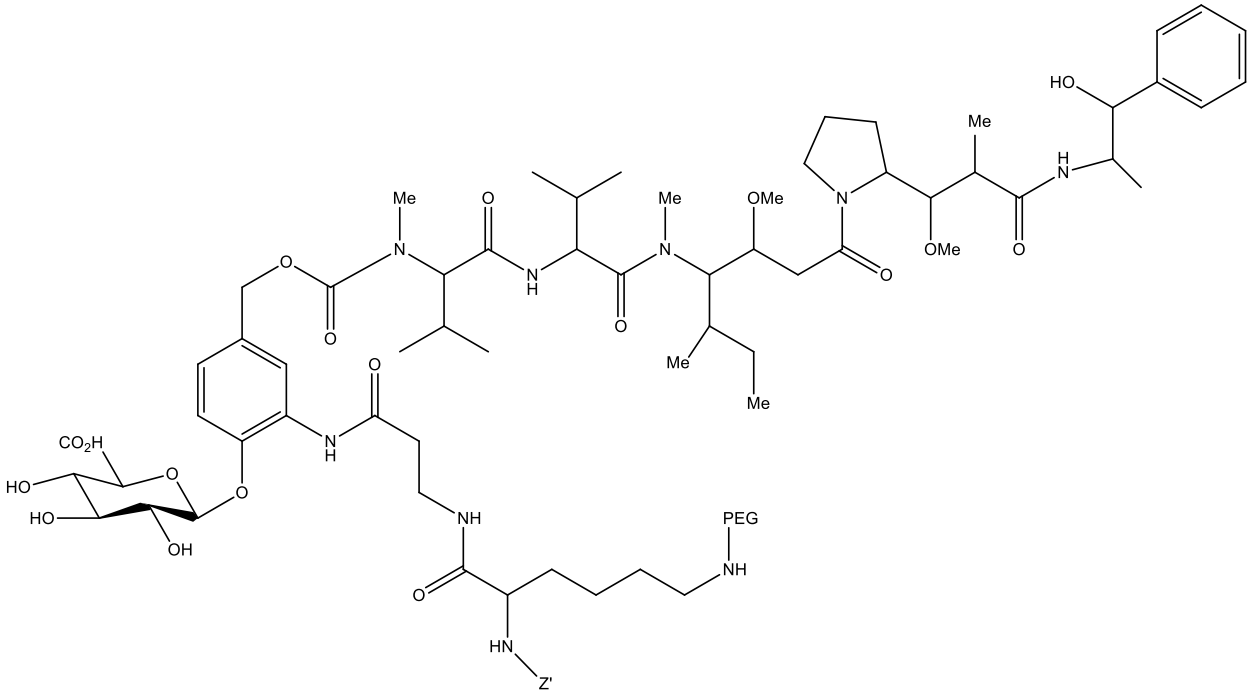


or a pharmaceutically acceptable salt thereof.

~~81~~67. **(** The Drug-Linker Compound of claim ~~69~~59, wherein the Drug-Linker Compound has the structure of:

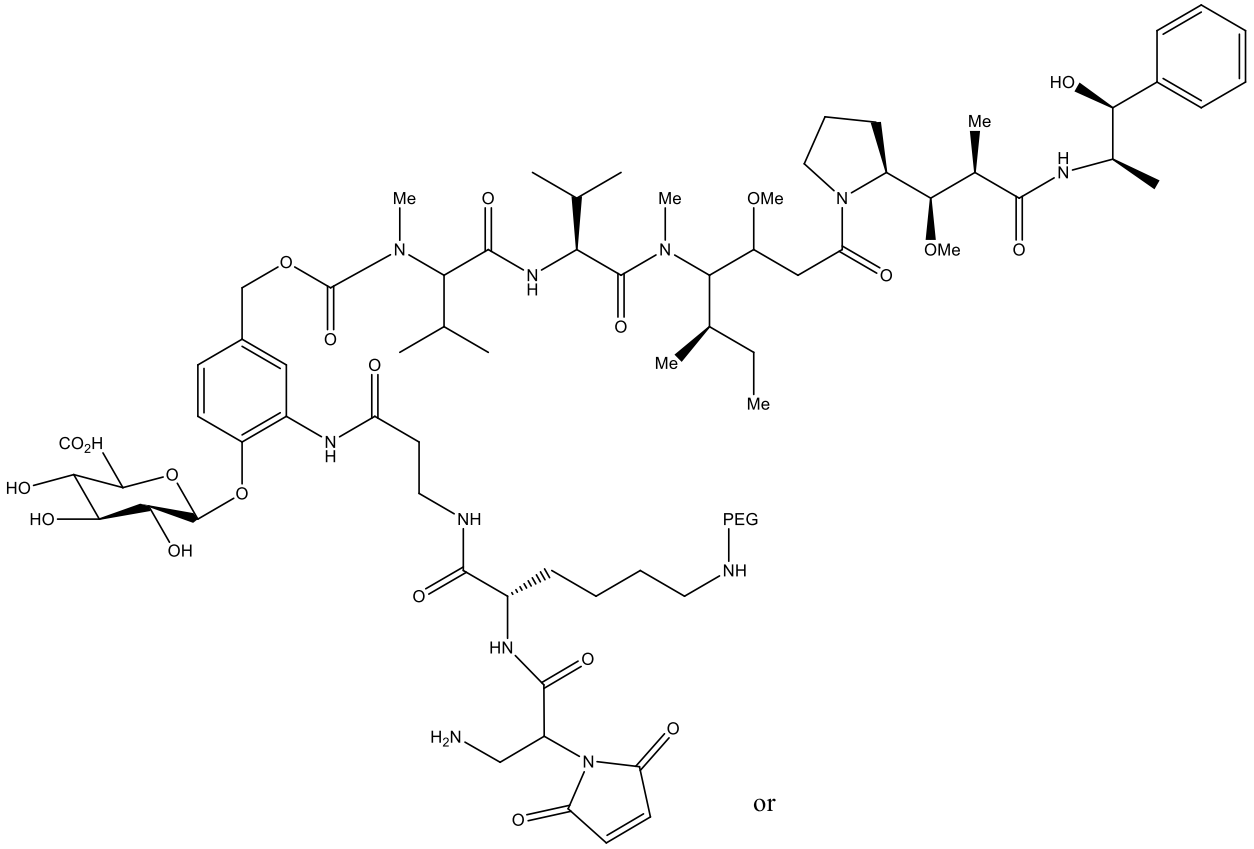


or

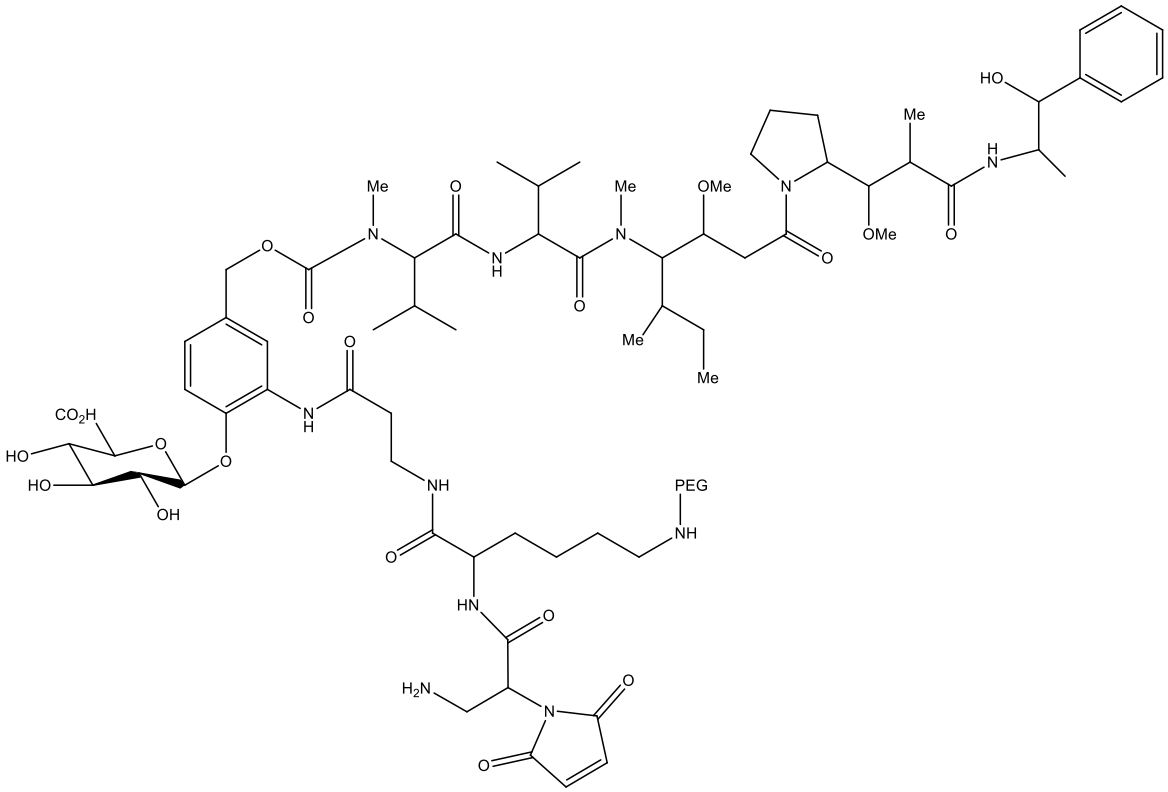


or a pharmaceutically acceptable salt thereof.

~~82~~68. The Drug-Linker Compound of claim ~~69~~59, wherein the Drug-Linker Compound has the structure of:

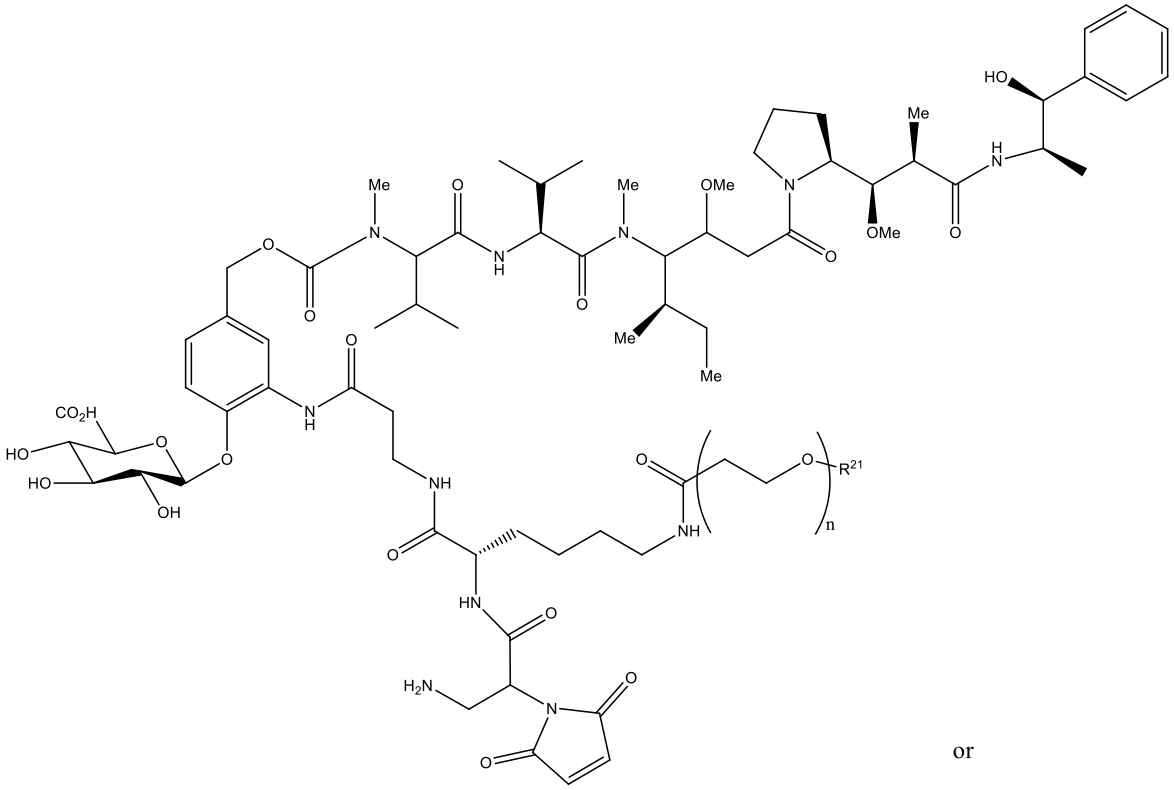


or

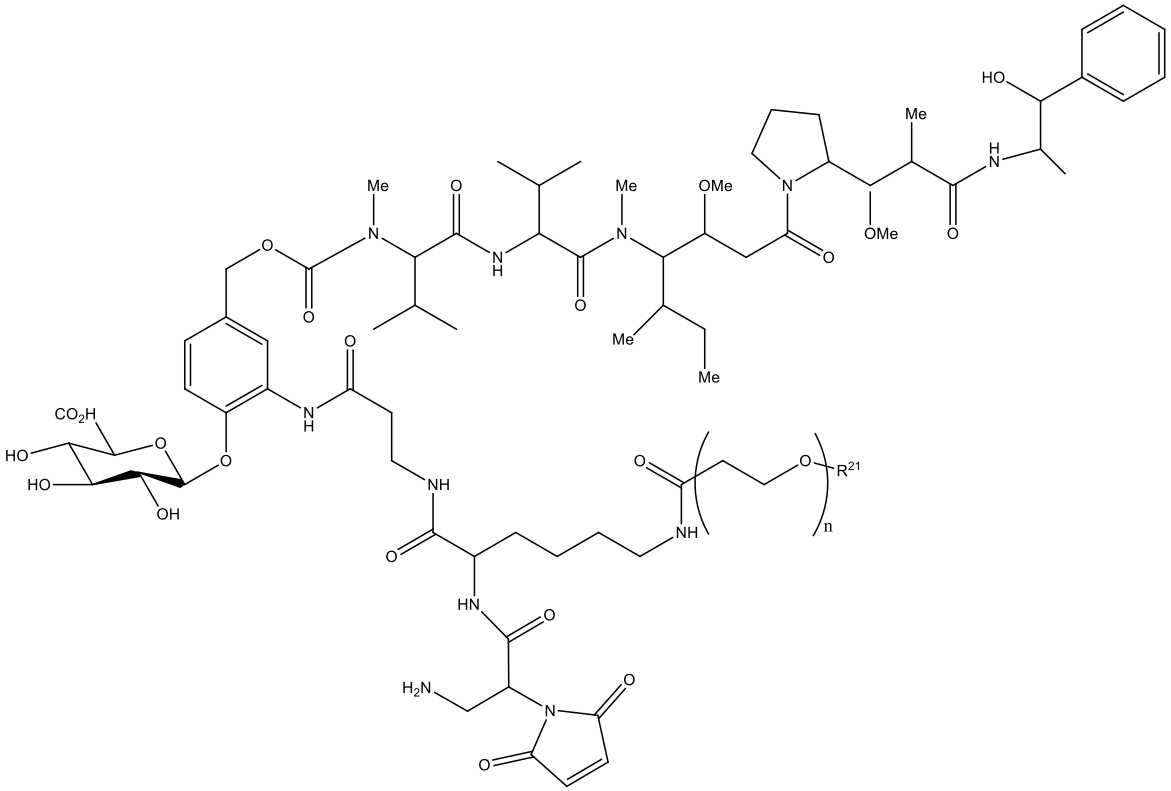


or a pharmaceutically acceptable salt thereof.

~~83~~69. The Drug-Linker Compound of claim ~~69~~59, wherein the Drug-Linker Compound has the structure of:

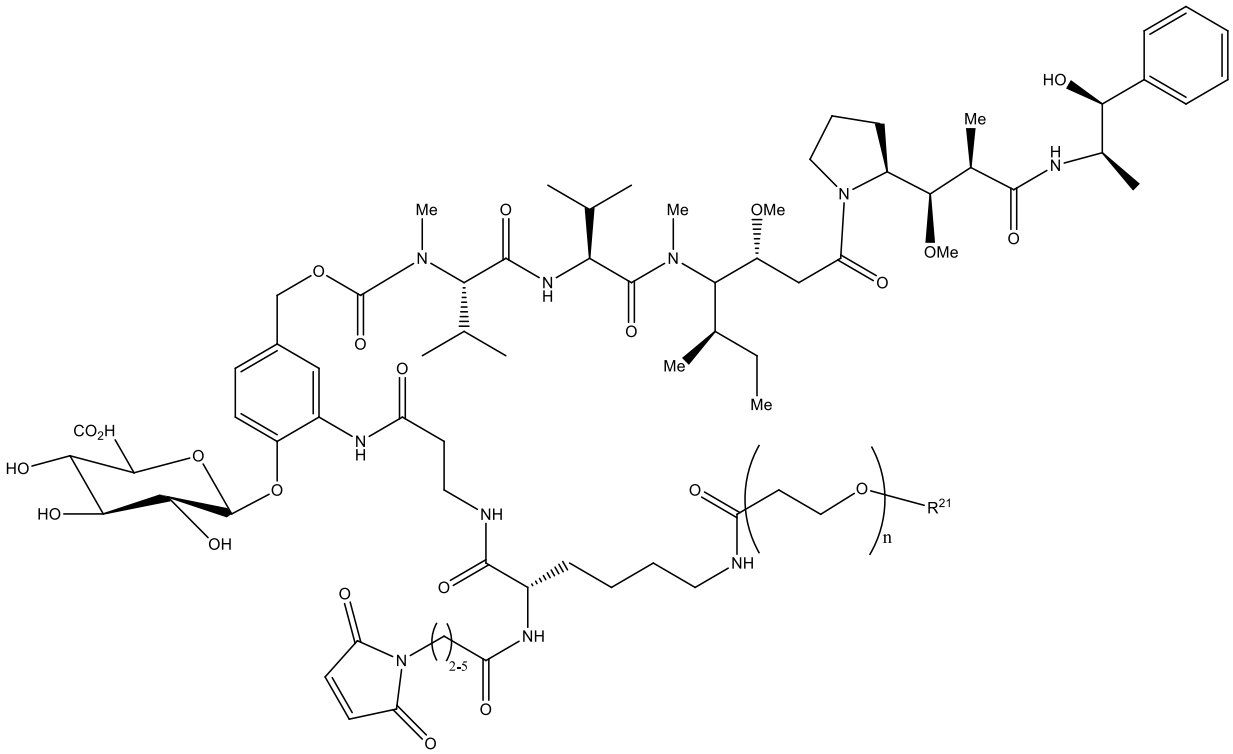


or

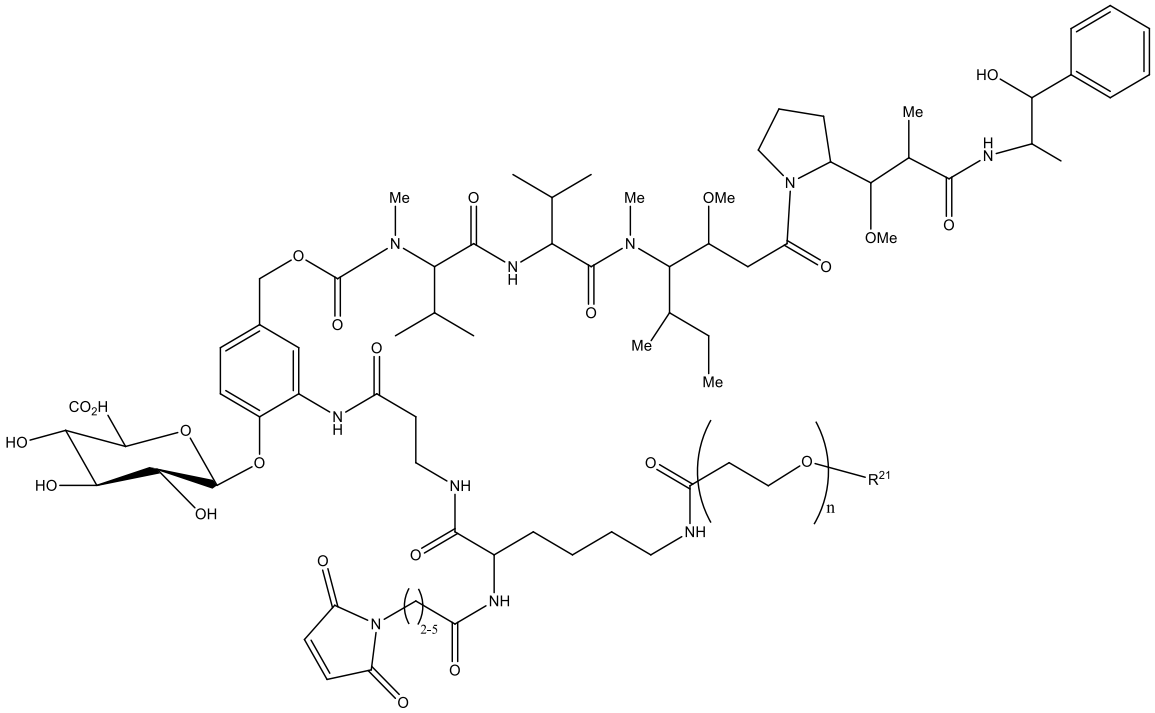


or a pharmaceutically acceptable salt thereof, wherein R^{21} is a PEG Capping Unit and n is an integer ranging from 6 to 72, 8 to 72, or 8 to 24.

~~84~~70. The Drug-Linker Compound of claim ~~69~~59, wherein the Drug-Linker Compound has the structure of:



or

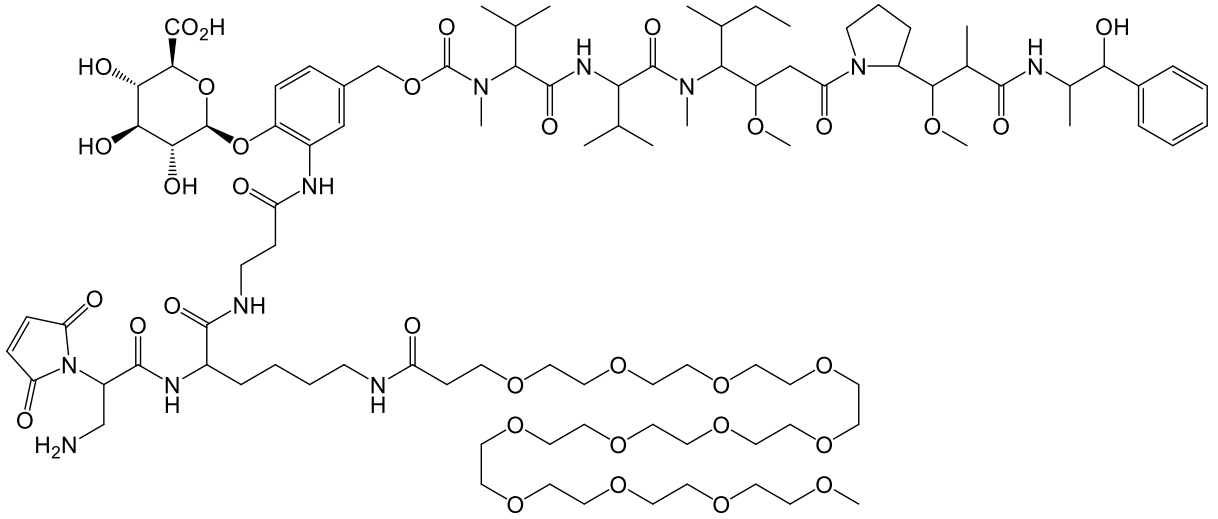


or a pharmaceutically acceptable salt thereof, wherein R^{21} is a PEG Capping Unit and n is 6 to 72~~, or 8 to 72, or 8 to 24~~.

~~85~~71. The Drug-Linker Compound of claim ~~83 or 84~~ 69 or 70, wherein n is 8, 12, or 24.

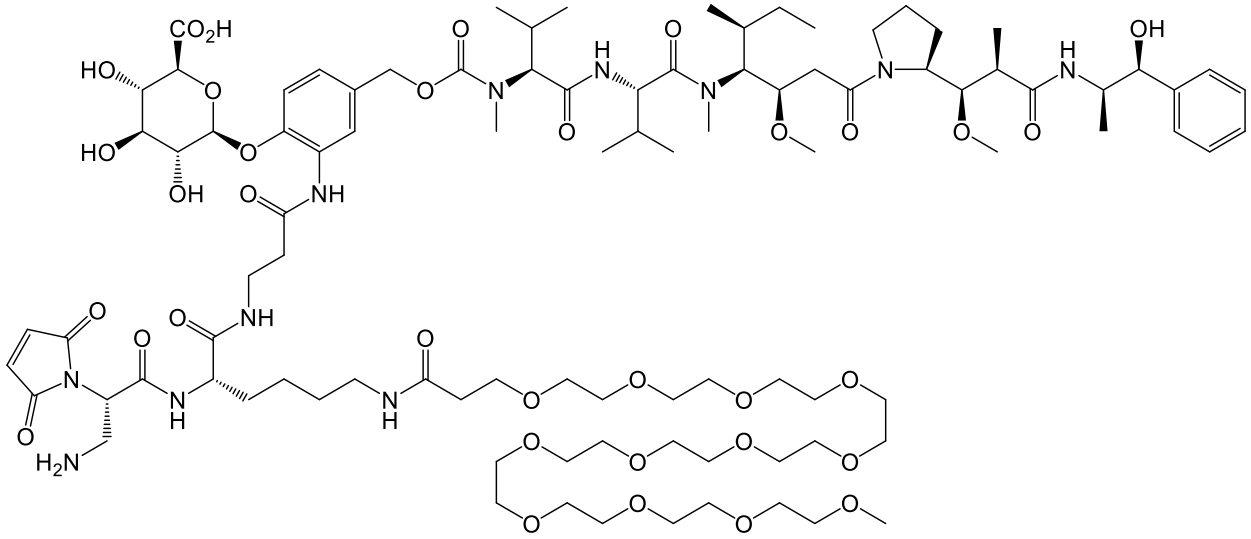
~~86~~72. The Drug-Linker Compound of ~~claim 83 or 84, or 85~~ any one of claims 69-71, wherein R^{21} is methyl, ethyl or propyl.

73. The Drug Linker Compound of claim ~~63~~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.

87. A pharmaceutical composition comprising a population of Ligand-Drug Conjugates having a Drug-Linker moiety corresponding in structure to a Drug-linker compound of any one of claims 69 to 86 conjugated to a Ligand Unit.; and a pharmaceutically acceptable carrier, wherein the average number of molecules of drug-linkers per Ligand in the composition ranges from about 8 to about 14.

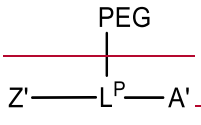
88. The pharmaceutical composition of any one of claims 64 – 68, and 87 wherein each parallel oriented PEG unit of a Ligand Drug Conjugate has at least 8 to no more than 24 PEG subunits.

89. The pharmaceutical composition of any one of claims 64 – 68 and 87 wherein each parallel oriented PEG unit of a Ligand Drug Conjugate has at least 12 to no more than 24 PEG subunits.

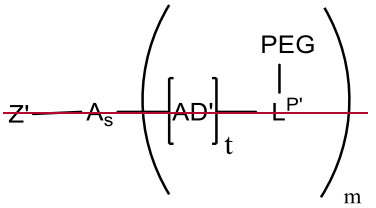
90. The pharmaceutical composition of any one of claims 64 – 69 and 87 – 89 wherein the value for the average Drug-linker loading also represents the Drug-Linker loading of the predominate Ligand-Drug Conjugate in the composition.

91. A Ligand-Drug Conjugate of any one claims 1 - 63 wherein, apart from the PEG Unit, there are no other PEG subunits present in the Ligand-Drug Conjugate.

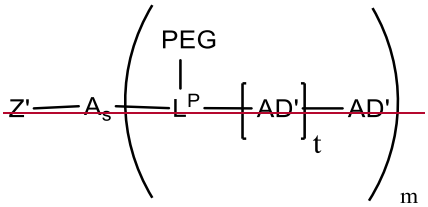
92. A Linker Compound having the formula VII, VIII or IX:



(VII)



(VIII)



(IX)

or a pharmaceutically acceptable salt thereof wherein

PEG is a Polyethylene Glycol Unit;

Z' is a Stretcher Unit capable of forming a covalent attachment to a Ligand Unit;

X-D is a Releasable Assembly Unit attached to a Drug Unit;

A' is a Branching Unit capable of forming a covalent attachment to two to four X-D Units, preferably two X-D Units;

A is an optional Branching Unit;

AD' is a Drug Attachment Unit capable of forming a covalent attachment to a X-D Unit;

L^{P} is a Parallel Connector Unit;

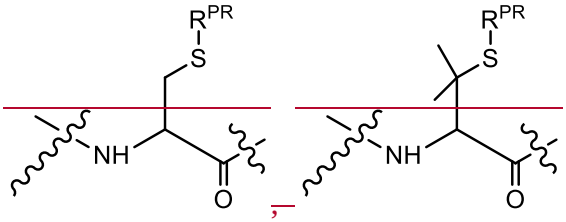
$L^{P'}$ is a Parallel Connector Unit capable of forming a covalent attachment to X-D;

the subscript t is an integer and is 0 to 8, preferably 0, 1, 2, or 3;

the subscript m is an integer and is 1 to 4; preferably 1 or 2;

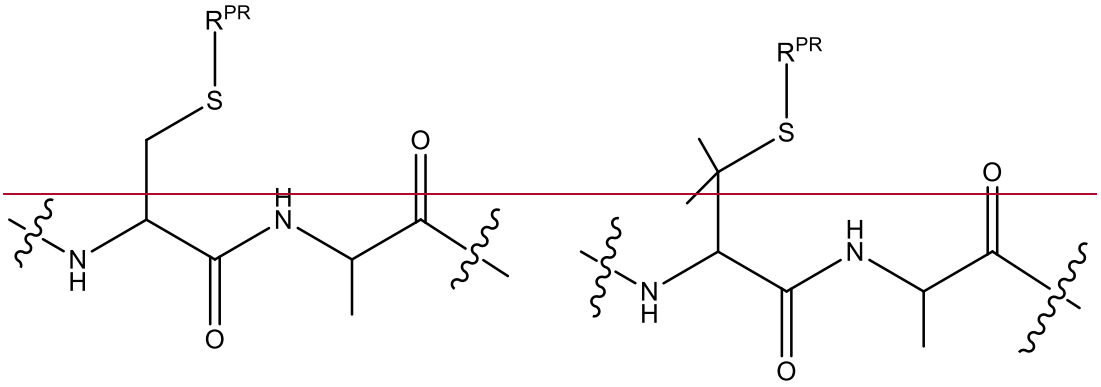
the subscript s is an integer and is 0 or 1,with the proviso that when s is 0, m is 1 and when s is 1, m is 2 to 4.

93. A Linker Compound of claim 92 wherein $L^{P'}$ is a protected cysteine or penicillamine as shown in the formula below:.



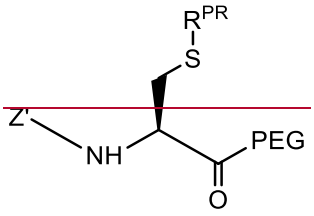
wherein the wavy line indicates covalent attachment within the Compound and R^{PR} is a thiol protecting group.

94. A Linker Compound of claim 92 having Formula VIII wherein t is 1 and wherein AD' is



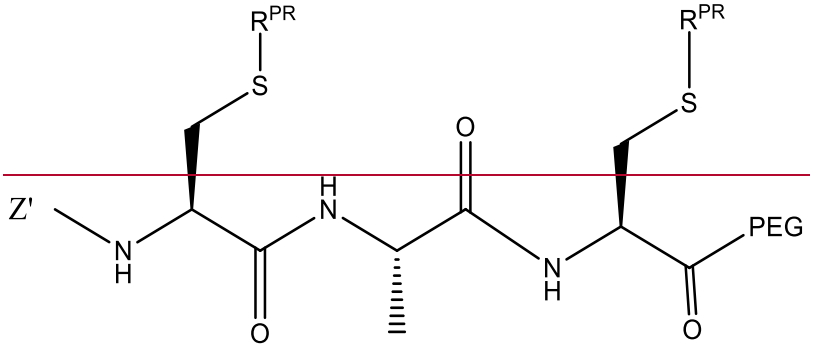
wherein R^{PR} is a thiol protecting group and the wavy line indicates covalent attachment within the Compound.

95. A Linker Compound of claim 92 having the formula:



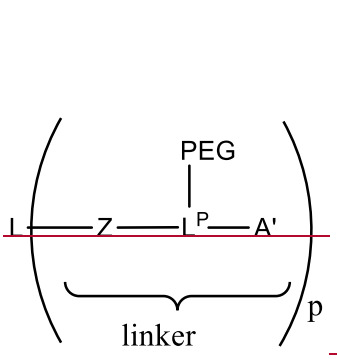
or a pharmaceutically acceptable salt thereof, wherein R^{PR} is a thiol protecting group.

96. A Linker Compound of claim 92 having the formula

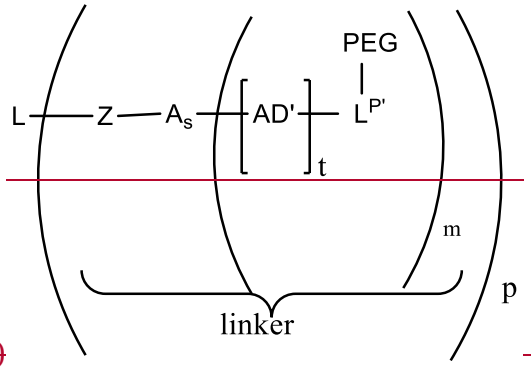


or a pharmaceutically acceptable salt thereof, wherein R^{PR} is a thiol protecting group

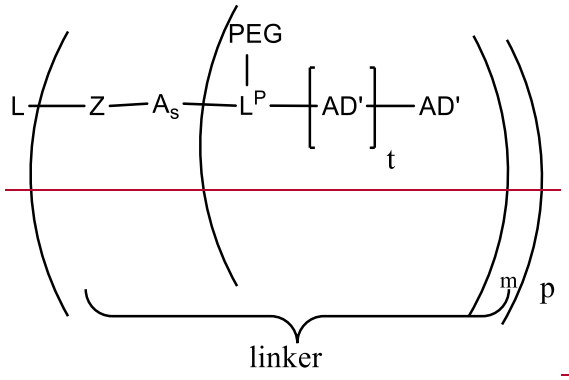
97. A Ligand-Linker Compound having the formula X, XI, XII as follows:



(X)



(XI)



(XII)

or a pharmaceutically acceptable salt thereof wherein

L is a Ligand Unit;

PEG is a Polyethylene Glycol Unit;

Z is a Stretcher Unit;

X-D is a Releasable Assembly Unit attached to a Drug Unit;

L^P is a Parallel Connector Unit;

$L^{P'}$ is a Parallel Connector Unit capable of forming a covalent attachment to X-D;

$A^{'}$ is a Branching Unit capable of forming a covalent attachment to two to four X-D Units, preferably two X-D Units;

A is an optional Branching Unit;

$AD^{'}$ is a Drug Attachment Unit capable of forming a covalent attachment to a X-D Unit;

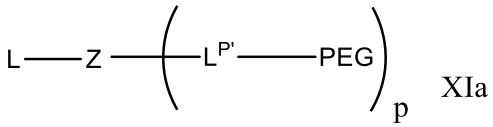
the subscript p is an integer and is 1 to 14, preferably about 2 to about 12 (preferably about 6 to about 14, about 6 to about 12, about 8 to about 14 or about 8 to about 12);

the subscript t is an integer and is 0 to 8; preferably 0, 1, 2, or 3

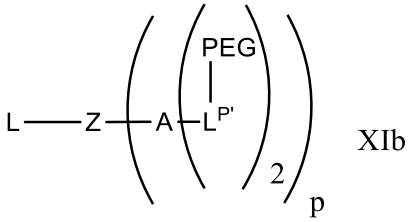
the subscript m is an integer and is 1 to 4; preferably 1 or 2; and

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

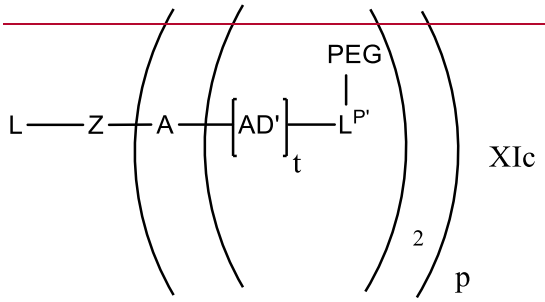
98. The Ligand-Linker compound of claim 97 wherein the Linker-Ligand Linker compound has the structure of fomula XIa, XIb, XIc, XId, XIIa or XIIb:



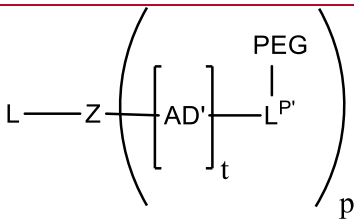
XIa



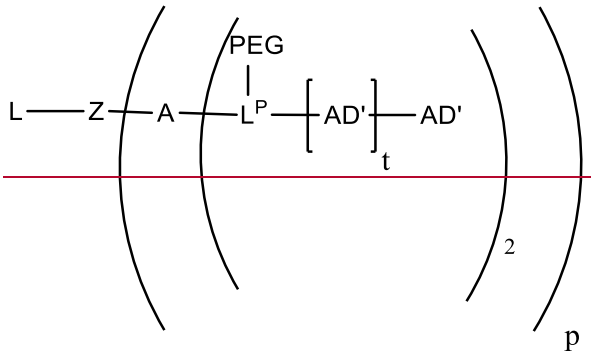
XIb



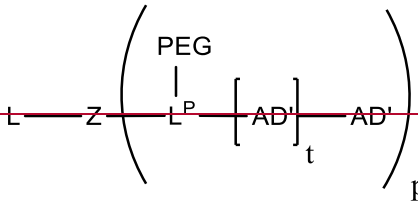
XIc



XId



XIIa



XIIb

or a pharmaceutically acceptable salt thereof .

~~**99**. The pharmaceutical composition of any one of claims 64-68 and 87 - 90 wherein the composition exhibits improved pharmacokinetic properties as compared to a pharmaceutical composition comprising ligand-drug conjugates lacking the PEG Unit or containing the PEG Unit but placed in a serial orientation in relation to the antibody and drug.~~

~~**100.** The pharmaceutical composition of any one of claims 64-68 and 87 - 90 wherein the composition exhibits pharmacokinetic properties the same or substantially the same as compared to a pharmaceutical composition comprising the corresponding unconjugated Ligand.~~

~~**101**. A method of treating cancer comprising administering to a subject in need thereof, an effective amount of a Ligand-Drug Conjugate of any one of claims 1 to 63 or a pharmaceutical composition of any one of claims 64-68, 87-90, or 99-100 wherein the Ligand Unit of the Ligand-Drug Conjugate specifically binds to a target antigen expressed by cancer cells.~~

~~**102**~~**75**. ~~A~~ The Ligand-Drug Conjugate compound of any one of claims 1 to ~~63~~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.