respectively, can occur. Those biodistribution effects may even become the dominant factors over preferential proteolysis, which could be difficult to observe *in vivo*.

[0008] Thus, Conjugate compounds having peptide sequences providing enhanced exposure of released free cytotoxic compound to tumor tissue in comparison to normal tissue should exhibit reduced undesired toxicities due to the peptide sequences being overall less susceptible to proteolysis within normal tissue or cells thereof in comparison to those of the tumor and/or from improved pharmacokinetic properties for Conjugate compounds incorporating those peptide sequences that favor tumor tissue over normal tissue.

[0009] The Ligand Drug Conjugates of the present invention therefore have two levels of selectivity for targeted cells over non-targeted normal cells: (1) selective entry into targeted cells and (2) decreased exposure of normal tissue in comparison to tumor tissue to the Conjugate compound. From that second level of selectivity, reduction in normal tissue toxicities is expected to provide reduced adverse events associated with conventional targeted therapies.

SUMMARY ~~OF THE INVENTION~~

[0009a] In an aspect of the present disclosure, there is provided a Ligand Drug Conjugate composition represented by Formula **1**:

$$L\text{-}[LU\text{-}D']_p \qquad (1)$$

or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

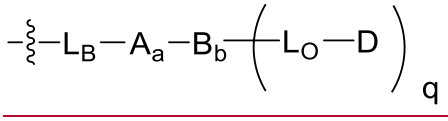
LU is a Linker Unit;

D' represents from 1 to 4 Drug Units (D) in each drug linker moiety of formula -LU-D'; and

subscript p is a number from 1 to 12, from 1 to 10 or from 1 to 8 or is about 4 or about 8,

wherein the Ligand Unit is from an antibody or an antigen-binding fragment of an antibody that is capable of selective binding to an antigen of tumor tissue for subsequent release of the Drug Unit(s) as free drug,

wherein the drug linker moiety of formula -LU-D' in each of the Ligand Drug Conjugate compounds of the composition has the structure of Formula **1A**:



(1A)

or a salt thereof,

wherein the wavy line indicates covalent attachment to L;

D is the Drug Unit;

L_B is a ligand covalent binding moiety;

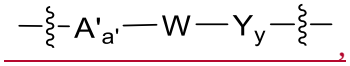
A is a first optional Stretcher Unit;

subscript a is 0 or 1, indicating the absence or presence of A, respectively;

B is an optional Branching Unit;

subscript b is 0 or 1, indicating the absence or presence of B, respectively;

L_O is a secondary linker moiety, wherein the secondary linker has the formula of;



wherein the wavy line adjacent to Y indicates the site of covalent attachment of L_O to the Drug Unit and the wavy line adjacent to A' indicates the site of covalent attachment to the remainder of the drug linker moiety;

A' is a second optional Stretcher Unit, which in the absence of B becomes a subunit of A,

subscript a' is 0 or 1, indicating the absence or presence of A', respectively,

W is a Peptide Cleavable Unit, wherein the Peptide Cleavable Unit comprises a tripeptide having the sequence -P3-P2-P1-, wherein P1, P2, and P3 are each an amino acid, wherein:

a first one of the amino acids P1, P2, or P3 is negatively charged;

a second one of the amino acids P1, P2, or P3 has an aliphatic side chain with hydrophobicity no greater than that of leucine; and

a third one of the amino acids P1, P2, or P3 has hydrophobicity lower than that of leucine,

wherein the first one of the amino acids P1, P2, or P3 corresponds to any one of P1, P2, or P3, the second one of the amino acids P1, P2, or P3 corresponds to one of the two remaining amino acids P1, P2, or P3, and the third one of the amino acids P1, P2, or P3 corresponds to the last remaining amino acids P1, P2, or P3,

provided that -P3-P2-P1- is not -Glu-Val-Cit- or -Asp-Val-Cit-;

Y is a self-immolative Spacer Unit;

subscript y is 0, 1 or 2 indicating the absence or presence of 1 or 2 of Y, respectively; and

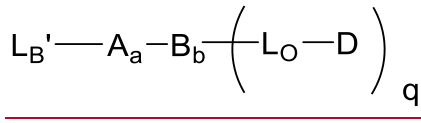
subscript q is an integer ranging from 1 to 4,

provided that subscript q is 1 when subscript b is 0 and subscript q is 2, 3 or 4 when subscript b is 1; and

wherein the Ligand Drug Conjugate compounds of the composition have the structure of Formula **1** in which subscript p is replaced by subscript p', wherein subscript p' is an integer from 1 to 12, 1 to 10 or 1 to 8 or is 4 or 8.

[0009b] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable formulation, wherein the formulation comprises an effective amount of a Ligand Drug Conjugate composition or an equivalent amount of a non-binding control Conjugate disclosed herein and at least one pharmaceutically acceptable excipient.

[0009c] In a further aspect of the present disclosure, there is provided a Drug Linker compound of Formula **IA**:



(IA)

or a salt thereof, wherein

D is a Drug Unit;

L_B' is a ligand covalent binding precursor moiety;

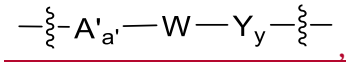
A is a first optional Stretcher Unit;

subscript a is 0 or 1, indicating the absence or presence of A, respectively;

B is an optional Branching Unit;

subscript b is 0 or 1, indicating the absence or presence of B, respectively;

L_O is a secondary linker moiety, wherein the secondary linker has the formula of;



wherein the wavy line adjacent to Y indicates the site of covalent attachment of L_O to the Drug Unit and the wavy line adjacent to A' indicates the site of covalent attachment to the remainder of the Drug Linker compound;

A' is a second optional Stretcher Unit, which in the absence of B becomes a subunit of A;

subscript a′ is 0 or 1, indicating the absence or presence of A', respectively,

W is a Peptide Cleavable Unit, wherein the Peptide Cleavable Unit comprises a tripeptide having the sequence -P3-P2-P1-, wherein P1, P2, and P3 are each an amino acid, wherein:

a first one of the amino acids P1, P2, or P3 is negatively charged;

a second one of the amino acids P1, P2, or P3 has an aliphatic side chain with hydrophobicity no greater than that of leucine; and

a third one of the amino acids P1, P2, or P3 has hydrophobicity lower than that of leucine,

wherein the first one of the amino acids P1, P2, or P3 corresponds to any one of P1, P2, or P3, the second one of the amino acids P1, P2, or P3 corresponds to one of the two remaining amino acids P1, P2, or P3, and the third one of the amino acids P1, P2, or P3 corresponds to the last remaining amino acids P1, P2, or P3,

provided that -P3-P2-P1- is not -Glu-Val-Cit- or -Asp-Val-Cit-;

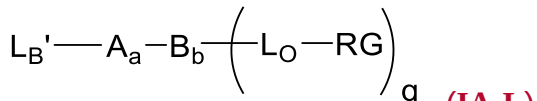
Y is a self-immolative Spacer Unit;

subscript y is 0, 1 or 2 indicating the absence or presence of 1 or 2 of Y, respectively; and

subscript q is an integer ranging from 1 to 4,

provided that subscript q is 1 when subscript b is 0 and subscript q is 2, 3 or 4 when subscript b is 1.

[0009d] In another aspect of the present disclosure, theres is provided a Linker compound of Formula **IA-L**:



(IA-L)

or a salt thereof, wherein

RG is a reactive group;

L_B' is a ligand covalent binding precursor moiety;

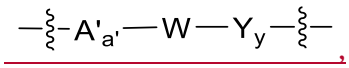
A is a first optional Stretcher Unit;

subscript a is 0 or 1, indicating the absence or presence of A, respectively;

B is an optional Branching Unit;

subscript b is 0 or 1, indicating the absence or presence of B, respectively;

L_O is a secondary linker moiety, wherein the secondary linker has the formula of;



wherein the wavy line adjacent to Y indicates the site of covalent attachment of L_O to the Drug Unit and the wavy line adjacent to A' indicates the site of covalent attachment to the remainder of the Drug Linker compound;

A' is a second optional Stretcher Unit, which in the absence of B becomes a subunit of A;

subscript a' is 0 or 1, indicating the absence or presence of A', respectively,

W is a Peptide Cleavable Unit, wherein the Peptide Cleavable Unit comprises a tripeptide having the sequence -P3-P2-P1-, wherein P1, P2, and P3 are each an amino acid, wherein:

a first one of the amino acids P1, P2, or P3 is negatively charged;

a second one of the amino acids P1, P2, or P3 has an aliphatic side chain with hydrophobicity no greater than that of leucine; and

a third one of the amino acids P1, P2, or P3 has hydrophobicity lower than that of leucine,

wherein the first one of the amino acids P1, P2, or P3 corresponds to any one of P1, P2, or P3, the second one of the amino acids P1, P2, or P3 corresponds to one of the two remaining amino acids P1, P2, or P3, and the third one of the amino acids P1, P2, or P3 corresponds to the last remaining amino acids P1, P2, or P3,

provided that -P3-P2-P1- is not -Glu-Val-Cit- or -Asp-Val-Cit-;

Y is a self-immolative Spacer Unit;

subscript y is 0, 1 or 2 indicating the absence or presence of 1 or 2 of Y, respectively; and

subscript q is an integer ranging from 1 to 4,

provided that subscript q is 1 when subscript b is 0 and subscript q is 2, 3 or 4 when subscript b is 1.

[0010] One principle ~~embodiment~~example of the ~~invention~~ present disclosure provides a Ligand Drug Conjugate composition represented by Formula 1:

$$L\text{-}[LU\text{-}D']_p \qquad (\mathbf{1})$$

or a salt thereof, in particular a pharmaceutically acceptable salt, wherein

L is a Ligand Unit;

LU is a Linker Unit; and

D’ represents from 1 to Drug Units (D) in each drug linker moiety of formula -LU-D’; and

subscript p is a number from 1 to 12, from 1 to 10 or from 1 to 8 or is about 4 or about 8,

wherein the Ligand Unit is of an antibody, or an antigen-binding fragment of an antibody, that is capable of selective binding to an antigen of tumor tissue for subsequent release of the Drug Unit as free cytotoxic compound,

wherein the drug linker moiety of formula -LU-D’ in each of the Ligand Drug Conjugate compounds of the composition has the structure of Formula **1A**:

showing a reduction in plasma concentration of the free cytotoxic compound released from the Ligand Drug Conjugate compounds of the composition, and/or preservation of normal cells in tissue when administered at the same effective amount and dose schedule as in the tumor xenograft model to a non-tumor bearing rodent in comparison to the equivalent (e.g., same) administration of the comparator Ligand-Drug Conjugate composition in which the Ligand Units of both conjugate compositions are replaced by a non-binding antibody,

wherein cytotoxicity to cells in human tissue of the same type as the normal cells in the tissue of the non-tumor bearing rodent is responsible at least in part to an adverse event in a human subject to whom is administered a therapeutically effective amount of the comparator conjugate composition;

Y is a self-immolative Spacer Unit; and

subscript y is 0, 1 or 2 indicating the absence or presence of 1 or 2 of Y, respectively;

subscript q is an integer ranging from 1 to 4,

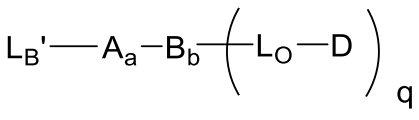
provided that subscript q is 1 when subscript b is 0 and subscript q is 2, 3 or 4 when subscript b is 1; and

wherein the Ligand Drug Conjugate compounds of the composition have the structure of Formula **1** in which subscript p is replaced by subscript p', wherein subscript p' is an integer from 1 to 12, 1 to 10 or 1 to 8 or is 4 or 8.

[0011] A related principle ~~embodiment~~example provides for a Drug Linker compound of Formula **I**:

$$LU'\text{-}(D') \quad (\mathbf{I})$$

[0012] or a salt thereof, in particular a pharmaceutically acceptable salt thereof, wherein LU' is capable of providing a covalent bond between L and LU of Formula **1**, and therefore is sometimes referred to as a Linker Unit precursor; and D' represents from 1 to 4 Drug Units, wherein the Drug Linker compound is further defined by the structure of Formula **IA**:



(**IA**)

[0013] wherein L_B' is capable of transformation to L_B of Formula **1A** thereby forming a covalent bond to L of Formula **1**, and therefore is sometimes referred to a ligand

covalent binding precursor moiety, and the remaining variable groups of Formula **IA** are as defined for Formula **1A**.

[0014] In some ~~embodiment~~examples, provided herein is a Ligand Drug Conjugate composition represented by Formula **1**:

$$L\text{-}[LU\text{-}D']_p \qquad (\mathbf{1})$$

or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

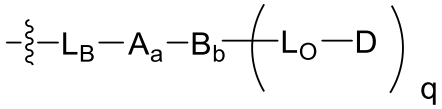
LU is a Linker Unit;

D' represents from 1 to 4 Drug Units (D) in each drug linker moiety of formula -LU-D'; and

subscript p is a number from 1 to 12, from 1 to 10 or from 1 to 8 or is about 4 or about 8,

wherein the Ligand Unit is from an antibody or an antigen-binding fragment of an antibody that is capable of selective binding to an antigen of tumor tissue for subsequent release of the Drug Unit(s) as free drug,

wherein the drug linker moiety of formula -LU-D' in each of the Ligand Drug Conjugate compounds of the composition has the structure of Formula **1A**:



(1A)

or a salt thereof, in particular a pharmaceutically acceptable salt,

wherein the wavy line indicates covalent attachment to L;

D is the Drug Unit;

L_B is a ligand covalent binding moiety;

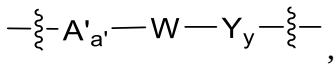
A is a first optional Stretcher Unit;

subscript a is 0 or 1, indicating the absence or presence of A, respectively;

B is an optional Branching Unit;

subscript b is 0 or 1, indicating the absence or presence of B, respectively;

L_O is a secondary linker moiety, wherein the secondary linker has the formula of;



,

wherein the wavy line adjacent to Y indicates the site of covalent attachment of L_O to the Drug Unit and the wavy line adjacent to A' indicates the site of covalent attachment to the remainder of the drug linker moiety;

A’ is a second optional Stretcher Unit, which in the absence of B becomes a subunit of A,

subscript a′ is 0 or 1, indicating the absence or presence of A’, respectively,

W is a Peptide Cleavable Unit, wherein the Peptide Cleavable Unit comprises a tripeptide having the sequence -P3-P2-P1-, wherein P1, P2, and P3 are each an amino acid, wherein:

a first one of the amino acids P1, P2, or P3 is negatively charged;

a second one of the amino acids P1, P2, or P3 has an aliphatic side chain with hydrophobicity no greater than that of leucine; and

a third one of the amino acids P1, P2, or P3 has hydrophobicity lower than that of leucine,

wherein the first one of the amino acids P1, P2, or P3 corresponds to any one of P1, P2, or P3, the second one of the amino acids P1, P2, or P3 corresponds to one of the two remaining amino acids P1, P2, or P3, and the third one of the amino acids P1, P2, or P3 corresponds to the last remaining amino acids P1, P2, or P3,

provided that -P3-P2-P1- is not -Glu-Val-Cit- or -Asp-Val-Cit-;

Y is a self-immolative Spacer Unit;

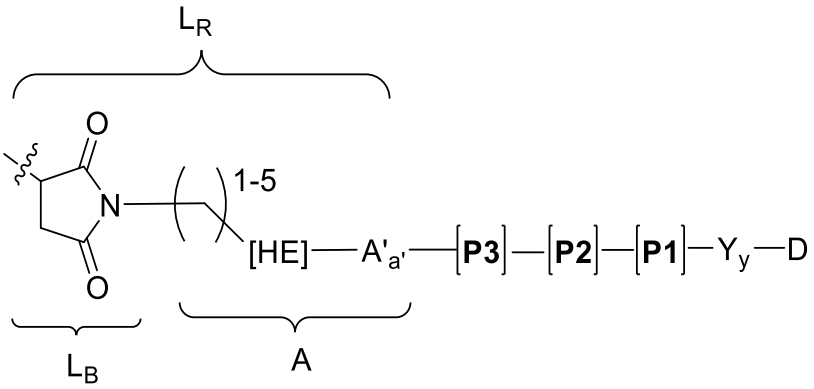
subscript y is 0, 1 or 2 indicating the absence or presence of 1 or 2 of Y, respectively; and

subscript q is an integer ranging from 1 to 4,

provided that subscript q is 1 when subscript b is 0 and subscript q is 2, 3 or 4 when subscript b is 1; and

wherein the Ligand Drug Conjugate compounds of the composition have the structure of Formula **1** in which subscript p is replaced by subscript p’, wherein subscript p’ is independently an integer from 1 to 12, 1 to 10 or 1 to 8 or is 4 or 8.

[0015] In some ~~embodiment~~example<u></u>s, provided herein is the Ligand Drug Conjugate composition of Formula **1**, wherein the Ligand Drug Conjugate compounds in the Ligand Drug Conjugate composition predominately have drug linker moieties of Formula 1H:



(Formula 1H)

or pharmaceutically acceptable salts thereof, and optionally having a minority of Ligand Drug Conjugate compounds in which one or more of the drug linker moieties in each of such compounds has its succinimide ring in hydrolyzed form and wherein

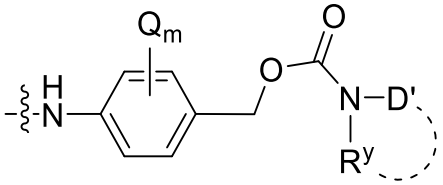
HE is a Hydrolysis Enhancing Unit;

A' is a subunit, when present, of the indicated first Stretcher Unit (A); subscript a' is 0 or 1, indicating the absence or presence of A'; and

the wavy line indicates the site of covalent binding to a sulfur atom of the Ligand Unit.

[0016] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Ligand Drug Conjugate composition wherein HE is –(C=O).

[0017] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Ligand Drug Conjugate composition wherein -Y_y-D has the structure of:



wherein -N(R^y)D' represents D, wherein D' is the remainder of D;

the wavy line indicates the site of covalent attachment to P1;

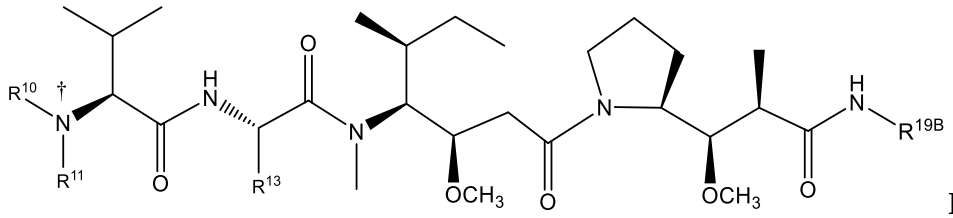
the dotted line indicates optional cyclization of R^y to D';

R^y is optionally substituted C_1-C_6 alkyl in absence of cyclization to D' or optionally substituted C_1-C_6 alkylene when cyclized to D';

each Q is independently selected from the group consisting of -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), halogen, nitro and cyano; and

subscript m is 0, 1 or 2.

[0018] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Ligand Drug Conjugate composition wherein D is a cytotoxic drug wherein the cytotoxic drug is a secondary amine-containing auristatin compound wherein the nitrogen atom of the secondary amine is the site of covalent attachment to the drug linker moiety and the secondary amine-containing auristatin compound has the structure of Formula $\mathbf{D_{F/E\text{-}3}}$:



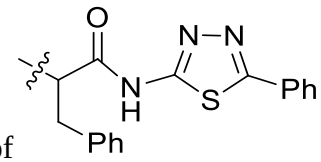
$\mathbf{D_{F/E\text{-}3}}$

wherein the dagger indicates the site of covalent attachment of the nitrogen atom that provides the carbamate functional group;

one of R^{10} and R^{11} is hydrogen and the other is methyl;

R^{13} is isopropyl or –CH_2-$CH(CH_3)_2$; and

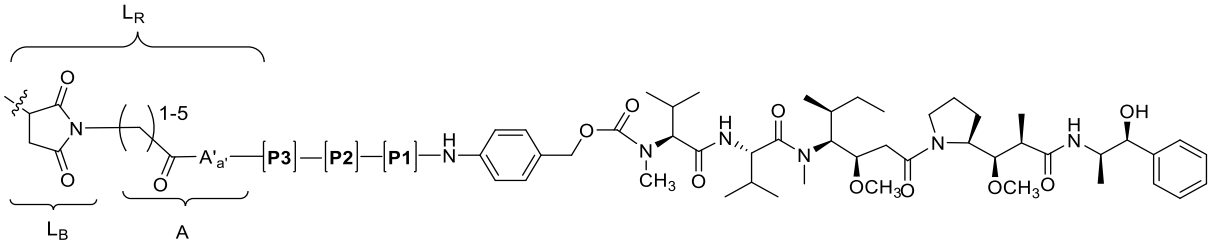
R^{19B} is –$CH(CH_3)$-CH(OH)-Ph, –$CH(CO_2H)$-CH(OH)-CH_3, –$CH(CO_2H)$-CH_2Ph, -CH(CH_2Ph)-2-thiazolyl, -CH(CH_2Ph)-2-pyridyl, -CH(CH_2-p-Cl-Ph), -CH(CO_2Me)-CH_2Ph, -CH(CO_2Me)-$CH_2CH_2SCH_3$, -CH($CH_2CH_2SCH_3$)C(=O)NH-quinol-3-yl, -CH(CH_2Ph)C(=O)NH-p-Cl-Ph, or

R^{19B} has the structure of 

, wherein the wavy line indicates covalent attachment to the remainder of the auristatin compound.

[0019] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Ligand Drug Conjugate composition wherein the secondary amine-containing auristatin compound is monomethylauristatin E (MMAE) or monomethylauristatin F (MMAF).

[0020] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Ligand Drug Conjugate composition wherein subscript q is 1 and the Ligand Drug Conjugate compounds in the Ligand Drug Conjugate composition predominately have drug linker moieties of Formula 1H-MMAE:



(Formula 1H-MMAE)

or a pharmaceutical acceptable salt thereof, and optionally having a minority of Ligand Drug Conjugate compounds in which one or more of the drug linker moieties in each of such compounds has its the succinimide ring in hydrolyzed form and wherein:

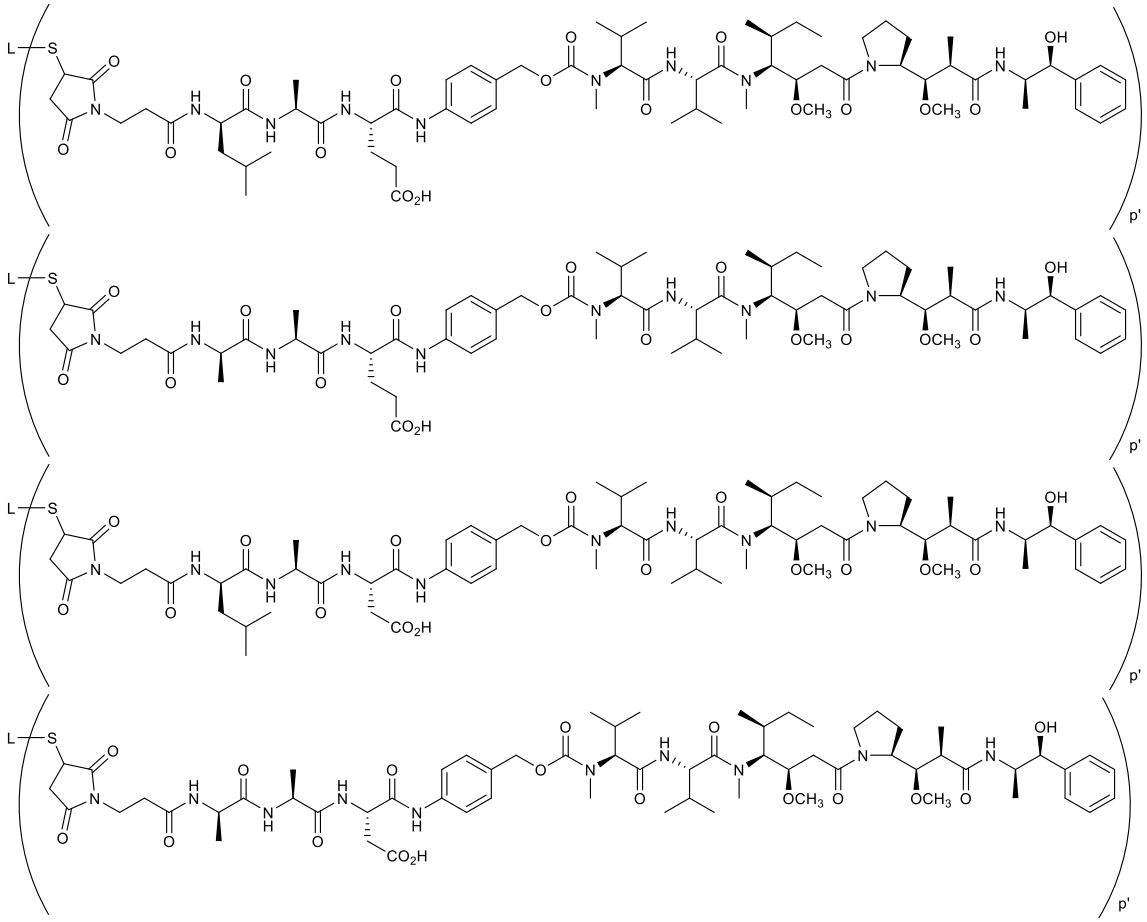
subscript a' is 0, and A' is absent; and

the wavy line indicates the site of covalent binding to a sulfur atom of the Ligand Unit.

[0021] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Ligand Drug Conjugate composition wherein the Peptide Cleavable Unit is a tripeptide having the sequence -P3-P2-P1-, wherein P1, P2, and P3 are each an amino acid, wherein: the P3 amino acid of the tripeptide is in the D-amino acid configuration; one of the P2 and P1 amino acids has an aliphatic side chain with hydrophobicity lower than that of leucine; and the other of the P2 and P1 amino acids is negatively charged. In some ~~embodiment~~examples, the P3 amino acid is D-Leu or D-Ala. Ins ome ~~embodiment~~examples, one of the P2 or P1 amino acid has an aliphatic side chain with hydrophobicity no greater than that of valine, and the other of the P2 or P1 amino acid is negatively charged at plasma physiological pH. In some ~~embodiment~~examples, P2 amino acid has an aliphatic side chain with hydrophobicity no greater than that of valine, and the P1 amino acid is negatively charged at plasma physiological pH. In some ~~embodiment~~examples, -P2-P1- is -Ala-Glu- or -Ala-Asp-. In some ~~embodiment~~examples, -P3-P2-P1- is -D-Leu-Ala-Asp-, -D-Leu-Ala-Glu-, -D-Ala-Ala-Asp-, or -D-Ala-Ala-Glu-. In some ~~embodiment~~examples, the P3 amino

acid is D-Leu or D-Ala, the P2 amino acid is Ala, Glu, or Asp, and the P1 amino acid is Ala, Glu, or Asp.

[0022] In some ~~embodiment~~examples, provided herein is the Ligand Drug Conjugate composition wherein the compound has the structure of:



, or

or a pharmaceutically acceptable salt thereof,

wherein L is a Ligand Unit, and subscript p' is an integer from 1 to 24.

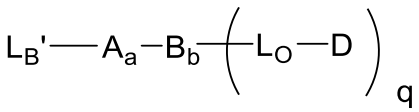
[0023] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Ligand Drug Conjugate composition wherein L is an antibody Ligand Unit of an intact antibody or an antigen-binding fragment thereof. In

some ~~embodiment~~examples, the intact antibody or fragment thereof is capable of selectively binding to a cancer cell antigen. In some ~~embodiment~~examples, the intact antibody is a chimeric, humanized or human antibody, wherein the antibody is capable of selectively binding to a cancer cell antigen or the antibody is a non-binding control antibody thereby defining a non-binding control Conjugate composition.

[0024] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Ligand Drug Conjugate composition wherein subscript p ranges from about 2 to about 12, or from about 2 to about 10, or from about 2 to about 8, in particular subscript p is about 2, about 4 or about 8.

[0025] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein are pharmaceutically acceptable formulations, wherein the formulation comprises an effective amount of a Ligand Drug Conjugate composition or an equivalent amount of a non-binding control Conjugate described herein and at least one pharmaceutically acceptable excipient. In some ~~embodiment~~examples, the least one pharmaceutically acceptable excipient is a liquid carrier that provides a liquid formulation, wherein the liquid formulation is suitable for lyophilization or administration to a subject in need thereof. In some ~~embodiment~~examples, the formulation is a solid from lyophilization or a liquid formulation described herein, wherein the at least one excipient of the solid formulation is a lyoprotectant

[0026] In some ~~embodiment~~examples, provided herein is a Drug Linker compound of Formula **IA:**



(**IA**)

or a salt thereof, wherein

D is a Drug Unit;

L_B' is a ligand covalent binding precursor moiety;

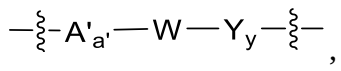
A is a first optional Stretcher Unit;

subscript a is 0 or 1, indicating the absence or presence of A, respectively;

B is an optional Branching Unit;

subscript b is 0 or 1, indicating the absence or presence of B, respectively;

L_O is a secondary linker moiety, wherein the secondary linker has the formula of;



wherein the wavy line adjacent to Y indicates the site of covalent attachment of L_O to the Drug Unit and the wavy line adjacent to A' indicates the site of covalent attachment to the remainder of the Drug Linker compound;

A' is a second optional Stretcher Unit, which in the absence of B becomes a subunit of A;

subscript a' is 0 or 1, indicating the absence or presence of A', respectively,

W is a Peptide Cleavable Unit, wherein the Peptide Cleavable Unit comprises a tripeptide having the sequence -P3-P2-P1-, wherein P1, P2, and P3 are each an amino acid, wherein:

a first one of the amino acids P1, P2, or P3 is negatively charged;

a second one of the amino acids P1, P2, or P3 has an aliphatic side chain with hydrophobicity no greater than that of leucine; and

a third one of the amino acids P1, P2, or P3 has hydrophobicity lower than that of leucine,

wherein the first one of the amino acids P1, P2, or P3 corresponds to any one of P1, P2, or P3, the second one of the amino acids P1, P2, or P3 corresponds to one of the two remaining amino acids P1, P2, or P3, and the third one of the amino acids P1, P2, or P3 corresponds to the last remaining amino acids P1, P2, or P3,

provided that -P3-P2-P1- is not -Glu-Val-Cit- or -Asp-Val-Cit-;

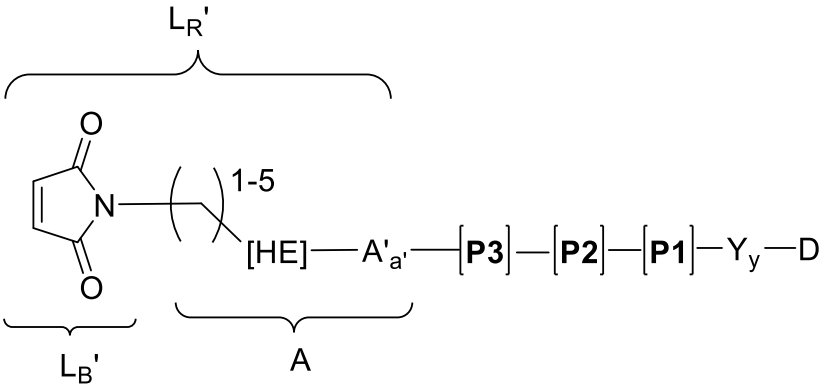
Y is a self-immolative Spacer Unit;

subscript y is 0, 1 or 2 indicating the absence or presence of 1 or 2 of Y, respectively; and

subscript q is an integer ranging from 1 to 4,

provided that subscript q is 1 when subscript b is 0 and subscript q is 2, 3 or 4 when subscript b is 1.

[0027] In some ~~embodiment~~examples, provided herein is the Drug Linker compound of Formula **IA,** wherein the Drug Linker compound has the structure of Formula IH:



(Formula IH)

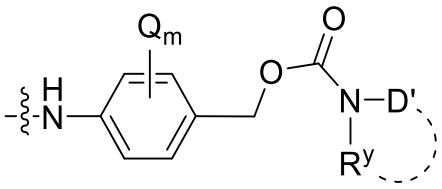
or salt thereof, wherein:

HE is a Hydrolysis Enhancing Unit; and

A' is a subunit, when present, of the indicated first Stretcher Unit (A); subscript a' is 0 or 1, indicating the absence or presence of A'.

[0028] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Drug Linker compound wherein HE is –(C=O).

[0029] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Drug Linker compound wherein -Y_y-D has the structure of:



wherein -N(R^y)D' represents D, wherein D' is the remainder of D;

the wavy line indicates the site of covalent attachment to P1;

the dotted line indicates optional cyclization of R^y to D';

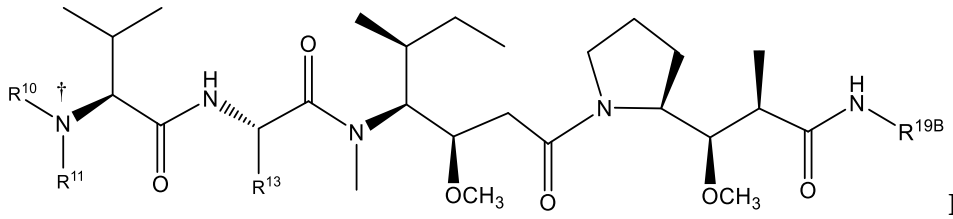
R^y is optionally substituted C_1-C_6 alkyl in absence of cyclization to D' or optionally substituted C_1-C_6 alkylene when cyclized to D';

each Q is independently selected from the group consisting of -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), halogen, nitro and cyano; and

subscript m is 0, 1 or 2.

[0030] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Drug Linker compound wherein D is a cytotoxic drug

wherein the cytotoxic drug is a secondary amine-containing auristatin compound wherein the nitrogen atom of the secondary amine is the site of covalent attachment to the drug linker moiety and the secondary amine-containing auristatin compound has the structure of Formula $\mathbf{D_{F/E-3}}$:



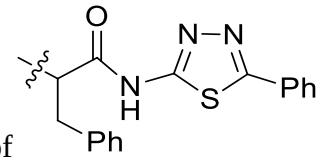
$\mathbf{D_{F/E-3}}$

wherein the dagger indicates the site of covalent attachment of the nitrogen atom that provides the carbamate functional group;

one of R^{10} and R^{11} is hydrogen and the other is methyl;

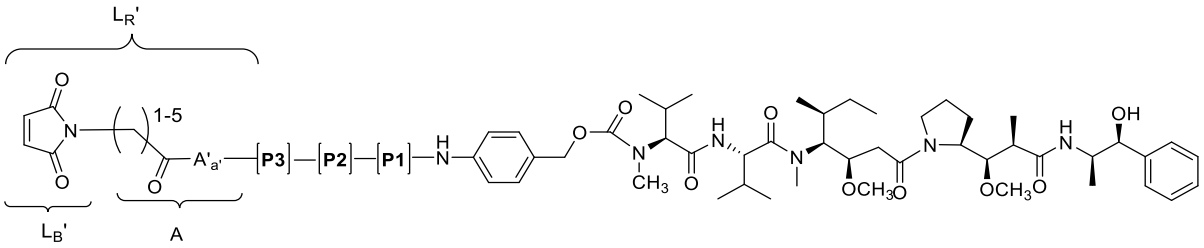
R^{13} is isopropyl or $–CH_2$-$CH(CH_3)_2$; and

R^{19B} is $–CH(CH_3)$-CH(OH)-Ph, $–CH(CO_2H)$-CH(OH)-CH_3, $–CH(CO_2H)$-CH_2Ph, -CH(CH_2Ph)-2-thiazolyl, -CH(CH_2Ph)-2-pyridyl, -CH(CH_2-p-Cl-Ph), -CH(CO_2Me)-CH_2Ph, -CH(CO_2Me)-$CH_2CH_2SCH_3$, -CH($CH_2CH_2SCH_3$)C(=O)NH-quinol-3-yl, -CH(CH_2Ph)C(=O)NH-p-Cl-Ph, or

R^{19B} has the structure of , wherein the wavy line indicates covalent attachment to the remainder of the auristatin compound.

[0031] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Drug Linker compound wherein the secondary amine-containing auristatin compound is monomethylauristatin E (MMAE) or monomethylauristatin F (MMAF).

[0032] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Drug Linker compound wherein the Drug Linker compound has the structure of Formula IH-MMAE:



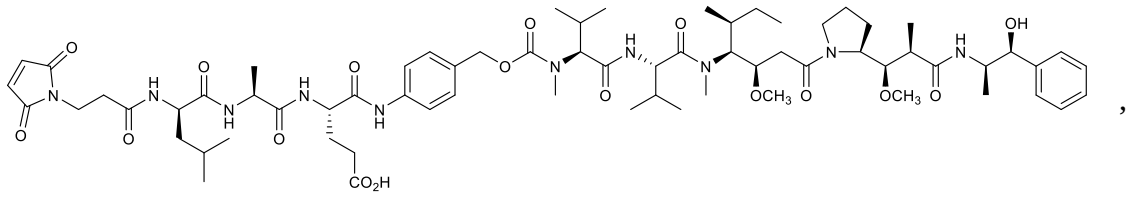
(Formula IH-MMAE)

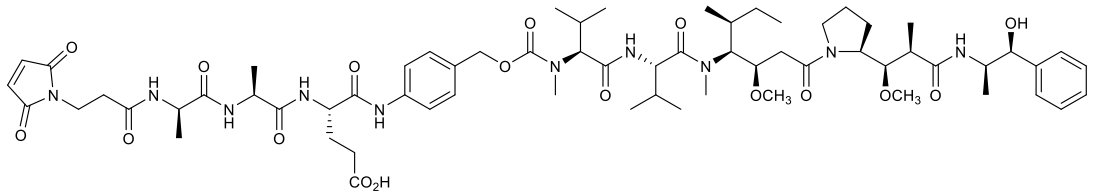
or a salt thereof, wherein

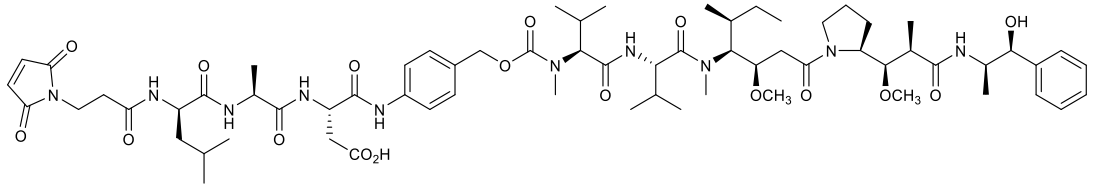
subscript a' is 0, and A' is absent.

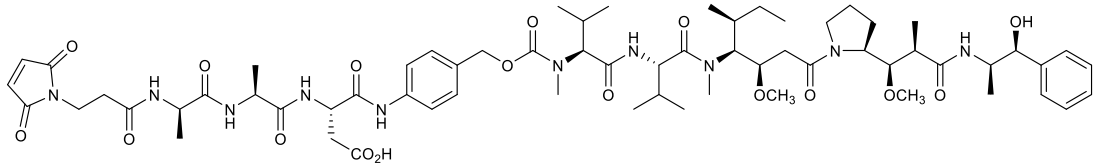
[0033] In some ~~embodiment~~examples, which may be combined with any of the preceding ~~embodiment~~examples, provided herein is the Drug Linker compound wherein the Peptide Cleavable Unit is a tripeptide having the sequence -P3-P2-P1-, wherein P1, P2, and P3 are each an amino acid, wherein: the P3 amino acid of the tripeptide is in the D-amino acid configuration; one of the P2 and P1 amino acids has an aliphatic side chain with hydrophobicity lower than that of leucine; and the other of the P2 and P1 amino acids is negatively charged. In some ~~embodiment~~examples, the P3 amino acid is D-Leu or D-Ala. Ins ome ~~embodiment~~examples, one of the P2 or P1 amino acid has an aliphatic side chain with hydrophobicity no greater than that of valine, and the other of the P2 or P1 amino acid is negatively charged at plasma physiological pH. In some ~~embodiment~~examples, P2 amino acid has an aliphatic side chain with hydrophobicity no greater than that of valine, and the P1 amino acid is negatively charged at plasma physiological pH. In some ~~embodiment~~examples, -P2-P1- is -Ala-Glu- or -Ala-Asp-. In some ~~embodiment~~examples, -P3-P2-P1- is -D-Leu-Ala-Asp-, -D-Leu-Ala-Glu-, -D-Ala-Ala-Asp-, or -D-Ala-Ala-Glu-. In some ~~embodiment~~examples, the P3 amino acid is D-Leu or D-Ala, the P2 amino acid is Ala, Glu, or Asp, and the P1 amino acid is Ala, Glu, or Asp.

[0034] In some ~~embodiment~~examples, provided herein is the Drug Linker compound wherein the Drug Linker compound has the structure of:


,

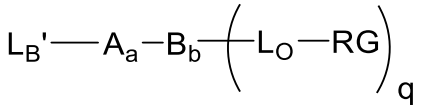

,


, or


,

or a salt thereof.

[0035] In some ~~embodiment~~examples, provided herein is a Linker compound of Formula **IA-L**:


(IA-L)

or a salt thereof, wherein

RG is a reactive group;

L_B' is a ligand covalent binding precursor moiety;

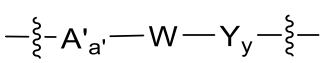
A is a first optional Stretcher Unit;

subscript a is 0 or 1, indicating the absence or presence of A, respectively;

B is an optional Branching Unit;

subscript b is 0 or 1, indicating the absence or presence of B, respectively;

L_O is a secondary linker moiety, wherein the secondary linker has the formula of;


,

wherein the wavy line adjacent to Y indicates the site of covalent attachment of L_O to the Drug Unit and the wavy line adjacent to A' indicates the site of covalent attachment to the remainder of the Drug Linker compound;

A' is a second optional Stretcher Unit, which in the absence of B becomes a subunit of A;

subscript a' is 0 or 1, indicating the absence or presence of A', respectively,

W is a Peptide Cleavable Unit, wherein the Peptide Cleavable Unit comprises a tripeptide having the sequence -P3-P2-P1-, wherein P1, P2, and P3 are each an amino acid, wherein:

a first one of the amino acids P1, P2, or P3 is negatively charged;

a second one of the amino acids P1, P2, or P3 has an aliphatic side chain with hydrophobicity no greater than that of leucine; and

a third one of the amino acids P1, P2, or P3 has hydrophobicity lower than that of leucine,

wherein the first one of the amino acids P1, P2, or P3 corresponds to any one of P1, P2, or P3, the second one of the amino acids P1, P2, or P3 corresponds to one of the two remaining amino acids P1, P2, or P3, and the third one of the amino acids P1, P2, or P3 corresponds to the last remaining amino acids P1, P2, or P3,

provided that -P3-P2-P1- is not -Glu-Val-Cit- or -Asp-Val-Cit-;

Y is a self-immolative Spacer Unit;

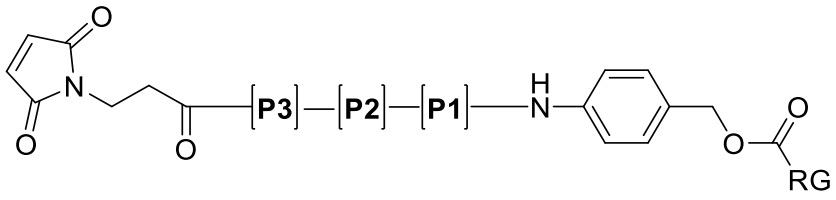
subscript y is 0, 1 or 2 indicating the absence or presence of 1 or 2 of Y, respectively; and

subscript q is an integer ranging from 1 to 4,

provided that subscript q is 1 when subscript b is 0 and subscript q is 2, 3 or 4 when subscript b is 1.

[0036] In some ~~embodiment~~examples, provided herein is the Linker compound, wherein the Peptide Cleavable Unit is a tripeptide having the sequence -P3-P2-P1-, wherein P1, P2, and P3 are each an amino acid, wherein: the P3 amino acid of the tripeptide is in the D-amino acid configuration; one of the P2 and P1 amino acids has an aliphatic side chain with hydrophobicity lower than that of leucine; and the other of the P2 and P1 amino acids is negatively charged.

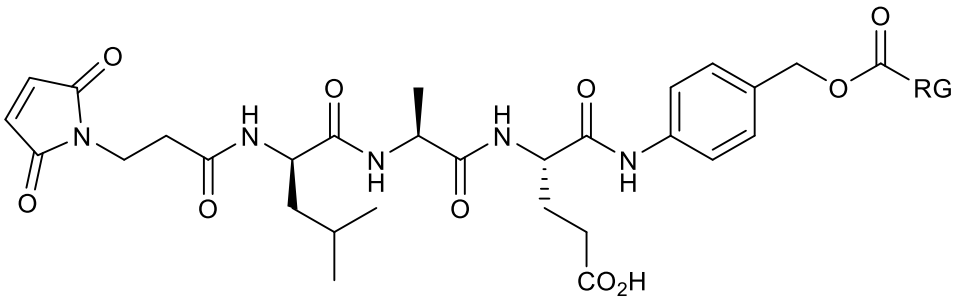
[0037] In some ~~embodiment~~examples, provide herein is the Linker compound wherein the Linker compound has the structure of Formula **IA-L-3**:



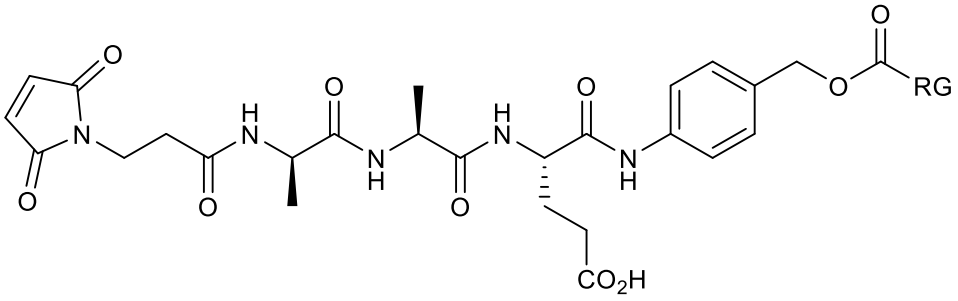
(IA-L-3),

or a salt thereof.

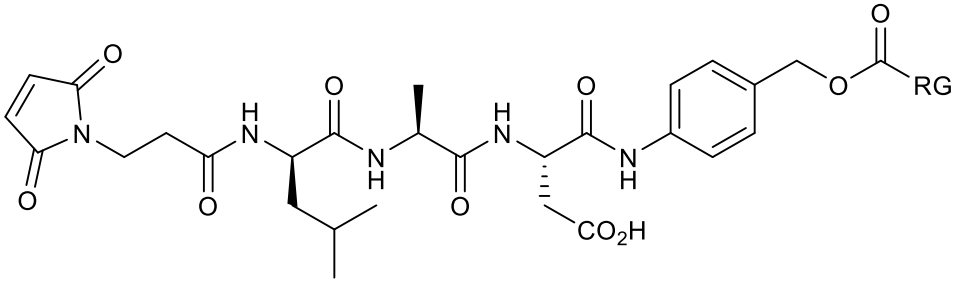
[0038] In some ~~embodiment~~examples, provided herein is a Linker comound wherein the Linker compound has the structure of:



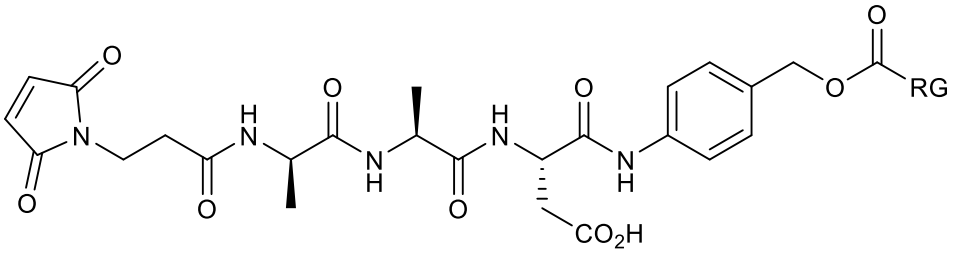
,



,



, or



,

or a salt thereof.

[0039] Those and other ~~embodiment~~examples of the present disclosure ~~invention~~ are described in more detail in the following "Detailed Description of the Invention" and "Claims".

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] Figures 1A, 1B, 1C, and 1D. Tumor volume vs days post implant in a xenograft model treated with a series of 4-loaded ADCs having varying tripeptide sequences as the Peptide Cleavable Unit with drug-linker moieties represented by the formula of mp-P_3-P_2-P_1-PABC-MMAE at sub-curative doses compared to a subcurative dose of a 4-loaded ADC targeting the same cancer cell antigen and having drug-linker moieties represented by the formula of mc-val-cit-PABC-MMAE. Compounds in Figure 1A were tested at at 4 mg/kg. Compounds in Figure 1B and Figure 1D were tested at 3 mg/kg. Compounds in Figure 1C were tested at 6 mg/kg.

[0041] Figure 2. Neutrophil counts after day 4 of 10 mg/Kg administration of a series of 4-loaded non-binding control conjugates having varying tripeptide sequences as the Peptide Cleavable Unit with drug-linker moieties represented by the formula of mp-P_3-P_2-P_1-PABC-MMAE in comparison to 4-loaded non-binding conjugates having drug-linker moieties represented by the formula of mc-val-cit-PABC-MMAE or mp-val-cit-PABC-MMAE.

[0042] Figure 3. Reticulocyte counts in rat plasma after day 4 from 10 mg/Kg administration to non-tumor bearing animals of a series of 4-loaded non-binding conjugates having varying tripeptide sequences as the Peptide Cleavable Unit with drug-linker moieties represented by the formula of mp-P_3-P_2-P_1-PABC-MMAE in comparison to 4-loaded non-binding conjugates having drug-linker moieties represented by the formula of mc-val-cit-PABC-MMAE or mp-val-cit-PABC-MMAE.

[0043] Figure 4. Histopathology of bone marrow of rat after administration to non-tumor bearing animals at day 4 of vehicle or 10 mg/Kg of 4-loaded non-binding conjugates having varying tripeptide sequences as the Peptide Cleavable Unit with drug-linker moieties represented by the formula of mp-P_3-P_2-P_1-PABC-MMAE in comparison to a 4-loaded non-binding conjugate having drug-linker moieties represented by the formula of mc-val-cit-PABC-MMAE.

[0044] Figures 5A and 5B. Free MMAE in rat plasma at various time points subsequent to administration to non-tumor bearing animals of vehicle and 10 mg/Kg of 4-loaded non-binding conjugates having varying tripeptide sequences as the Peptide