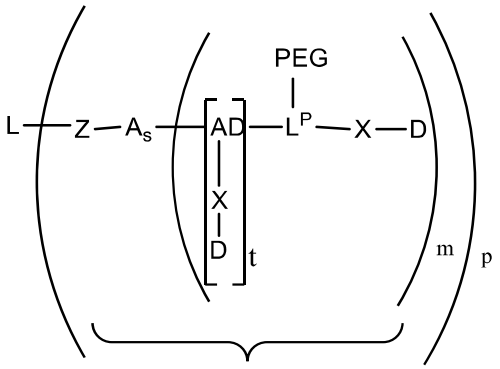
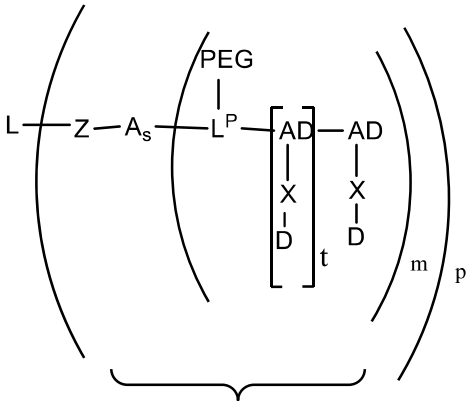
BRIEF SUMMARY

[0033a] In one aspect, the present disclosure refers to a Ligand-Drug Conjugate compound represented by the structure of Formula II or Formula III:



(II)



(III)

or a pharmaceutically acceptable salt thereof, wherein

subscript s is 0 and subscript m is 1, or subscript s is 1 and subscript m is 2, 3 or 4;

L is a Ligand Unit, wherein the Ligand Unit is selected from an antibody, an interferon, a lymphokine, a hormone, a growth factor, a colony-stimulating, a vitamin or a nutrient-transport molecule, wherein the Ligand Unit is a targeting agent that specifically binds to a target moiety, wherein said binding presents the Drug Unit of the Ligand-Drug Conjugate to the particular target cell population characterized by the target moiety with which the Ligand Unit interacts;

D is a hydrophobic Drug Unit, wherein the Drug Unit is a cytotoxic, cytostatic, or immunosuppressive drug having a hydrophobicity greater than or within 20% of monomethyl auristatin E when measured using SlogP;

PEG is a Polyethylene Glycol Unit, wherein the PEG Unit comprises from 4 to 72 (OCH_2CH_2) subunits;

Z is a Stretcher Unit, wherein Z links the Ligand Unit to L^P;

X is a Releasable Assembly Unit, wherein X comprises a peptide, disulfide, or glycosidic bond;

L^P is a Parallel Connector Unit, wherein L^P connects the Ligand Unit to the Polyethylene Glycol Unit and the hydrophobic Drug Unit so that Polyethylene Glycol Unit and the Drug Unit are in a parallel orientation, wherein the Polyethylene Glycol Unit in said parallel orientation masks the hydrophobicity of the hydrophobic Drug Unit;

A is an optional Branching Unit, wherein each A, when present, is one to 10 independently selected amino acid, amino alcohol, amino aldehyde, or polyamine residues, or a combination thereof, covalently bonded to one another;

AD is a Drug Attachment Unit, wherein each AD, when present, is one to 10 independently selected amino acid, amino alcohol, amino aldehyde, or polyamine residues, or a combination thereof, covalently bonded to one another;

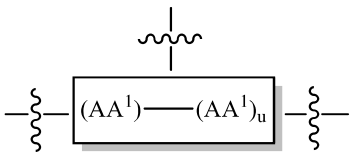
subscript t is an integer ranging from 0 to 8, or is 0, 1, 2 or 3;

subscript p is an integer ranging from 1 to 14, 2 to 12, 6 to 14, 6 to 12, 8 to 14 or 8 to 12 and;

each L^P is independently (i) or (ii):

(i) comprises an amino acid, amino alcohol, amino aldehyde, or a polyamine residue, or

(ii) the structure of L^P represented by Formula A:



Formula A

wherein

AA^1 is independently selected from an amino acid, 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; and

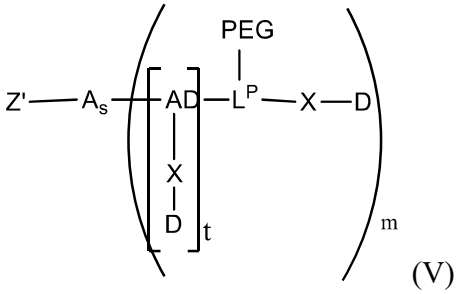
subscript u is an integer ranging from 0 to 4; wherein at least one AA^1 has a functionalized side chain that provides for an attachment site to a PEG, AD, A or Z unit or an X-D moiety, or

AA^1 is an 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 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, and

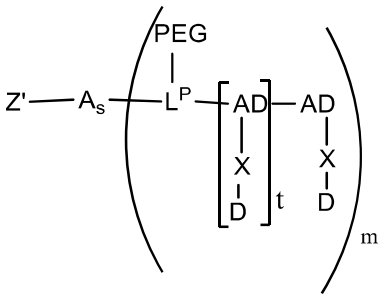
wherein the Polyethylene Glycol Unit is in parallel orientation relative to the Drug Units of each drug-linker moiety, and wherein the Releasable Assembly Units are capable of releasing free drug in proximity to a target site targeted by the Ligand Unit.

[0033b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a population of Ligand-Drug Conjugate compounds as disclosed herein wherein the average number of drug-linker moieties per Ligand Unit in the composition ranges from about 4 to about 14, from about 6 to about 14, from about 8 to about 14, or from about 8 to about 12, or the average number of molecules of drug-linker moieties per Ligand Unit in the composition is about 8; and a pharmaceutically acceptable carrier.

[0033c] In yet another aspect, the present disclosure refers to a Drug-Linker compound wherein the Drug-Linker compound has the structure of Formula V or VI:



(V)



(VI)

or a pharmaceutically acceptable salt thereof, wherein

D is a hydrophobic Drug Unit , wherein the Drug Unit is a cytotoxic, cytostatic, or immunosuppressive drug having a hydrophobicity greater than or within 20% of monomethyl auristatin E when measured using SlogP;

PEG is a Polyethylene Glycol Unit , wherein the PEG Unit comprises from 4 to 72 (OCH_2CH_2 subunits);

Z' is a Stretcher Unit capable of forming a covalent attachment to a Ligand Unit, wherein the covalent attachment would link the Ligand Unit to L_P;

X is a Releasable Assembly Unit , wherein X comprises a peptide, disulfide, or glycosidic bond;

L^P is a Parallel Connector Unit, wherein L^P connects the Ligand Unit to the Polyethylene Glycol Unit and the hydrophobic Drug Unit so that Polyethylene Glycol Unit and the Drug Unit are in a parallel orientation, wherein the Polyethylene Glycol Unit in said parallel orientation masks the hydrophobicity of the hydrophobic Drug Unit;

A is an optional Branching Unit, wherein each A, when present, is one to 10 independently selected amino acid, amino alcohol, amino aldehyde, or polyamine residues, or a combination thereof, covalently bonded to one another;

AD is a Drug Attachment Unit, wherein each AD, when present, is one to 10 independently selected amino acid, amino alcohol, amino aldehyde, or polyamine residues, or a combination thereof, covalently bonded to one another;

subscript t is an integer ranging from 0 to 8, or from 0 to 3;

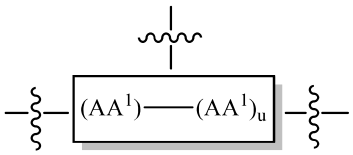
subscript m is an integer ranging from 1 to 4, or is 1 or 2;

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

each L^P is independently (i) or (ii):

(i) comprises an amino acid, amino alcohol, amino aldehyde, or a polyamine residue, or

(ii) the structure of L^P represented by Formula A:



Formula A

wherein

AA^1 is independently selected from an amino acid, 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; and

subscript u is an integer ranging from 0 to 4; wherein at least one AA^1 has a functionalized side chain that provides for an attachment site to a PEG, AD, A or Z unit or an X-D moiety, or

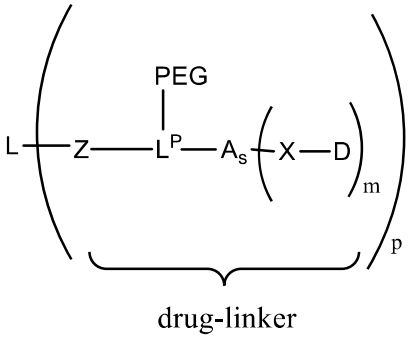
AA^1 is an amino acid or is an optionally substituted C_{1-20} heteroalkylene, optionally substituted C_{3-8} heterocyclo, optionally substituted C_{6-14} arylene, or optionally substituted C_3-C_8 carbocyclo, provided that no more than 2 of AA^1 is an optionally substituted C_{1-20} heteroalkylene, optionally substituted C_{3-8} heterocyclo, optionally substituted C_{6-14} arylene, or optionally substituted C_3-C_8 carbocyclo.

[0033d] In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising a population of Ligand-Drug Conjugate compounds each having a drug linker moiety corresponding in structure to a Drug-Linker compound as disclosed herein conjugated to a Ligand Unit; and a pharmaceutically acceptable carrier, wherein the average number of drug-linker moieties per Ligand Unit in the composition ranges from about 8 to about 14; and each PEG unit of a Ligand Drug Conjugate compound independently has at least 8 to no more than 24 PEG subunits, or has at least 12 to no more than 24 PEG subunits.

[0033e] In yet another aspect, the present disclosure refers to the use of a Ligand Drug Conjugate compound for preparing a medicament for the treatment of cancer wherein the Ligand Drug Conjugate compound has the structure as disclosed herein, and wherein the Ligand Unit binds to a tumor cell or cancer cell.

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

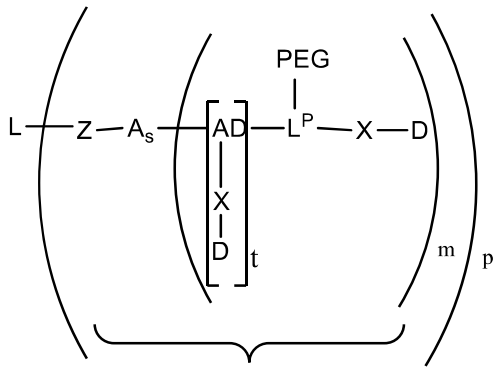
[0035] In some examples, an LDC of the present disclosure is represented by the structure of Formula I below:



(I)

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

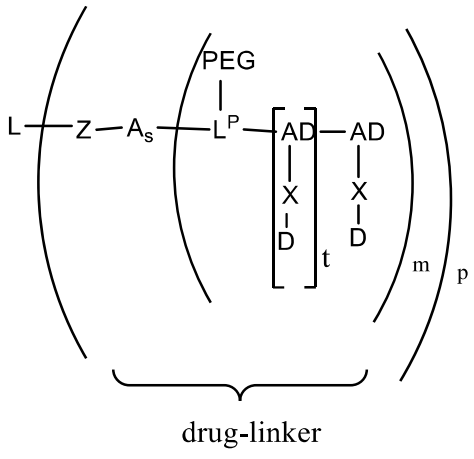
[0036] In other examples, an LDC of the present disclosure is represented by the structure of Formula II below:



(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 examples an LDC of the present 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.

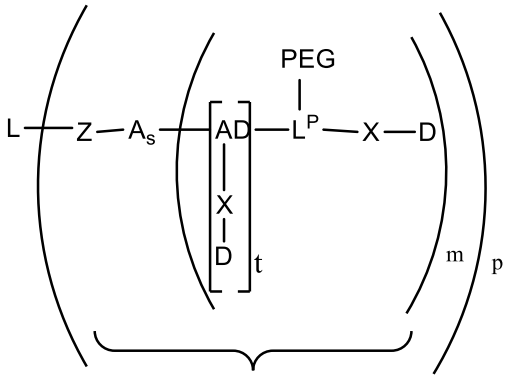
DESCRIPTION OF THE INVENTION

General

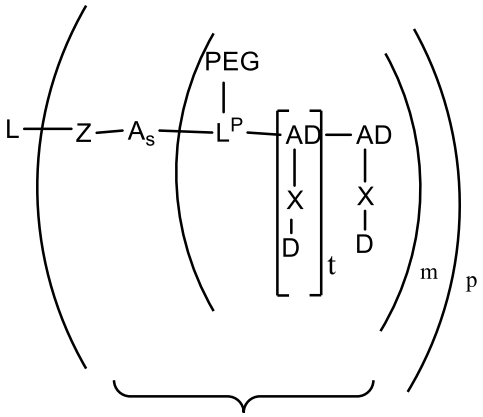
[0038] The present invention is based, in part, on the surprising discovery that the orientation of a polyethylene glycol component (PEG Unit) of a Ligand-Drug Conjugate, can have a profound influence on the resulting pha*r*macokinetics of the conjugate. Specifically, the present

What is claimed is:

1. A Ligand-Drug Conjugate compound represented by the structure of Formula II or Formula III:



(II)



(III)

or a pharmaceutically acceptable salt thereof, wherein

subscript s is 0 and subscript m is 1, or subscript s is 1 and subscript m is 2, 3 or 4;

L is a Ligand Unit, wherein the Ligand Unit is selected from an antibody, an interferon, a lymphokine, a hormone, a growth factor, a colony-stimulating, a vitamin or a nutrient-transport molecule, wherein the Ligand Unit is a targeting agent that specifically binds to a target moiety, wherein said binding presents the Drug Unit of the Ligand-Drug Conjugate to the particular target cell population characterized by the target moiety with which the Ligand Unit interacts;

D is a hydrophobic Drug Unit, wherein the Drug Unit is a cytotoxic, cytostatic, or immunosuppressive drug having a hydrophobicity greater than or within 20% of monomethyl auristatin E when measured using SlogP;

PEG is a Polyethylene Glycol Unit, wherein the PEG Unit comprises from 4 to 72 (OCH_2CH_2) subunits;

Z is a Stretcher Unit, wherein Z links the Ligand Unit to L^P;

X is a Releasable Assembly Unit, wherein X comprises a peptide, disulfide, or glycosidic bond;

L^P is a Parallel Connector Unit, wherein L^P connects the Ligand Unit to the Polyethylene Glycol Unit and the hydrophobic Drug Unit so that Polyethylene Glycol Unit and the Drug Unit are in a parallel orientation, wherein the Polyethylene Glycol Unit in said parallel orientation masks the hydrophobicity of the hydrophobic Drug Unit;

A is an optional Branching Unit, wherein each A, when present, is one to 10 independently selected amino acid, amino alcohol, amino aldehyde, or polyamine residues, or a combination thereof, covalently bonded to one another;

AD is a Drug Attachment Unit, wherein each AD, when present, is one to 10 independently selected amino acid, amino alcohol, amino aldehyde, or polyamine residues, or a combination thereof, covalently bonded to one another;

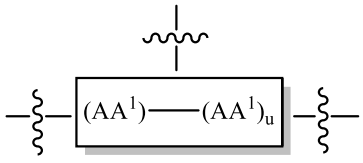
subscript t is an integer ranging from 0 to 8, or is 0, 1, 2 or 3;

subscript p is an integer ranging from 1 to 14, 2 to 12, 6 to 14, 6 to 12, 8 to 14 or 8 to 12; and

each L^P is independently (i) or (ii):

(i) comprises an amino acid, amino alcohol, amino aldehyde, or a polyamine residue, or

(ii) the structure of L^P represented by Formula A:



Formula A

wherein

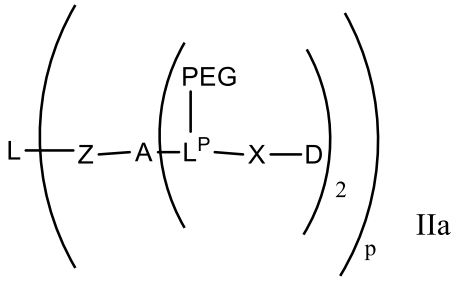
AA^1 is independently selected from an amino acid, optionally substituted C_{1-20} heteroalkylene, optionally substituted C_{3-8} heterocyclo, optionally substituted C_{6-14} arylene, or optionally substituted C_3-C_8 carbocyclo; and

subscript u is an integer ranging from 0 to 4; wherein at least one AA^1 has a functionalized side chain that provides for an attachment site to a PEG, AD, A or Z unit or an X-D moiety, or

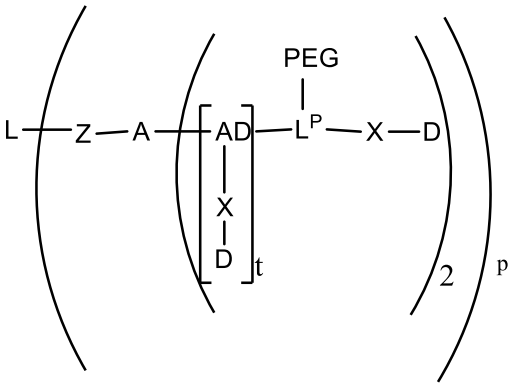
AA^1 is an amino acid or is an optionally substituted C_{1-20} heteroalkylene, optionally substituted C_{3-8} heterocyclo, optionally substituted C_{6-14} arylene, or optionally substituted C_3-C_8 carbocyclo, provided that no more than 2 of AA^1 is an optionally substituted C_{1-20} heteroalkylene, optionally substituted C_{3-8} heterocyclo, optionally substituted C_{6-14} arylene, or optionally substituted C_3-C_8 carbocyclo, and

wherein the Polyethylene Glycol Unit is in parallel orientation relative to the Drug Units of each drug-linker moiety, and wherein the Releasable Assembly Units are capable of releasing free drug in proximity to a target site targeted by the Ligand Unit.

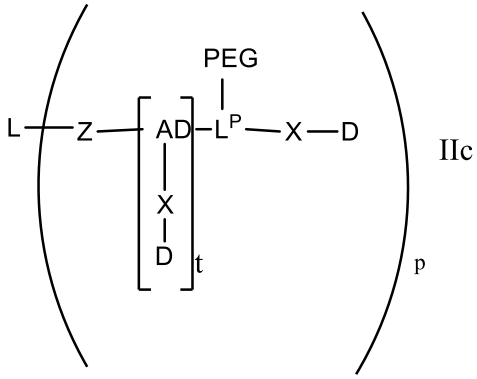
2. The Ligand-Drug Conjugate compound of claim 1, wherein the Ligand-Drug Conjugate compound has the structure represented by Formula IIa, IIb, IIc, IIIa, or IIIb:



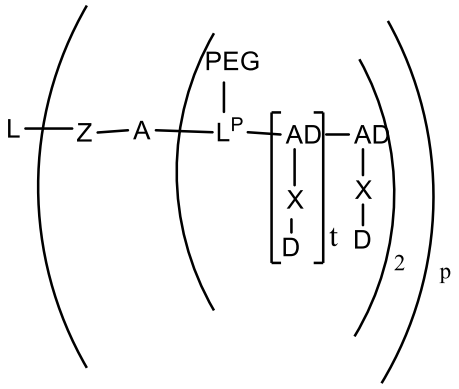
IIa



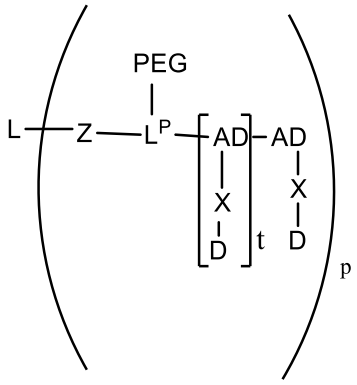
IIb



IIc



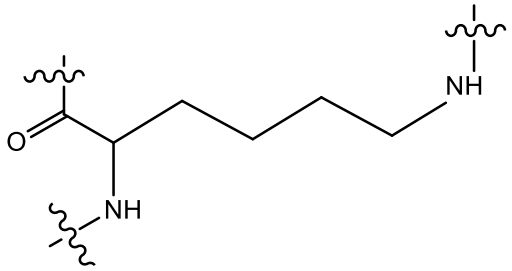
IIIa

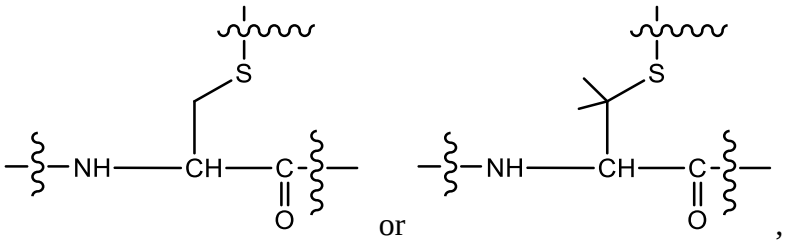


IIIb

or a pharmaceutically acceptable salt thereof, wherein each Parallel Connector Unit (L^P) comprises an amino acid, an amino alcohol, an amino aldehyde or a polyamine residue.

3. The Ligand-Drug Conjugate compound of claim 2, wherein each Parallel Connector (L^P) Unit has the structure of:

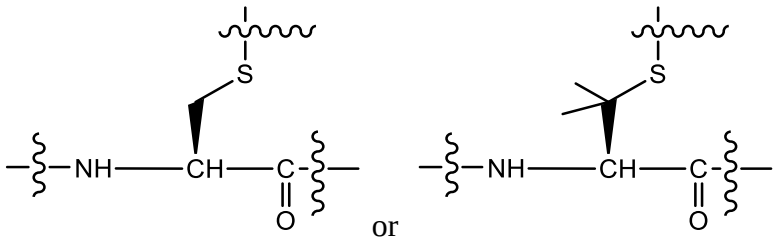




,

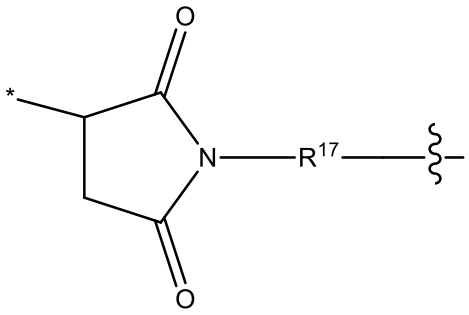
wherein the wavy lines indicates covalent attachment sites of L^P within the Ligand-Drug Conjugate compound.

4. The Ligand-Drug Conjugate compound of claim 3, wherein each Parallel Connector (L^P) Unit has the structure of:



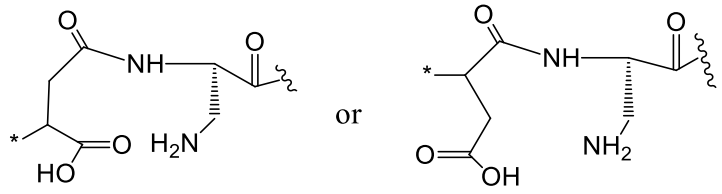
wherein the wavy line adjacent to the sulfur atom indicates covalent attachment to a Releasable Assembly Unit.

5. The Ligand-Drug Conjugate compound of claim 1 or 2, 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 drug-linker moiety within the Ligand-Drug Conjugate compound.

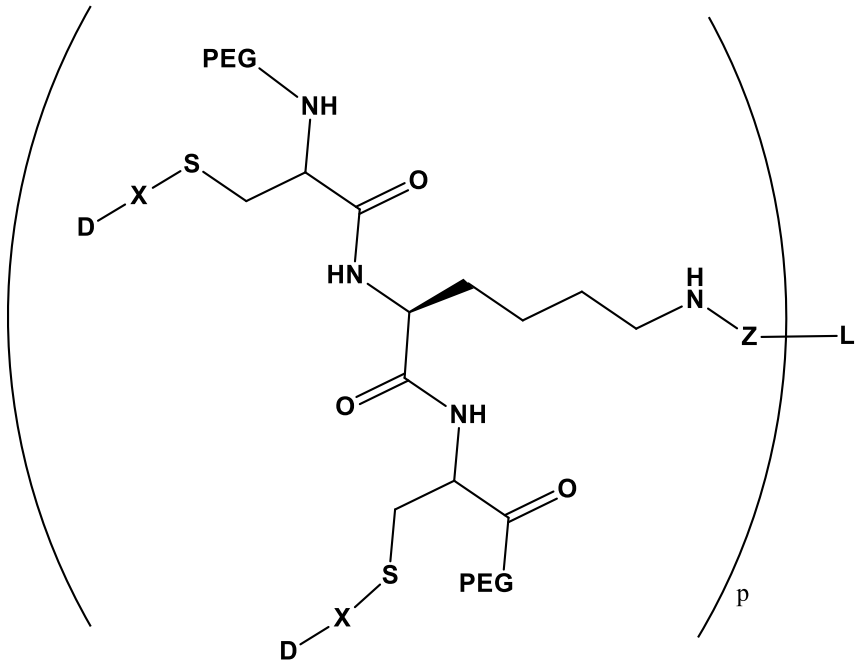
6. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein Z has the structure of



wherein 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 drug-linker moiety within the Ligand-Drug Conjugate compound.

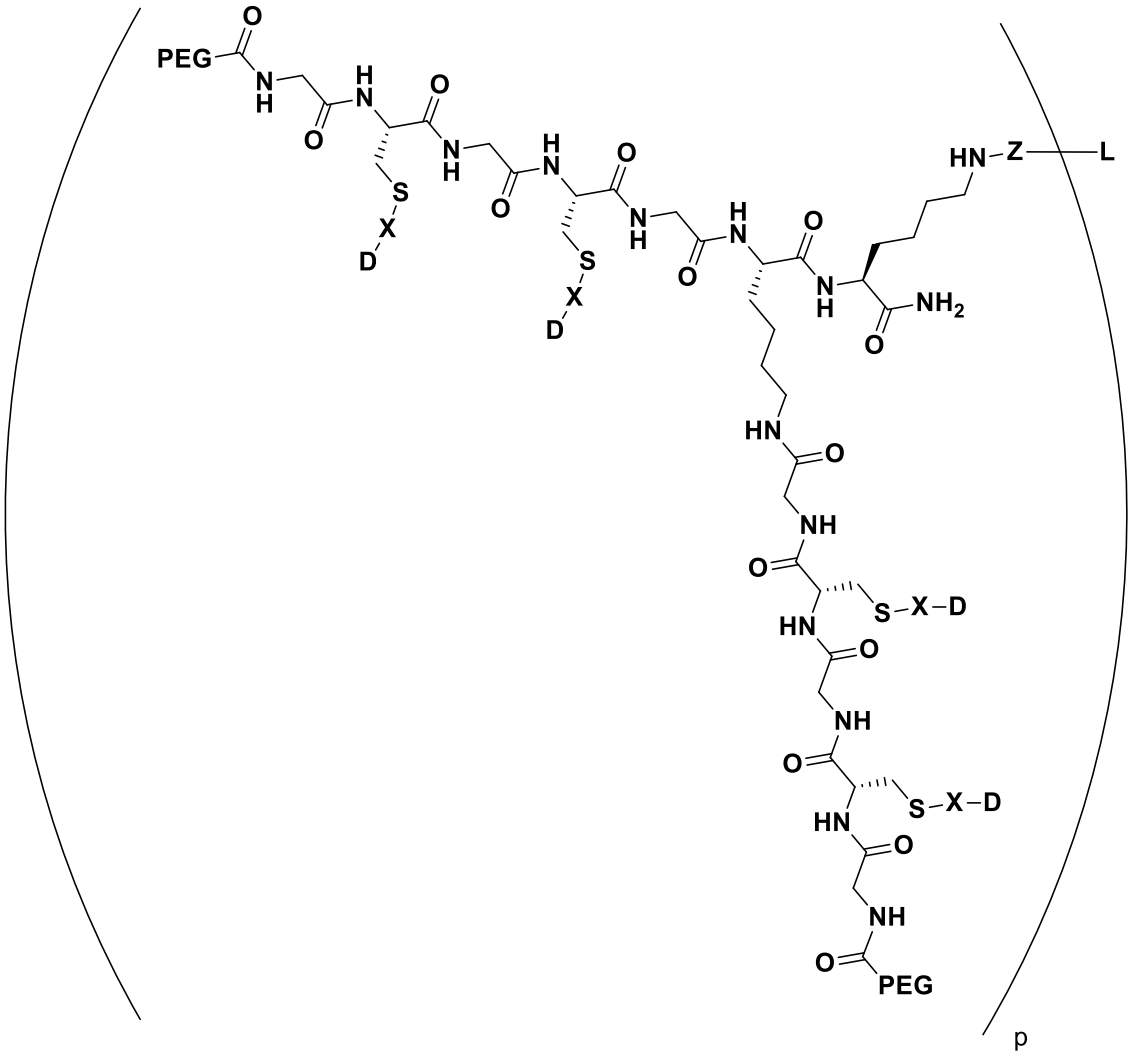
7. The Ligand-Drug Conjugate compound of any one of claims 1-6, wherein subscript t is 0, 1 or 2, and subscript p is an integer ranging from 6 to 14.

8. The Ligand-Drug Conjugate compound of claims 1 or 2, wherein the Ligand-Drug Conjugate compound is represented by the structure of

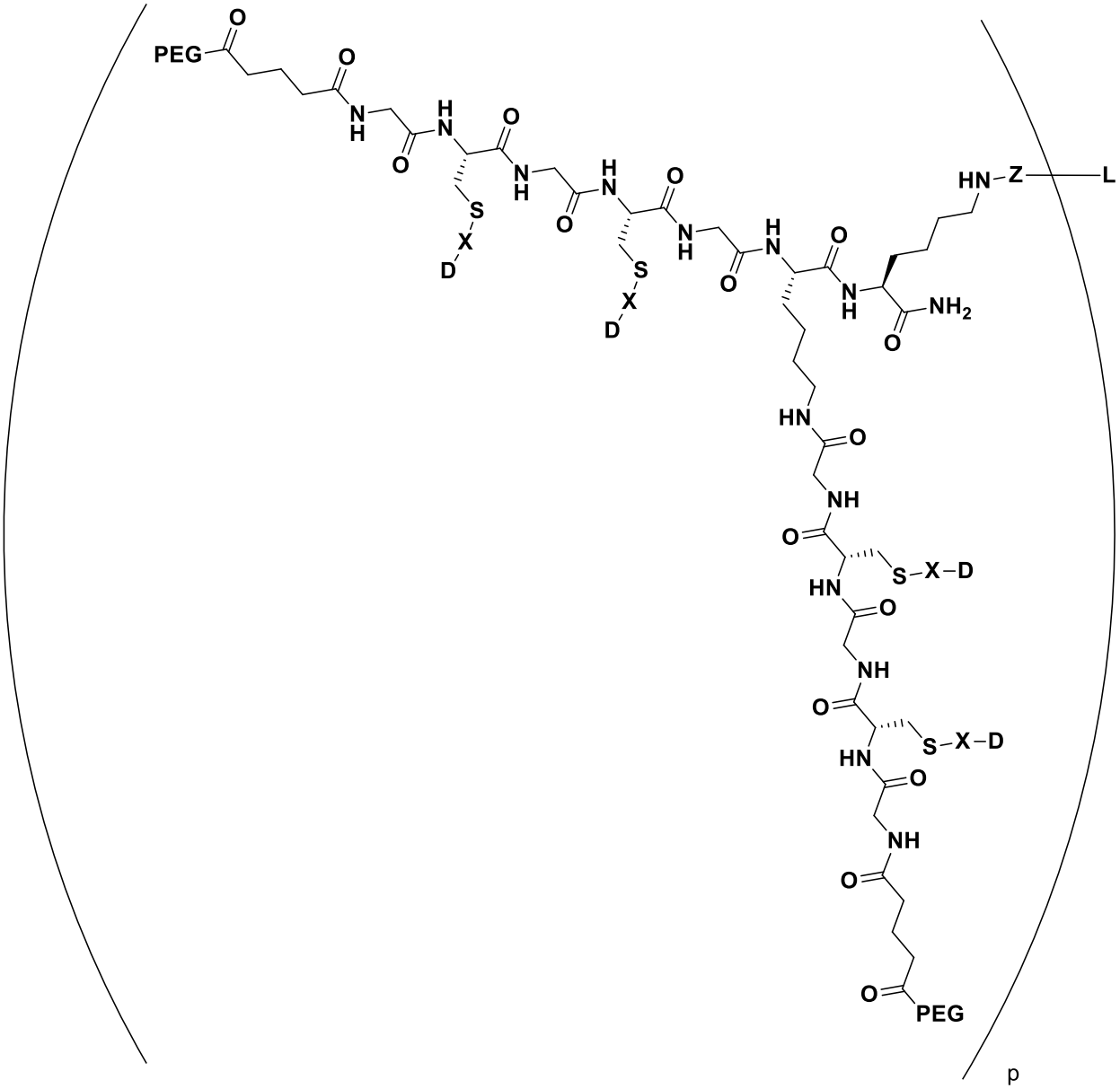


or a pharmaceutically acceptable salt thereof.

9. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the Ligand-Drug Conjugate compound is represented by the structure of


PEG
HN
Z
L
NH2
HN
NH
S
X
D
p

,



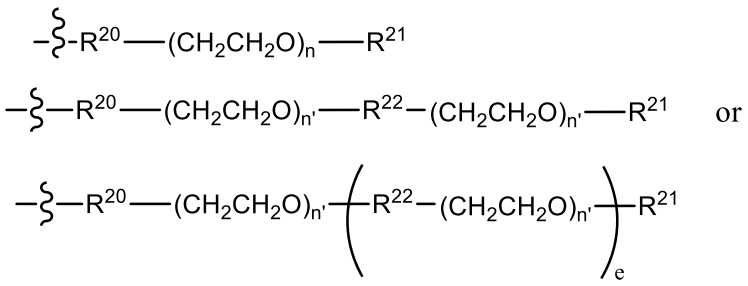
or a pharmaceutically acceptable salt thereof.

10. The Ligand-Drug Conjugate compound of any one of claims 1-9, wherein the Polyethylene Glycol Unit (PEG) comprises no more than about 72 (OCH_2CH_2) subunits, or no more than about 36 (OCH_2CH_2) subunits.

11. The Ligand-Drug Conjugate compound of any one of claims 1-10, wherein the Polyethylene Glycol Unit (PEG) comprises one or more linear polyethylene glycol chains having a combined total of 8 to 72, 8 to 60, 8 to 48, 8 to 36 or 8 to 24 (OCH_2CH_2) subunits, a combined

total of 10 to 72, 10 to 60, 10 to 48, 10 to 36 or 10 to 24 (OCH_2CH_2) subunits, or a combined total of 12 to 72, 12 to 60, 12 to 48, 12 to 36 or 12 to 24 (OCH_2CH_2) subunits.

12. The Ligand-Drug Conjugate compound of any one of claims 1-11, wherein the Polyethylene Glycol Unit (PEG) has the structure of:



or

wherein the wavy line indicates site of attachment of the Polyethylene Glycol Unit (PEG) to the Parallel Connector Unit;

R^{20} is a PEG Attachment Unit;

R^{21} is a PEG Capping Unit;

R^{22} is a PEG Coupling Unit;

subscript n independently ranges from 4 to 72, 6 to 72, 8 to 72, 10 to 72 or 12 to 72;

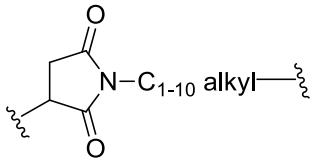
subscript e independently ranges from 2 to 5; and

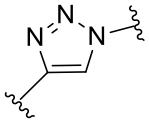
each subscript n' independently ranges from 1 to 72, provided that there are at least 4, at least 6, at least 8, at least 10, or at least 12 polyethylene glycol (OCH_2CH_2) subunits in the Polyethylene Glycol Unit.

13. The Ligand-Drug Conjugate compound of claim 12, wherein

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 

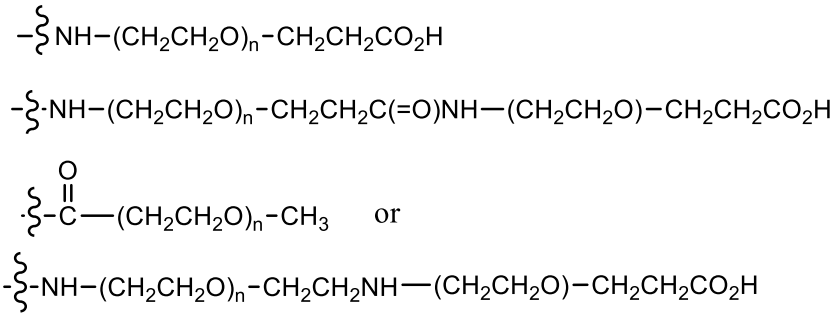
, or R^{20} is -NH- or -C(O)-;

and

each R^{21} is independently selected from the group consisting of -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), and C_{2-10} alkyl-N(C_{1-3} alkyl)$_2$; and

each R^{22} is independently selected from the group consisting of -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-, and –C_{2-10} alkyl-NH-.

14. The Ligand-Drug Conjugate compound of claim 12, wherein the Polyethylene Glycol Unit (PEG) has the structure of:

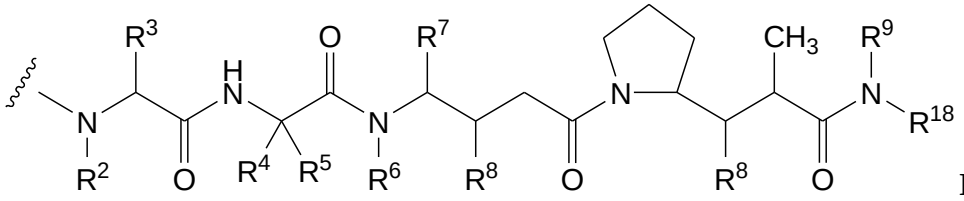


wherein the wavy line indicates site of attachment to the Parallel Connector Unit, and each subscript n is independently an integer ranging from 4 to 72, or each subscript n is independently an integer ranging from 6 to 24, or from 8 to 24.

15. The Ligand-Drug Conjugate compound of claim 12, wherein the Polyethylene Glycol Unit (PEG) has at least 6 –CH_2CH_2O- subunits and no more than 72 –CH_2CH_2O- subunits, or has at least 8 -CH_2CH_2O- subunits and no more than 36 -CH_2CH_2O- subunits.

16. The Ligand-Drug Conjugate compound of claim 15, wherein the Drug Unit is an auristatin thereby defining an auristatin Drug Unit.

17. The Ligand-Drug Conjugate compound of claim 16, 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);

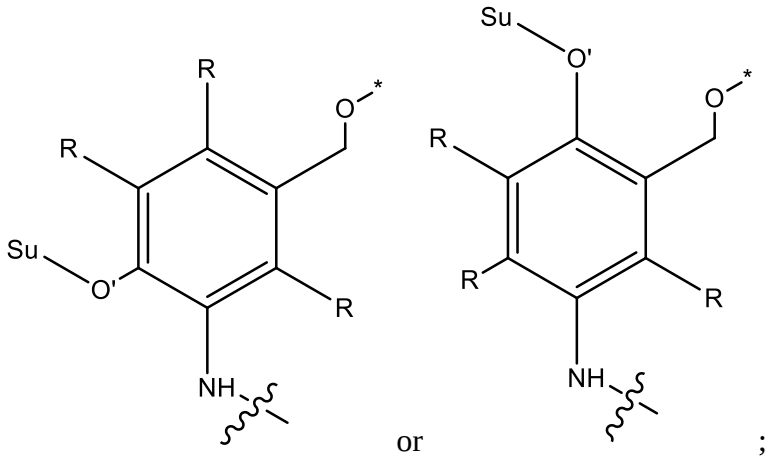
R^9 is selected from the group consisting of H and C_1-C_8 alkyl; and

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).

18. The Ligand-Drug Conjugate compound of any one of claims 1 to 17, 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 Unit results in release of free hydrophobic drug from the Ligand-Drug Conjugate compound.

19. The Ligand-Drug Conjugate compound of claim 18, wherein the Releasable Assembly Unit comprises a glucuronide unit represented by the formula:



;

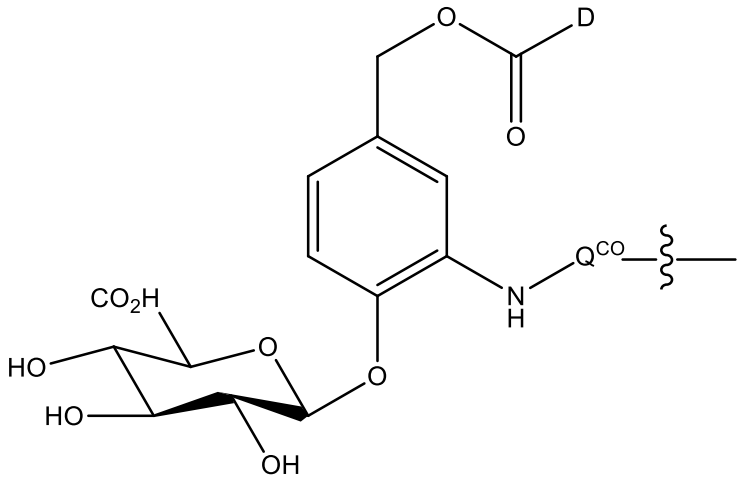
wherein Su is the sugar moiety, -O'- represents an oxygen atom of a glycosidic bond;

each R is independently selected from the group consisting of hydrogen, a halogen, -CN, and $-NO_2$; and wherein the wavy line indicates attachment of the self-immolative group to L^P or AD, either directly or indirectly through a Covalent Attachment Unit; and

the asterisk indicates covalent attachment of the self-immolative group to the hydrophobic Drug Unit either directly or indirectly via a Spacer Unit.

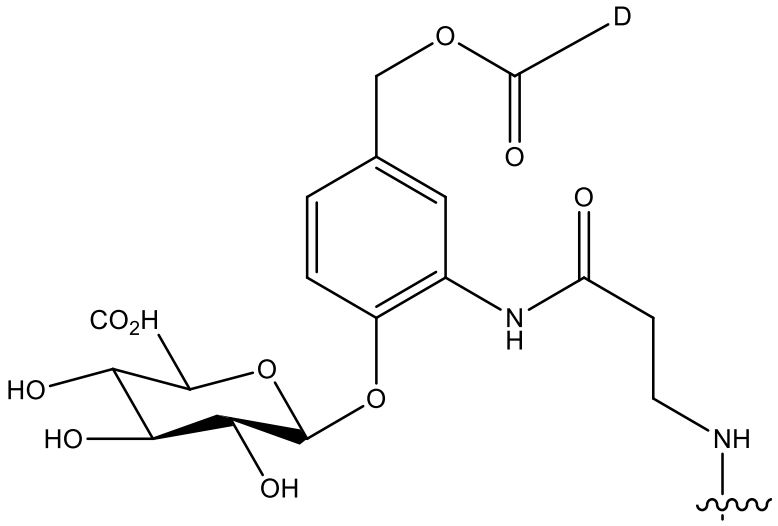
20. The Ligand-Drug Conjugate compound of claim 1, wherein the Releasable Assembly Unit (X) comprises a peptide cleavable by cathepsin B.

21. The Ligand-Drug Conjugate compound of any one of claims 1 to 20, wherein –X-D has the structure of:



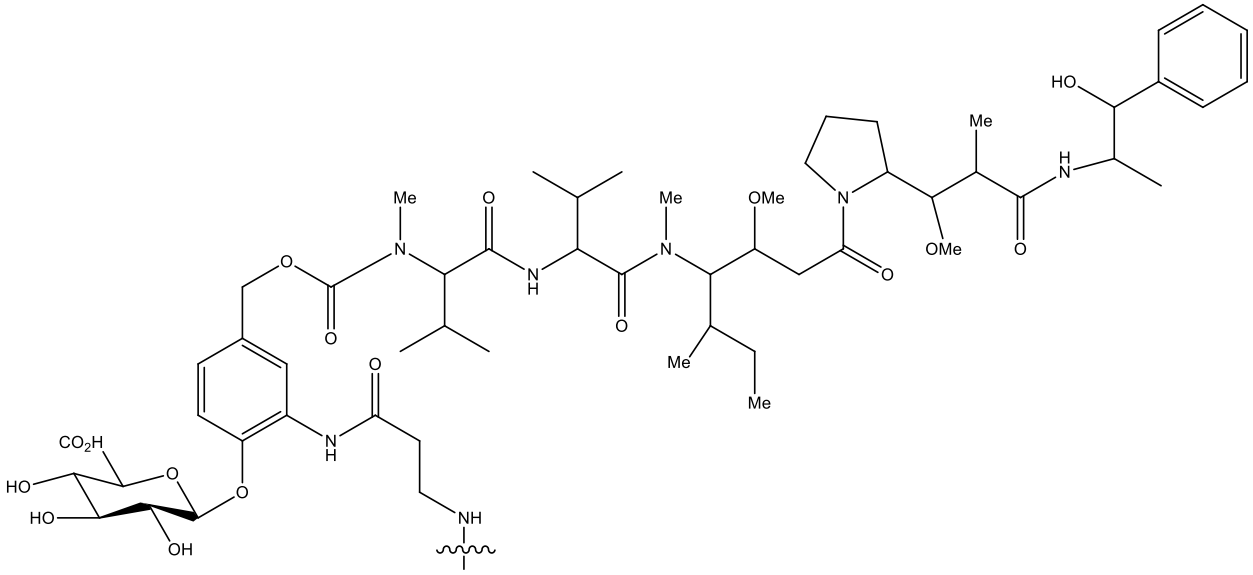
wherein Q^{CO} is an optional Covalent Attachment Unit and the wavy line indicates covalent attachment to the remainder of the Ligand-Drug Conjugate compound.

22. The Ligand-Drug Conjugate compound of claim 21, wherein –X-D has the structure of:

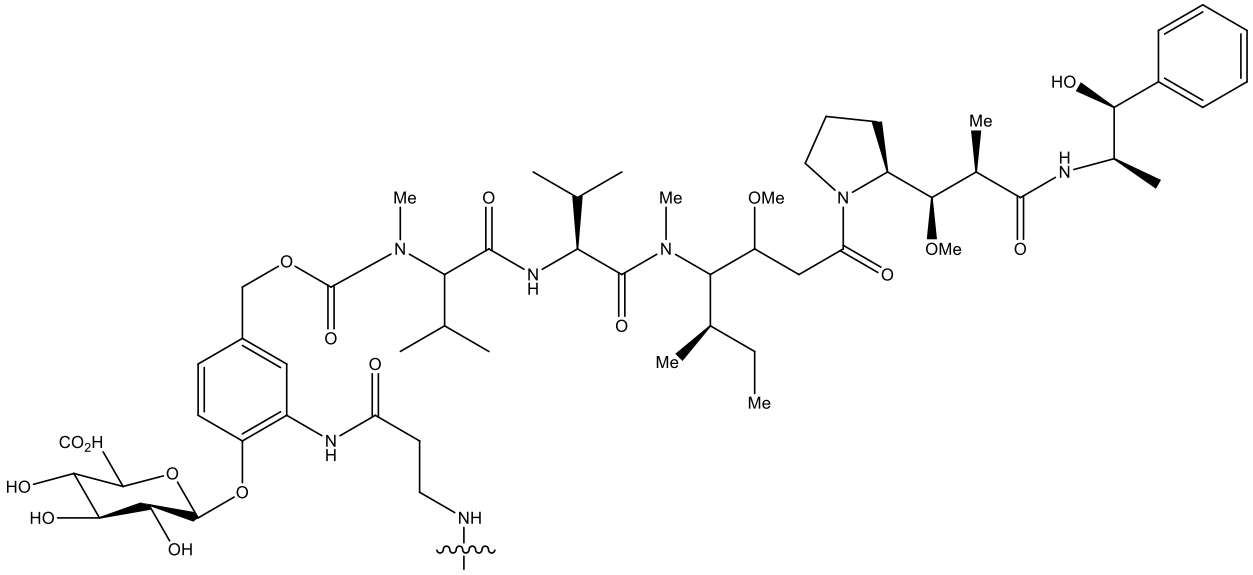


wherein the wavy line indicates covalent attachment to the remainder of the Ligand-Drug Conjugate compound.

23. The Ligand-Drug Conjugate compound of any one of claims 1-22, wherein –X-D has the structure of:



or

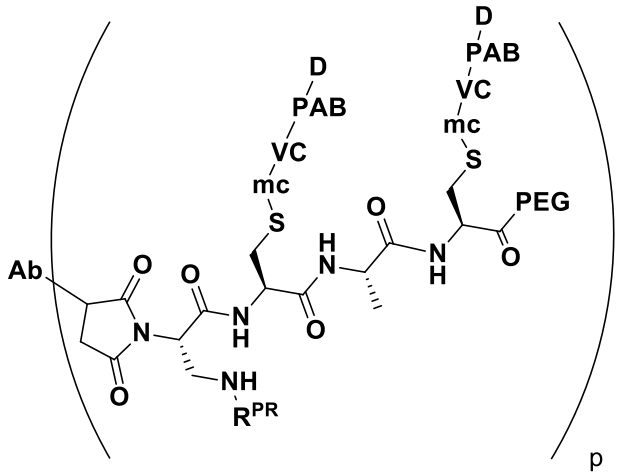


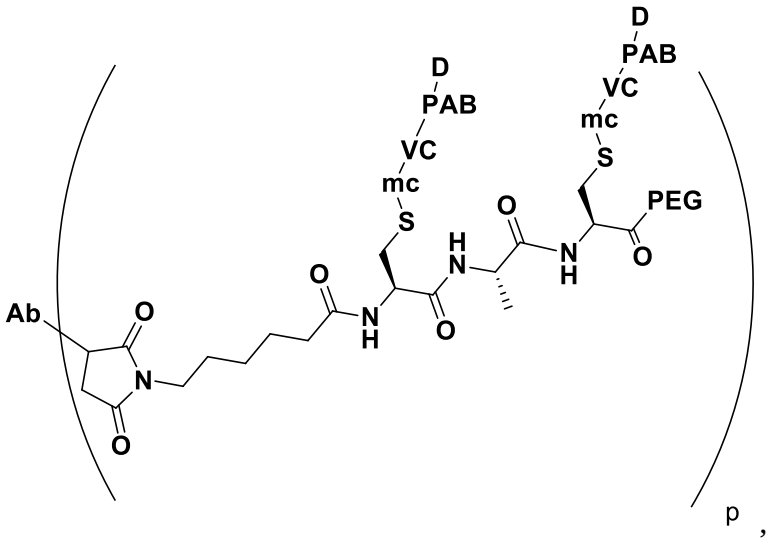
wherein the wavy line indicates covalent attachment to the to the remainder of the Ligand-Drug Conjugate compound.

24. The Ligand-Drug Conjugate compound of any one of claims 1 to 23, wherein the Ligand Unit is a monoclonal antibody.

25. The Ligand-Drug Conjugate compound of any one of claims 1 to 24, wherein the Ligand Unit is an antibody, thereby defining an antibody Ligand Unit, and the antibody is conjugated to each Stretcher Unit (Z) via a sulfur atom of a cysteine residue of the antibody.

26. The Ligand-Drug Conjugate compound of claim 25, having the structure of:



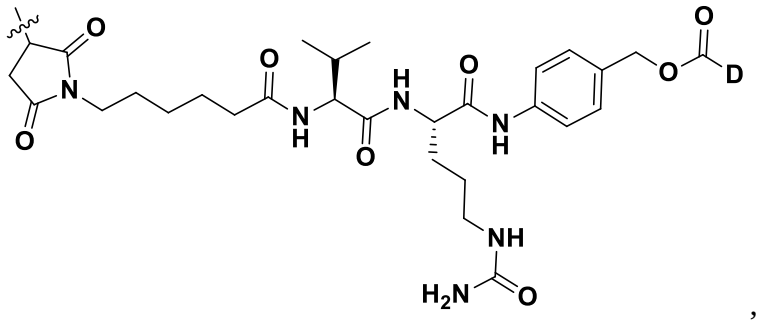


or a pharmaceutically acceptable salt thereof, optionally having the succinimide in hydrolyzed form, wherein

Ab is the antibody Ligand Unit;

R^{PR} is hydrogen or an acid labile protecting group:

mc-VC-PAB-D has the structure of:



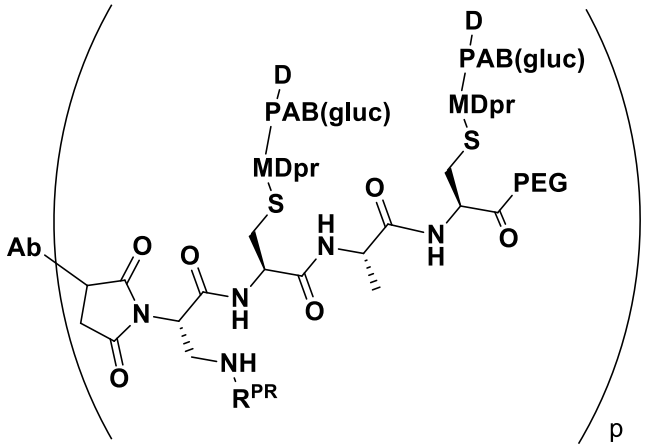
,

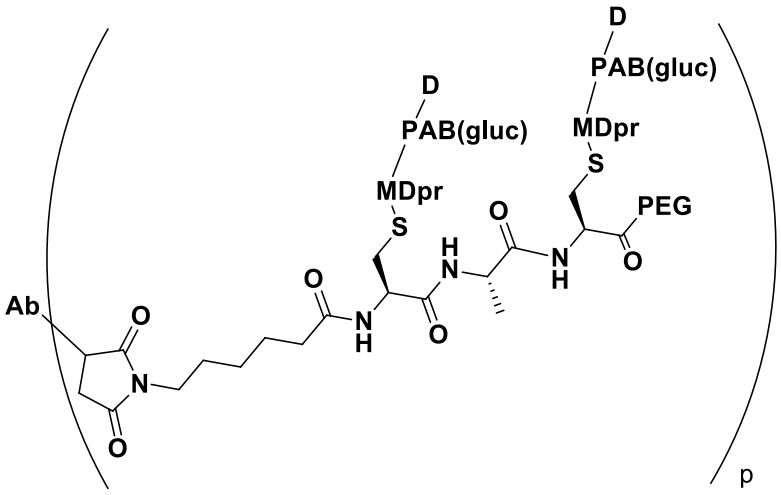
optionally having the succinimide in hydrolyzed form;

the wavy line indicates covalent attachment of mc to a sulfur atom; and

PEG is a non-dispersive PEG Unit that from 8 to 24 -CH_2CH_2O- subunits or from 12 to 38 -CH_2CH_2O- subunits.

27. The Ligand-Drug Conjugate compound of claim 25, having the structure of:



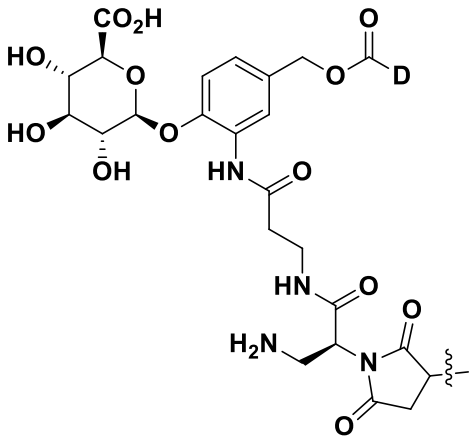


or a pharmaceutically acceptable salt thereof, optionally having the succinimide in hydrolyzed form, wherein

Ab is the antibody Ligand Unit;

R^{PR} is hydrogen or an acid labile protecting group;

MDpr-PAB(gluc)-D has the structure of:



optionally in salt form and optionally having the succinimide in hydrolyzed form;

the wavy line indicates covalent attachment of MDpr to a sulfur atom; and

PEG is a non-dispersive PEG Unit that has from 8 to 24 -CH_2CH_2O- subunits or from 12 to 38 -CH_2CH_2O-subunits.

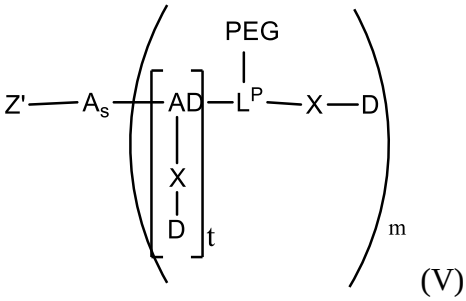
28. The Ligand-Drug Conjugate compound of any one of claims 25-27, wherein the cysteine residue is from reduction of an interchain disulfide bond of the antibody or the cysteine residue from introduction into the antibody.

29. The Ligand-Drug Conjugate compound of claim 28, wherein subscript p is 8, and the antibody is conjugated to Stretcher Units (Z) through the sulfur atoms of cysteine residues from the reduction of the interchain disulfide bonds of the antibody, or subscript p is an integer ranging from 10 to 14 or 10 to 12, and the antibody is conjugated to the Stretcher Units through sulfur atoms of cysteine residues from reduction of the interchain disulfide bonds of the antibody and through sulfur atoms of cysteine residues introduced into the antibody.

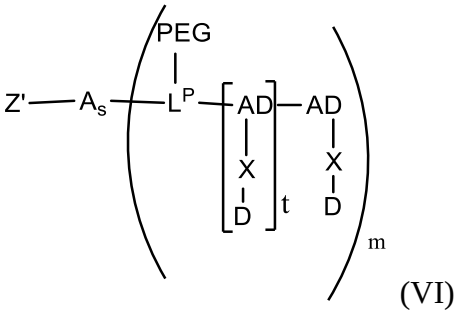
30. The Ligand-Drug Conjugate compound of claim 29, wherein the cysteine residue is at position 239 according to the EU index.

31. A pharmaceutical composition comprising a population of Ligand-Drug Conjugate compounds of any one of claims 1 to 28 wherein the average number of drug-linker moieties per Ligand Unit in the composition ranges from about 4 to about 14, from about 6 to about 14, from about 8 to about 14, or from about 8 to about 12, or the average number of molecules of drug-linker moieties per Ligand Unit in the composition is about 8; and a pharmaceutically acceptable carrier.

32. A Drug-Linker compound, wherein the Drug-Linker compound has the structure of Formula V or VI:



(V)



(VI)

or a pharmaceutically acceptable salt thereof, wherein

D is a hydrophobic Drug Unit, wherein the Drug Unit is a cytotoxic, cytostatic, or immunosuppressive drug having a hydrophobicity greater than or within 20% of monomethyl auristatin E when measured using SlogP;

PEG is a Polyethylene Glycol Unit, wherein the PEG Unit comprises from 4 to 72 (OCH_2CH_2 subunits);

Z' is a Stretcher Unit capable of forming a covalent attachment to a Ligand Unit, wherein the covalent attachment would link the Ligand Unit to L^P;

X is a Releasable Assembly Unit, wherein X comprises a peptide, disulfide, or glycosidic bond;

L^P is a Parallel Connector Unit, wherein L^P connects the Ligand Unit to the Polyethylene Glycol Unit and the hydrophobic Drug Unit so that Polyethylene Glycol Unit and the Drug Unit are in a parallel orientation, wherein the Polyethylene Glycol Unit in said parallel orientation masks the hydrophobicity of the hydrophobic Drug Unit;

A is an optional Branching Unit, wherein each A, when present, is one to 10 independently selected amino acid, amino alcohol, amino aldehyde, or polyamine residues, or a combination thereof, covalently bonded to one another;

AD is a Drug Attachment Unit, wherein each AD, when present, is one to 10 independently selected amino acid, amino alcohol, amino aldehyde, or polyamine residues, or a combination thereof, covalently bonded to one another;

subscript t is an integer ranging from 0 to 8, or from 0 to 3;

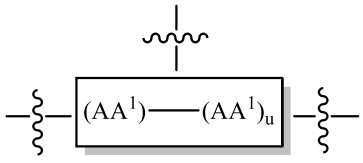
subscript m is an integer ranging from 1 to 4, or is 1 or 2;

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

each L^P is independently (i) or (ii):

(i) comprises an amino acid, amino alcohol, amino aldehyde, or a polyamine residue, or

(ii) the structure of L^P represented by Formula A:



Formula A

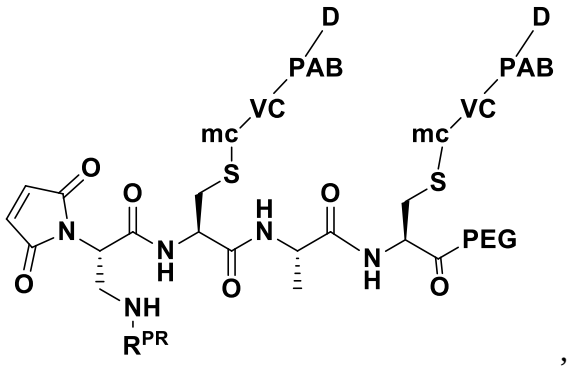
wherein

AA^1 is independently selected from an amino acid, 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; and

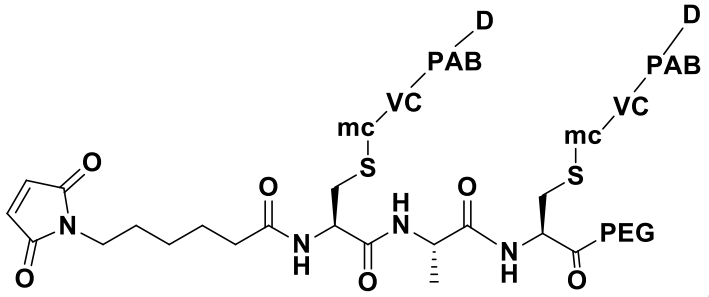
subscript u is an integer ranging from 0 to 4; wherein at least one AA^1 has a functionalized side chain that provides for an attachment site to a PEG, AD, A or Z unit or an X-D moiety, or

AA^1 is an 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 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.

33. The Drug-Linker compound of claim 32, wherein the Drug-Linker compound has the structure of:



,

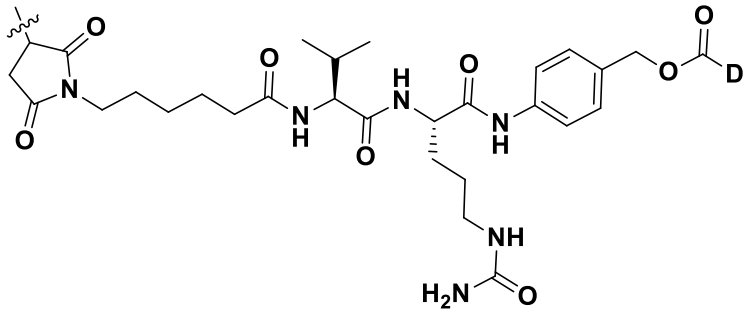


,

or a pharmaceutically acceptable salt thereof, wherein

R^{PR} is hydrogen or an acid labile protecting group, and

mc-VC-PAB-D has the structure of:

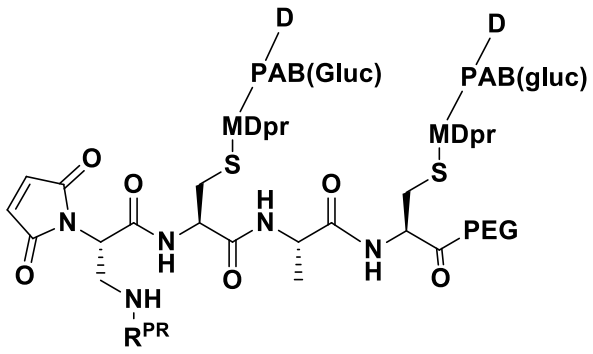


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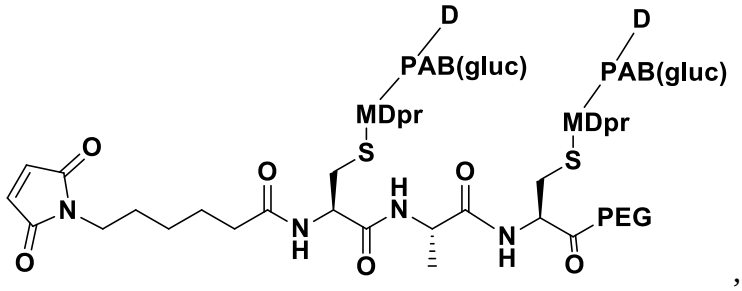
optionally having the succinimide in hydrolyzed form; and wherein

the wavy line indicates covalent attachment of mc to a sulfur atom.

34. The Drug-Linker Compound of claim 32, wherein the Drug-Linker Compound has the structure of:



,

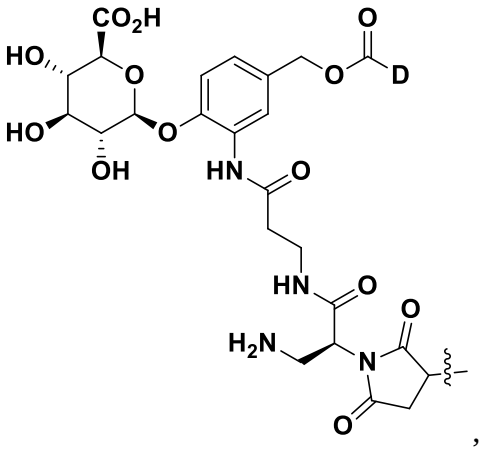


,

or a pharmaceutically acceptable salt thereof, wherein

R^{PR} is hydrogen or an acid labile protecting group, and

MDpr-PAB(gluc)-D has the structure of:

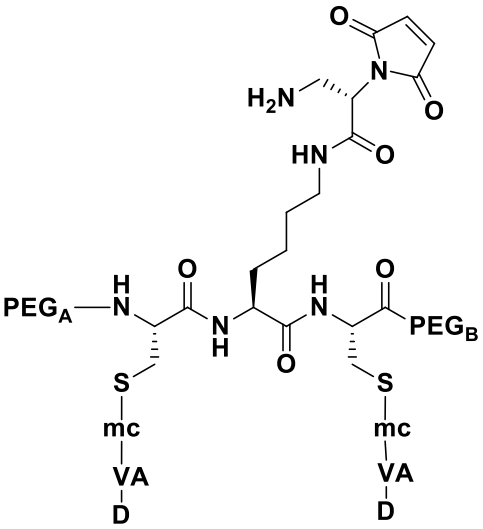


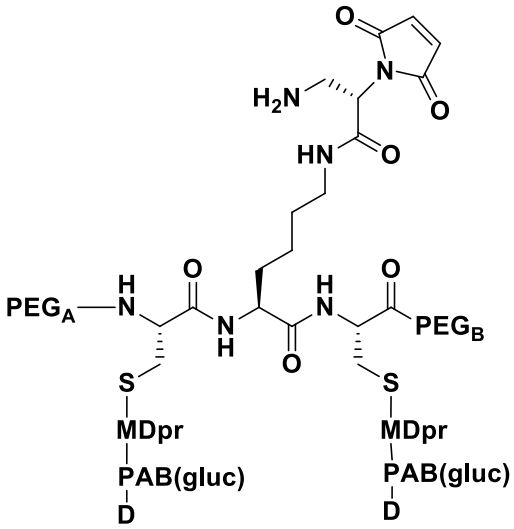
,

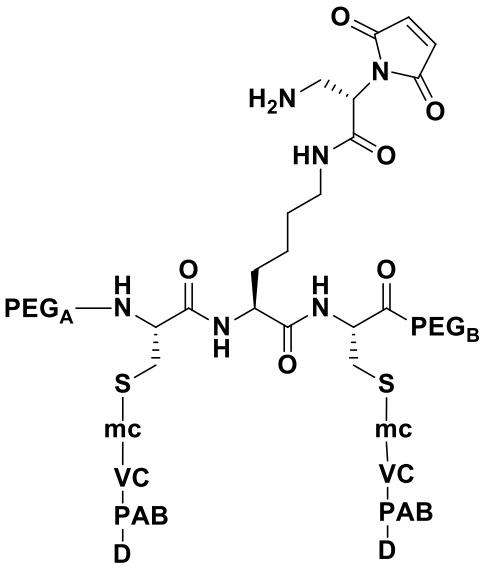
or a pharmaceutically acceptable salt thereof, optionally having the succinimide in hydrolyzed form; and wherein

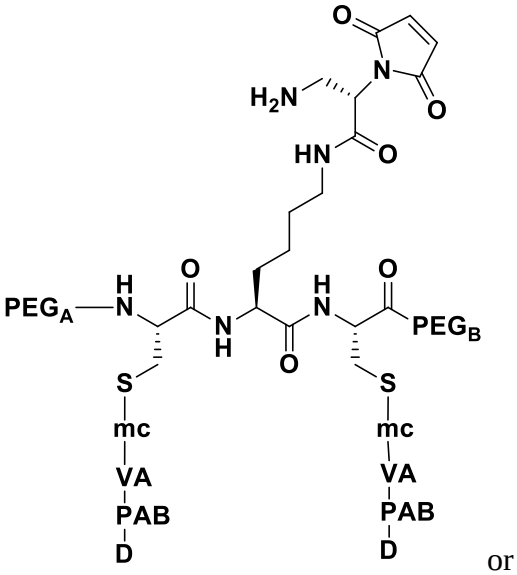
the wavy line indicates covalent attachment to a sulfur atom.

35. The Drug-Linker compound of claim 32, wherein the Drug-Linker Compound has the structure of:





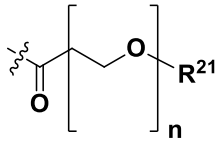




or

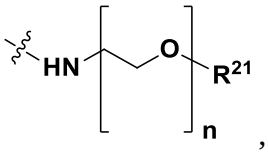
a pharmaceutically acceptable salt thereof, wherein

PEG_A has the structure of:



; and

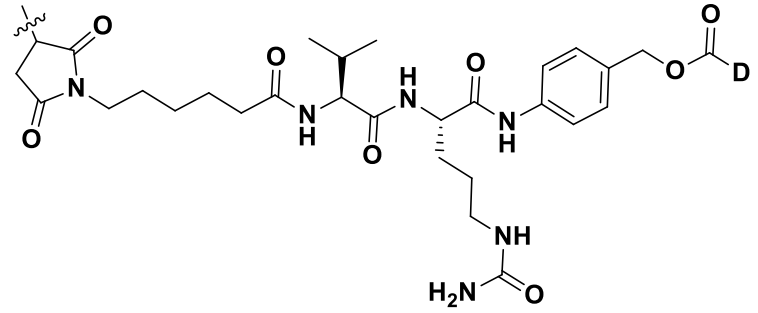
PEG_B has the structure of:



,

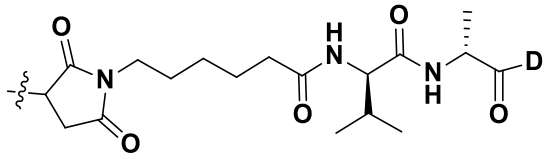
wherein each R^{21} is independently $–CH_3$ or $–CH_2CH_2CO_2H$; the wavy line indicates covalent bonding to the remainder of the Drug Linker compound; and subscript n is an integer ranging from 8 to 24 or from 12 to 38;

mc-VC-PAB-D has the structure of:



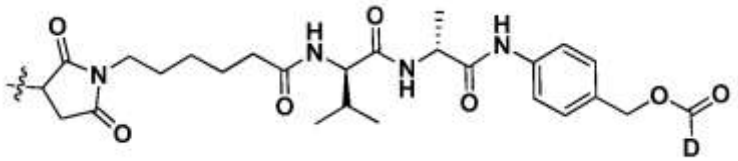
;

mc-VA-D has the structure of:



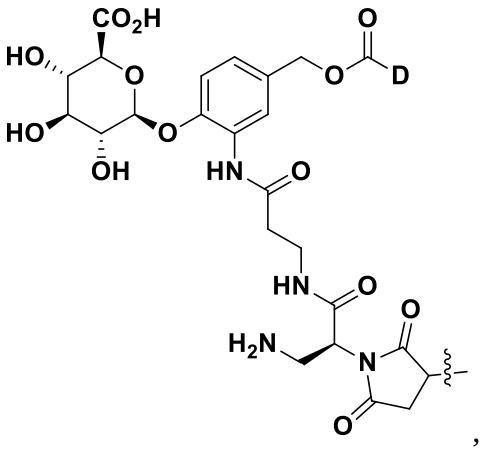
;

mc-VA-PAB-D has the structure of:



; and

MDpr-PAB(gluc)-D has the structure of:

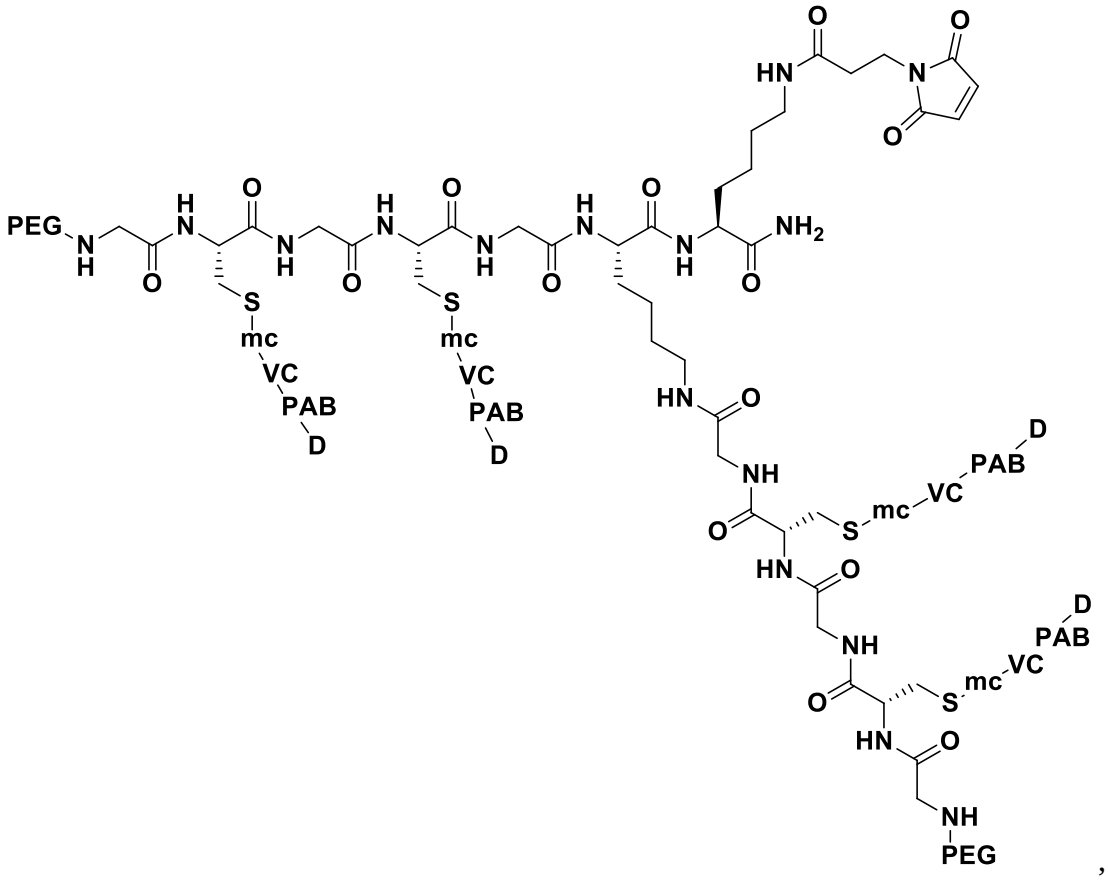


,

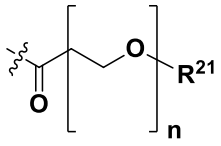
or a pharmaceutically acceptable salt thereof; and optionally having the succinimide of mc-VC-PAB-D, mc-VA-D, mc-VC-PAB-D or MDpr-PAB(gluc)-D in hydrolyzed form; and wherein

the wavy line indicates covalent attachment of mc or MDpr to a sulfur atom.

36. The Drug-Linker Compound of claim 32, wherein the Drug-Linker Compound has the structure of:

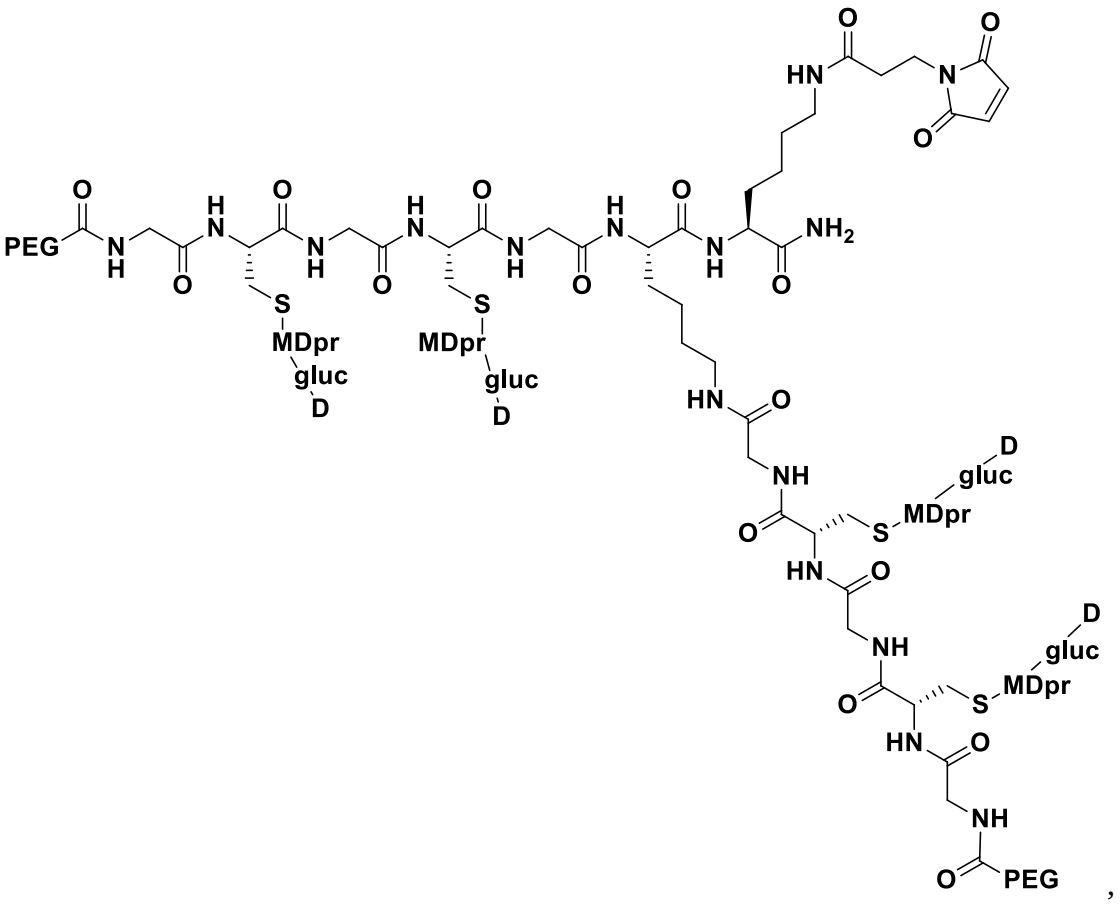


or a pharmaceutically acceptable salt thereof, wherein each PEG independently has the structure of:



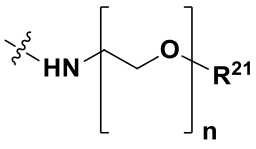
, or

the Drug-Linker Compound has the structure of:



or a pharmaceutically acceptable salt thereof, wherein

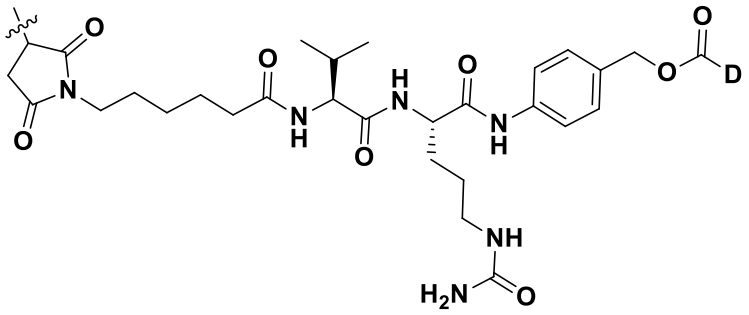
each PEG independently has the structure of:



, and

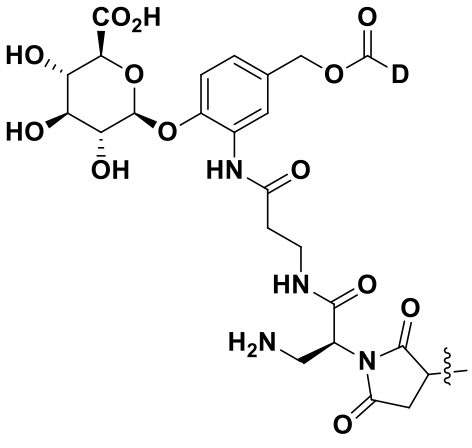
wherein each R^{21} is $–CH_3$ or $–CH_2CH_2CO_2H$; the wavy line indicates covalent bonding to the remainder of the Drug Linker compound; and subscript n is an integer ranging from 8 to 24 or from 12 to 38;

mc-VC-PAB-D has the structure of:



; and

MDpr-PAB(gluc)-D has the structure of:



, or

a pharmaceutically acceptable salt thereof; and optionally having the succinimide of mc-VC-PAB-D or MDpr-PAB(gluc)-D in hydrolyzed form.

37. A pharmaceutical composition comprising a population of Ligand-Drug Conjugate compounds each having a drug linker moiety corresponding in structure to a Drug-Linker compound of any one of claims 32-36, conjugated to a Ligand Unit; and a pharmaceutically acceptable carrier, wherein the average number of drug-linker moieties per Ligand Unit in the composition ranges from about 8 to about 14; and each PEG unit of a Ligand Drug Conjugate compound independently has at least 8 to no more than 24 PEG subunits, or has at least 12 to no more than 24 PEG subunits.

38. Use of a Ligand Drug Conjugate compound for preparing a medicament for the treatment of cancer, wherein the Ligand Drug Conjugate compound has the structure of any one of claims 1 to 30, and wherein the Ligand Unit binds to a tumor cell or cancer cell.