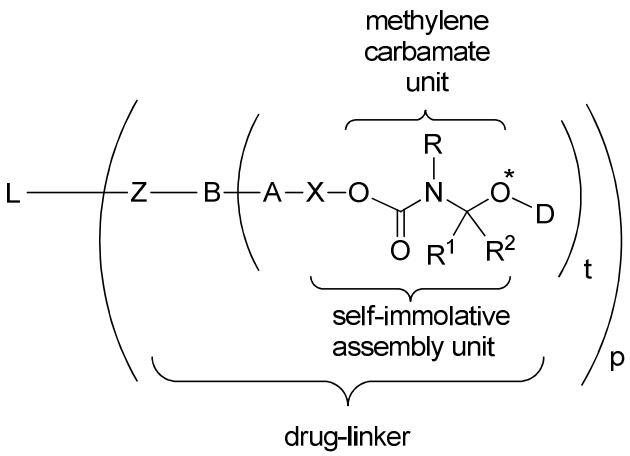
many aliphatic alcohol-containing drugs (see, for example, Toki, et al. *J. Org. Chem.* 2002, 67, 1866-1872). One reason for that may be due to the high pKa of aliphatic alcohol-containing drugs.

[0005] Therefore**,** a need exists for new linker technologies that can be used to attach drugs heretofore believed to be unsuitable for use as ADCs, and Ligand Drug Conjugates (LDCs) in general, including a need for more versatile methods for linking aromatic alcohol- and aliphatic alcohol-containing drugs to other targeting ligands in addition to antibodies. The present invention addresses those and other needs.

BRIEF SUMMARY OF THE DISCLOSURE

[0006] The disclosure provides *inter alia,* Ligand-Drug Conjugates, wherein the Ligand-Drug Conjugate is comprised of a Self-immolative Assembly Unit having a methylene carbamate unit for conjugation of a drug to a targeting ligand, methods of preparing and using them, and intermediates thereof. The Ligand-Drug Conjugates of the present disclosure are stable in circulation, yet capable of inflicting cell death once free drug is released from a Conjugate in the vicinity or within tumor cells.

[0006a] In one aspect, the present disclosure provides a Ligand-Drug Conjugate compound having the structure of:



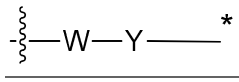
or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

Z is a Stretcher Unit comprising a thio-substituted succinimide or succinic acid-amide moiety;

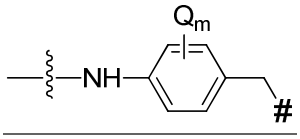
B is an optional Branching Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or polyamine residues or combinations thereof and is present when subscript t is greater than 1 and is absent when subscript t is 1;

A is an optional Connector Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or diamino residues or combinations thereof; D is a Drug Unit having a hydroxyl functional group incorporated into the indicated methylene carbamate unit; O* is the oxygen atom from said hydroxyl functional group; X is an activateable self-immolative moiety, wherein the activateable self-immolative moiety is of formula (i):

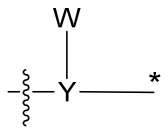


(i)

wherein the wavy line indicates covalent attachment of W to A, B, or Z depending on the presence or absence of A or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit; W is an Activation Unit; and Y is a self-immolative Spacer Unit, wherein the Activation Unit comprises a sequence of 1 to 12 amino acids having an amide linkage to the self-immolative Spacer Unit wherein the amide linkage is cleavable by the action of a tumor associated protease to initiate release of free drug, and the self-immolative Spacer Unit is a PAB group having the structure of:

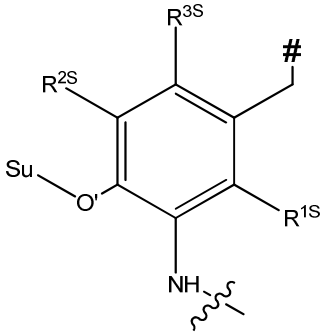


wherein the wavy line indicates the site of covalent attachment to the Activation Unit and the hashtag (#) indicates the site of covalent attachment to the benzylic carbon atom of the PAB group to the methylene carbamate unit; and Q is independently -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), or other electron donating group and subscript m is 0, 1 or 2, or the activateable self-immolative moiety is of formula (ii):

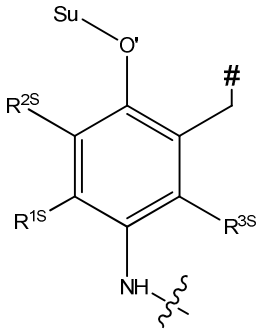


(ii)

wherein the wavy line indicates covalent attachment of Y to A, B, or Z, depending on the presence or absence of A or B, and the asterisk (*) indicates the site of covalent attachment of Y to the oxygen atom of the methylene carbamate unit, wherein formula (ii) is a Glucuronide Unit having the structure of formula XIXa or XIXb:



or



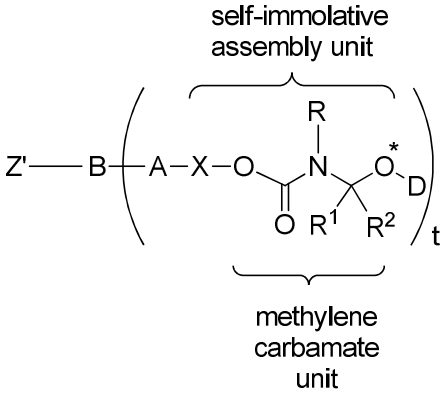
;

(XIXa) (XIXb)

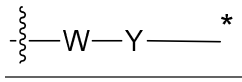
wherein Su is a Sugar moiety; -O'-represents the oxygen atom of glycosidic bond cleavable by a glycosidase; R^{1S}, R^{2S} and R^{3S} are independently selected from the group consisting of hydrogen, halogen, -CN and -NO_2; the wavy line indicates the site of covalent attachment to the Stretcher Unit (Z), either directly or indirectly through the Connector Unit (A); and # indicates the site of attachment to the oxygen atom of the methylene carbamate unit ~~, wherein activation of the activateable self-immolative moiety is by a protease or a glucosidase and results in release of D as free drug having said hydroxyl functional group~~; R is ~~a Basic Unit (BU), or R is~~ hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted C_{6-14} aryl; R^1 is hydrogen, and R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or both R and R^1 together with the nitrogen and carbon atoms to which they are attached define an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety and R^2 is hydrogen; and subscript t ranges from 1 to 4; subscript p is an integer ranging from 1 to 16; and wherein optional substituents are selected from the group consisting of -X, -R^{op}, -OH, -OR^{op}, -$N(R^{op})_2$, -$N(R^{op})_3$, -$NR^{op}C(=O)R^{op}$, -$C(=O)N(R^{op})_2$, -$S(=O)_2R^{op}$, -$S(=O)_2NR^{op}$, -$S(=O)R^{op}$, -$C(=O)R^{op}$, -$C(=O)N(R^{op})_2$, and -$C(=NR^{op})N(R^{op})_2$, wherein X is –F, and each R^{op} is independently selected from the group consisting of hydrogen, -C_1-C_{20} alkyl, -C_6-C_{20} aryl, -C_3-C_{14} heterocycle, and protecting groups~~, and prodrug moieties~~.

[0006b] In another aspect, the present disclosure provides a Ligand-Drug Conjugate composition comprising a plurality of Conjugate compounds, wherein each independently has the structure of a Ligand-Drug Conjugate compound as described herein, wherein the integer range of subscript p is replaced by a number ranging from 1 to 16, and a pharmaceutically acceptable carrier.

[0006c] In another aspect, the present disclosure provides a Drug-Linker compound having the structure of:

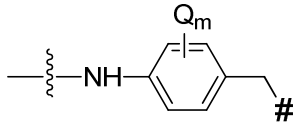


or a pharmaceutically acceptable salt thereof, wherein Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) and comprises a maleimide functional group that provides for covalent attachment of a Ligand Unit to Z; B is an optional Branching Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or polyamine residues or combinations thereof and is present when subscript t is greater than 1 and is absent when subscript t is 1; A is an optional Connector Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or diamino residues or combinations thereof; D is a Drug Unit having a hydroxyl functional group incorporated into the indicated methylene carbamate unit; O* is the oxygen atom from said hydroxyl functional group; X is an activateable self-immolative moiety, wherein the activateable self-immolative moiety is of formula (i):



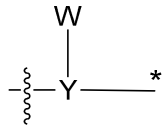
(i)

wherein the wavy line indicates covalent attachment of W to A, B, or Z depending on the presence or absence of A or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit; W is an Activation Unit; and Y is a self-immolative Spacer Unit, wherein the Activation Unit comprises a sequence of 1 to 12 amino acids having an amide linkage to the self-immolative Spacer Unit wherein the amide linkage is cleavable by the action of a tumor associated protease to initiate release of free drug, and the self-immolative Spacer Unit is a PAB group having the structure of:



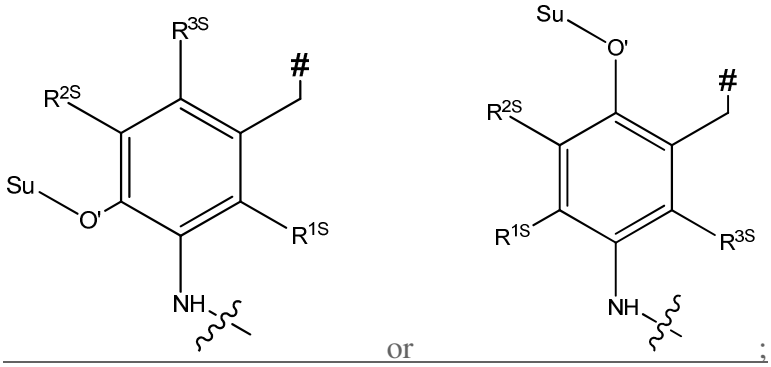
wherein the wavy line indicates the site of covalent attachment to the Activation Unit and the hashtag (#) indicates the site of covalent attachment to the benzylic carbon atom of the PAB

group to the methylene carbamate unit; and Q is independently -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), or other electron donating group and subscript m is 0, 1 or 2, or the activateable self-immolative moiety is of formula (ii):



(ii)

wherein the wavy line indicates covalent attachment of Y to A, B, or Z, depending on the presence or absence of A or B, and the asterisk (*) indicates the site of covalent attachment of Y to the oxygen atom of the methylene carbamate unit, wherein formula (ii) is a Glucuronide Unit having the structure of formula XIXa or XIXb:



or ;

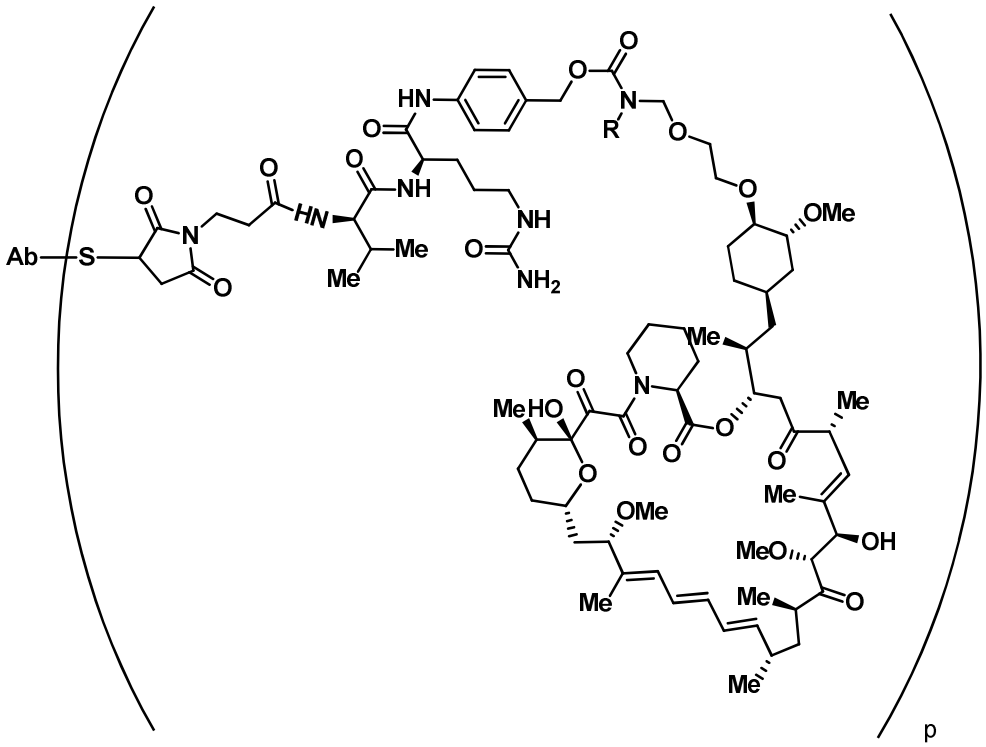
(XIXa) (XIXb)

wherein Su is a Sugar moiety; -O'-represents the oxygen atom of glycosidic bond cleavable by a glycosidase; R^{1S}, R^{2S} and R^{3S} are independently selected from the group consisting of hydrogen, halogen, -CN and -NO_2; the wavy line indicates the site of covalent attachment to the Stretcher Unit precursor (Z'), either directly or indirectly through the Connector Unit (A); and # indicates the site of attachment to the oxygen atom of the methylene carbamate unit~~,~~ ~~wherein activation of the activateable self-immolative moiety in the Drug-Linker compound or in a Ligand-Drug Conjugate prepared from the Drug-Linker compound is by a protease or a glucosidase and results in release of D as free drug having said hydroxyl functional group~~;

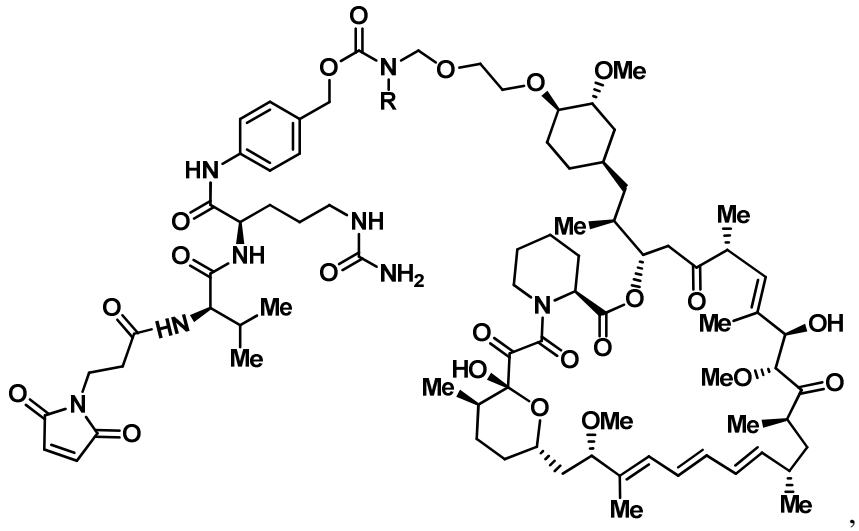
R is ~~a Basic Unit (BU), or R is~~ hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted C_{6-14} aryl; R^1 is hydrogen, and R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or both R and R^1 together with the nitrogen and carbon atoms to which they are attached define an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety and R^2 is hydrogen; and subscript t ranges from 1 to 4; subscript p is an integer ranging from 1 to 16; and wherein optional substituents are selected from the group consisting of -X, -R^{op}, -OH, -OR^{op}, -$N(R^{op})_2$, -$N(R^{op})_3$, -$NR^{op}C(=O)R^{op}$, -$C(=O)N(R^{op})_2$, -$S(=O)_2R^{op}$, -$S(=O)_2NR^{op}$, -$S(=O)R^{op}$, -$C(=O)R^{op}$, -$C(=O)N(R^{op})_2$, and -$C(=NR^{op})N(R^{op})_2$, wherein X is –F,

and each R^{op} is independently selected from the group consisting of hydrogen, -C_1-C_{20} alkyl, -C_6-C_{20} aryl, -C_3-C_{14} heterocycle, and a protecting group~~, and a prodrug moiety~~.

[0006d] In yet another aspect, the present disclosure provides a Ligand-Drug Conjugate compound as described herein, or composition thereof as described herein, or a Drug-Linker compound as described herein, wherein the hydroxyl functional group is that of an aliphatic alcohol-containing free drug so that O* represents the oxygen atom from that functional group, wherein the aliphatic alcohol-containing drug is capable of binding to FKBP for inhibition of mTOR or calcineurin effector function, wherein the Ligand-Drug Conjugate compound and composition and Drug-Linker compound, have structures of:



p and



,

respectively, wherein Ab is an antibody and S is a sulfur atom from the antibody; R is hydrogen, ethyl or $–CH_2CH_2N(CH_3)_2$; and subscript p is a number or an integer ranging from 1 to 16 or 1 to 8.

[0006e] In yet another aspect, the present disclosure provides a method of preparing an Antibody Drug Conjugate compound as described herein, or a composition thereof as described herein, in which Stretcher Unit (Z) comprises a succinimide moiety or an succinic acid-amide moiety; and wherein the Ligand Unit is an antibody, the method comprising the step of:

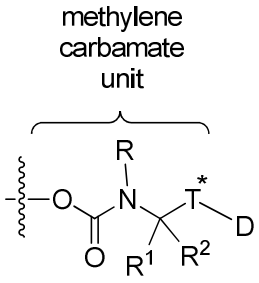
contacting a Drug-Linker compound as described herein in which Stretcher Unit precursor (Z') comprises a maleimide moiety with an antibody having a reactive cysteine thiol functional group obtained from interchain disulfide bond reduction and/or from an engineered cysteine residue,

wherein said contacting converts Z' to Z by formation of a covalent bond between the reactive cysteine sulfur atom of the antibody and the succinimide moiety of Z, optionally followed by spontaneous hydrolysis of the succinimide moiety to an acid amide moiety, whereby the Antibody Drug Conjugate compound or composition thereof is obtained.

[0006f] In yet another aspect, the present disclosure provides use of a Ligand-Drug Conjugate compound as described herein, or a composition thereof as described herein, for preparing a medicament.

[0006g] In yet another aspect, the present disclosure provides use of a Ligand-Drug Conjugate compound as described herein, or composition thereof as described herein, in the manufacture of a medicament for treating a cancer.

[0007] In one principle example, a Ligand Drug Conjugate (LDC), or composition thereof, is comprised of a Ligand Unit, a Drug Unit and a Linker Unit that connects the Ligand Unit to the Drug Unit, wherein the Linker Unit is comprised of a Self-immolative Assembly Unit having a methylene carbamate unit and an activateable self-immolative moiety, wherein activation of the activateable self-immolative moiety results in release of free drug from the LDC from self-immolation, and wherein the methylene carbamate unit is covalently attached to the Drug Unit and the activateable self-immolative moiety, wherein the methylene carbamate unit covalently attached to the Drug Unit is represented by the structure of formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

the wavy line indicates covalent attachment of the methylene carbamate unit to an activateable self-immolative moiety (X);

D is a Drug Unit having a functional group (e.g., hydroxyl, thiol, amide or amine functional group) that has been incorporated into the methylene carbamate unit,

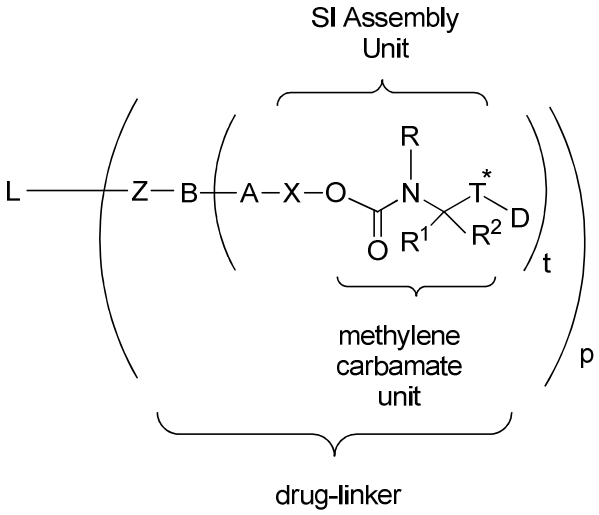
T* is a heteroatom from said functional group (e.g., oxygen, sulfur, optionally substituted nitrogen) that becomes incorporated into the methylene carbamate unit;

X is an activateable self-immolative moiety;

R, R^1 and R^2 independently are hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl,

or R and R^1 together with the nitrogen and carbon atoms to which they are attached comprise an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety, and R^2 is hydrogen.

[0008] In some of those examples, a Ligand Drug Conjugate, or composition thereof, having the methylene carbamate unit of formula I is represented by the structure of formula II:



(II)

or a pharmaceutically acceptable salt thereof; wherein

L is a Ligand Unit;

Z is a Stretcher Unit;

B is an optional Branching Unit and is present when t is greater than 1 and is absent when t is 1;

A is an optional Connector Unit;

X is an activateable self-immolative moiety;

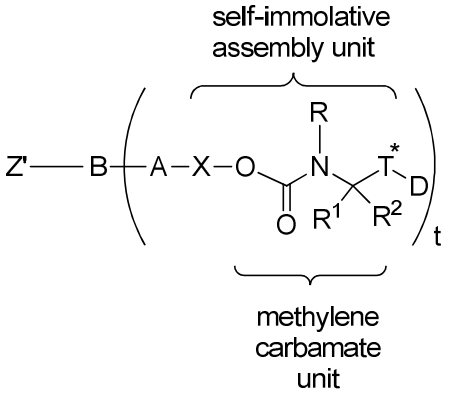
the subscript t ranges from 1 to 4;

the subscript p is an integer (for an individual LDC) or a number (for a population of LDCs in a LDC composition) ranging from 1 to 16; and

and D, T*, R, R^1 and R^2 are as defined in formula I.

[0009] Other principle examples are Drug-Linker Compounds useful as intermediates for preparing Ligand-Drug Conjugates, wherein the Drug-Linker Compound is comprised of a Drug Unit and a Linker Unit, wherein the Linker Unit is comprised of a Stretcher Unit precursor (Z') capable of forming a covalent bond to a targeting ligand that provides for a Ligand Unit, a Self-immolative Assembly Unit having a methylene carbamate unit and an activateable self-immolative moiety, wherein activation of the activateable self-immolative moiety in a LDC in which the Drug-Linker Compound is incorporated results in release of free drug from the LDC by self-immolation, and wherein the methylene carbamate unit is covalently attached to the Drug Unit and the activateable self-immolative moiety.

[0010] In some of those examples the Drug-Linker Compound having the methylene carbamate unit of formula I has the structure of formula V:



(V)

or a pharmaceutically acceptable salt thereof, wherein

Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) and is comprised of a functional group that provides for covalent attachment of a Ligand Unit to Z;

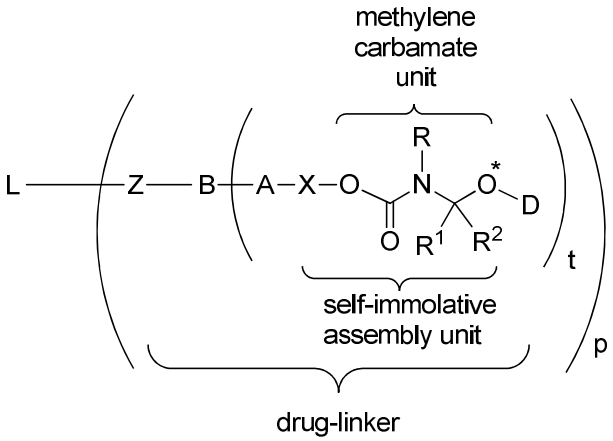
and B, A, X, R, R^1, R^2, T*, D, and the subscript t are as defined for Formula (II).

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1 demonstrates the stability *ex vivo* in rat and mouse plasma of an ADC composition having an average drug loading of 4 in which the ADCs of the composition are comprised of a methylene alkoxy carbamate unit (MAC unit) that incorporates the oxygen heteroatom from the hydroxyl functional group of Auristatin E.

WHAT IS CLAIMED IS:

1. A Ligand-Drug Conjugate compound having the structure of:



or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

Z is a Stretcher Unit comprising a thio-substituted succinimide or succinic acid-amide moiety;

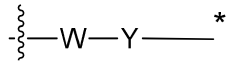
B is an optional Branching Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or polyamine residues or combinations thereof and is present when subscript t is greater than 1 and is absent when subscript t is 1;

A is an optional Connector Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or diamino residues or combinations thereof;

D is a Drug Unit having a hydroxyl functional group incorporated into the indicated methylene carbamate unit;

O* is the oxygen atom from said hydroxyl functional group;

X is an activateable self-immolative moiety, wherein the activateable self-immolative moiety is of formula (i):



(i)

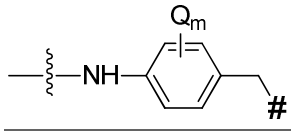
wherein the wavy line indicates covalent attachment of W to A, B, or Z depending on the presence or absence of A or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit;

W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

wherein the Activation Unit comprises a sequence of 1 to 12 amino acids having an amide linkage to the self-immolative Spacer Unit wherein the amide linkage is cleavable by the action of a tumor associated protease to initiate release of free drug, and

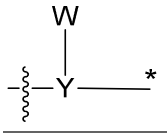
the self-immolative Spacer Unit is a PAB group having the structure of:



wherein the wavy line indicates the site of covalent attachment to the Activation Unit and the hashtag (#) indicates the site of covalent attachment to the benzylic carbon atom of the PAB group to the methylene carbamate unit; and

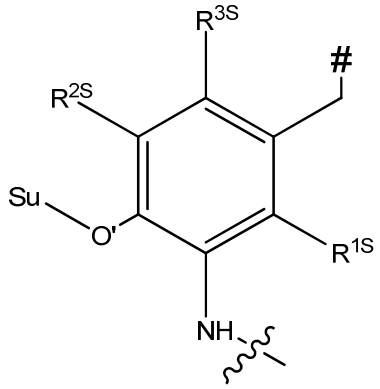
Q is independently -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), or other electron donating group and subscript m is 0, 1 or 2, or

the activateable self-immolative moiety is of formula (ii):

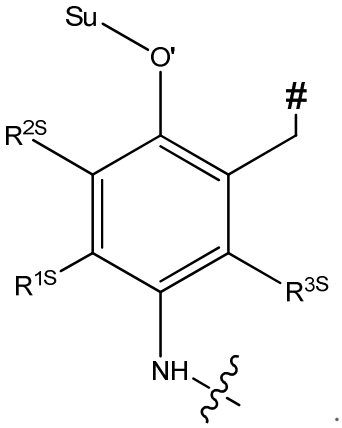


(ii)

wherein the wavy line indicates covalent attachment of Y to A, B, or Z, depending on the presence or absence of A or B, and the asterisk (*) indicates the site of covalent attachment of Y to the oxygen atom of the methylene carbamate unit, wherein formula (ii) is a Glucuronide Unit having the structure of formula XIXa or XIXb:



or



; (XIXa) (XIXb)

wherein Su is a Sugar moiety; -O'-represents the oxygen atom of glycosidic bond cleavable by a glycosidase;

R^{1S}, R^{2S} and R^{3S} are independently selected from the group consisting of hydrogen, halogen, -CN and -NO_2;

the wavy line indicates the site of covalent attachment to the Stretcher Unit (Z), either directly or indirectly through the Connector Unit (A); and

# indicates the site of attachment to the oxygen atom of the methylene carbamate unit

~~, wherein activation of the activateable self-immolative moiety is by a protease or a glucosidase and results in release of D as free drug having said hydroxyl functional group~~;

R is~~ a Basic Unit (BU), or R is~~ hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted C_{6-14} aryl;

R^1 is hydrogen, and R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or

both R and R^1 together with the nitrogen and carbon atoms to which they are attached define an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety and R^2 is hydrogen; and

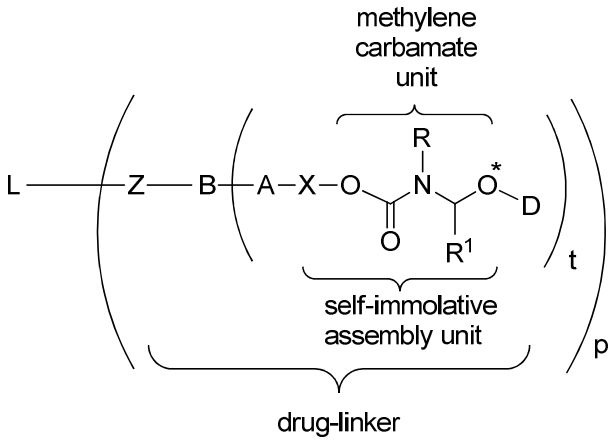
subscript t ranges from 1 to 4;

subscript p is an integer ranging from 1 to 16; and

wherein optional substituents are selected from the group consisting of -X, -R^{op}, -OH, -OR^{op}, -$N(R^{op})_2$, -$N(R^{op})_3$, -$NR^{op}C(=O)R^{op}$, -$C(=O)N(R^{op})_2$, -$S(=O)_2R^{op}$, -$S(=O)_2NR^{op}$, -$S(=O)R^{op}$, -$C(=O)R^{op}$, -$C(=O)N(R^{op})_2$, and -$C(=NR^{op})N(R^{op})_2$, wherein X is –F,

and each R^{op} is independently selected from the group consisting of hydrogen, -C_1-C_{20} alkyl, -C_6-C_{20} aryl, -C_3-C_{14} heterocycle, and protecting groups~~, and prodrug moieties~~.

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



or a pharmaceutically acceptable salt thereof.

3. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein R is a Basic Unit wherein the basic functional group of the Basic Unit is a basic amine or a basic nitrogen-containing 3-, 4-, 5-, or 6 -membered heterocycle that is C-linked or N-linked to 2-6 contiguous carbon atoms connecting the carbamate nitrogen of the indicated methylene carbamate unit to the basic functional group and is optionally substituted.

4. The Ligand-Drug Conjugate compound of claim 3 wherein, R is a Basic Unit, wherein the basic functional group of the Basic Unit is $–N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and C_{1-6} alkyl.

5. The Ligand-Drug Conjugate compound of claim 3, wherein R is a Basic Unit, wherein the basic functional group of the Basic Unit is $–N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and methyl.

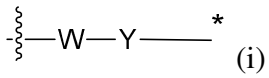
6. The Ligand-Drug Conjugate compound of claim 3, wherein R is a Basic Unit, wherein the Basic Unit is $–(CH_2)_xNH_2$, $–(CH_2)_xNHR^{op}$, or $–(CH_2)_xN(R^{op})_2$, wherein x is an integer ranging from 2-4 and R^{op} is C_{1-6} alkyl.

7. The Ligand-Drug Conjugate compound of claim 3, wherein R is a Basic Unit, wherein the Basic Unit is $–CH_2CH_2N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and methyl.

8. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the hydroxyl functional group is that of an aliphatic alcohol-containing free drug, so that O* represents the oxygen atom from that functional group.

9. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein B is absent and subscript t is 1 or B is present and subscript t is 2.

10. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the structure of the indicated activateable self-immolative moiety (X) is represented by formula (i):



(i)

wherein the wavy line indicates covalent attachment of W to A, B or Z depending on the presence or absence of A and/or B and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit; and wherein

W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

wherein activation of self-immolation of Y results in release of D as free drug.

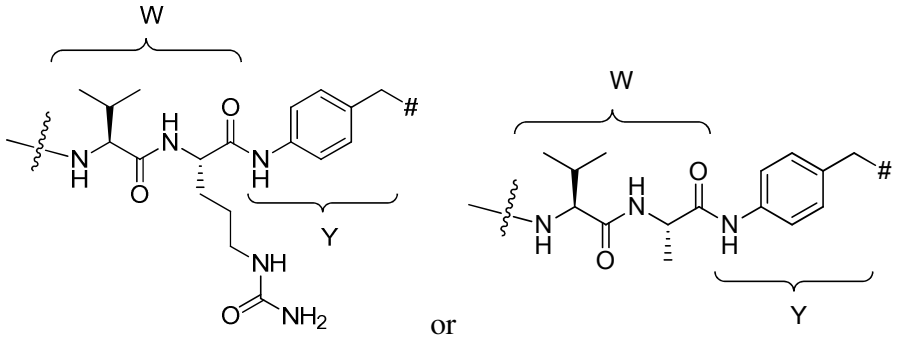
~~11. The Ligand-Drug Conjugate compound of claim 10, wherein activation for self-immolation of Y is by enzymatic cleavage of a covalent bond between W and Y.~~

~~12. The Ligand-Drug Conjugate compound of claim 11, wherein enzymatic cleavage is by a tumor associated protease.~~

~~13~~11. The Ligand-Drug Conjugate compound of claim ~~12~~10, wherein the tumor associated protease is cathepsin B.

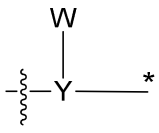
~~14~~12. The Ligand-Drug Conjugate compound of claim ~~12~~10, wherein W is -Val-Cit-, -Phe-Lys- or –Val-Ala-.

~~15~~13. The Ligand-Drug Conjugate compound of claim 10, wherein –W-Y- is represented by the structure of:



wherein the wavy bond to the nitrogen of W indicates covalent attachment to Z, A or B, depending on the presence or absence of A and/or B, and the hash mark (#) indicates covalent attachment of the benzylic carbon of Y to the oxygen atom of the methylene carbamate unit.

~~16~~14. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the structure of the activateable self-immolative moiety (X) is represented by formula (ii):



(ii),

wherein the wavy line indicates covalent attachment of Y to A, B or Z depending on the presence or absence of A and/or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit~~, and wherein~~;

W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

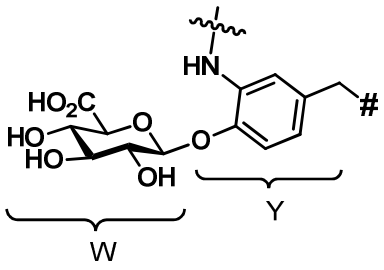
wherein activation of self-immolation of Y results in release of D as free drug.

~~17. The Ligand-Drug Conjugate compound of claim 16, wherein activation for self-immolation of Y is by enzymatic cleavage of a covalent bond between W and Y, wherein enzymatic cleavage is by a glycosidase.~~

~~18~~15. The Ligand-Drug Conjugate compound of claim ~~17~~14, wherein the glycosidase is a glucuronidase.

~~19.The Ligand-Drug Conjugate compound of claim 17, wherein W is a sugar moiety connected to Y via a glycosidic bond capable of cleavable by a glycosidase for activation of self-immolation of Y.~~

~~20~~16. The Ligand-Drug Conjugate compound of claim ~~19~~14, wherein –Y(W)- is represented by the structure of:

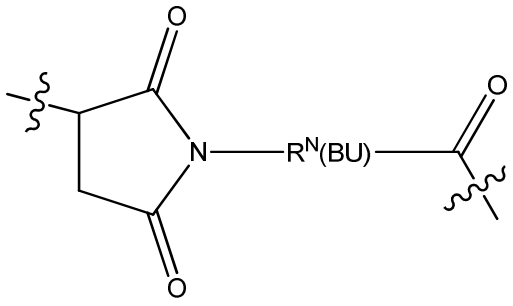


,

wherein the wavy bond adjacent to the nitrogen of Y indicates covalent attachment of Y to Z, A or B, depending on the presence or absence of A and/or B, and the hash mark (#) indicates covalent attachment of the benzylic carbon of Y to the oxygen atom of the methylene carbamate unit.

~~21. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the Stretcher unit (Z) comprises a succinimide moiety or an acid-amide moiety, wherein that moiety is attached to a sulfur atom of the Ligand Unit.~~

~~22~~17. The Ligand-Drug Conjugate compound of claim ~~21~~1 or 2, wherein the Stretcher unit (Z) comprises a succinimide moiety and is represented by the structure of formula **Xa':**



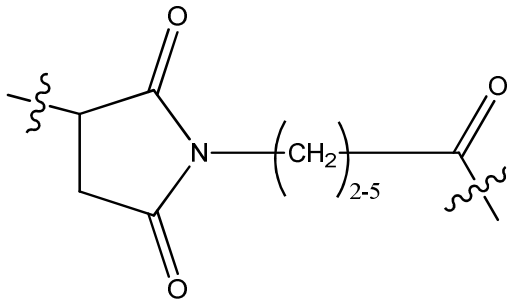
(**Xa'**),

wherein the wavy line adjacent to the succinimide ring system indicates covalent attachment to a sulfur atom of the Ligand Unit;

the wavy line adjacent to the carbonyl carbon indicates covalent attachment to the remainder of the drug linker moiety;

and R^N is -C_2-C_5 alkylene, wherein the alkylene is optionally substituted by a Basic Unit (BU), wherein BU is $–(CH_2)_xNH_2$, $–(CH_2)_xNHR^{op}$, or $–(CH_2)_xN(R^{op})_2$, wherein x is an integer ranging from 1 to 4; and R^{op} is C_{1-6} alkyl.

~~23~~18. The Ligand-Drug Conjugate compound of claim ~~21~~1 or 2, wherein the Stretcher unit (Z) comprises a succinimide moiety and is represented by the structure**:**

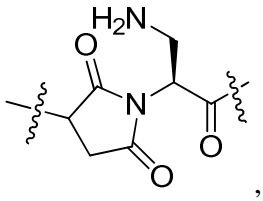


,

wherein the wavy line adjacent to the succinimide ring system indicates covalent attachment to a sulfur atom of the Ligand Unit, and

the wavy line adjacent to the carbonyl carbon indicates covalent attachment to the remainder of the drug linker moiety.

~~24~~19. The Ligand-Drug Conjugate compound of claim ~~21~~1 or 2, wherein the Stretcher unit (Z) comprises a succinimide moiety and is represented by the structure of:

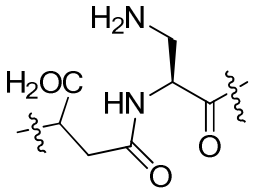


,

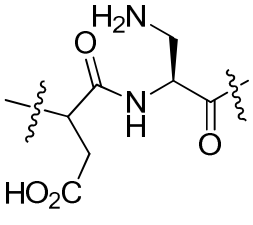
or an acid addition salt thereof,

or

wherein the Stretcher unit (Z) comprises a succinic acid-amide moiety and is represented by the structure of:



or



,

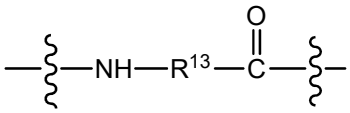
or an acid addition salt thereof;

and

wherein the wavy line adjacent to the carbonyl carbon indicates covalent attachment to the remainder of the drug linker moiety and the other wavy line indicates covalent attachment to a sulfur atom of the Ligand Unit.

~~25~~20. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein a Connector Unit (A) is present.

~~26~~21. The Ligand-Drug Conjugate Compound of claim ~~25~~1 or 2, wherein A is:

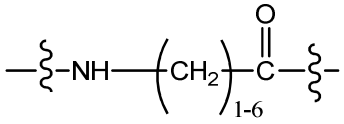


wherein the wavy line adjacent to the carbonyl indicates covalent attachment to the activateable self-immolative moiety X of the Self-immolative Assembly Unit, and

the other wavy line indicates covalent attachment to B, if present, or to Z if B is absent; and

R^{13} is -C_1-C_6 alkylene-, -C_3-C_8carbocyclo-, -arylene-, -C_1-C_{10} heteroalkylene-, -C_3-C_8heterocyclo-, -C_1-C_{10}alkylene-arylene-, -arylene-C_1-C_{10}alkylene-, -C_1-C_{10}alkylene-(C_3-C_8carbocyclo)-, -(C_3-C_8carbocyclo)-C_1-C_{10}alkylene-, -C_1-C_{10}alkylene-(C_3-C_8 heterocyclo)-, or -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-.

~~27~~22. The Ligand-Drug Conjugate compound of claim ~~26~~21, wherein A has the formula of:



.

~~28~~23. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein A is absent.

~~29~~24. The Ligand-Drug Conjugate compound of claim 1, wherein p is an integer ranging from 1 to 10.

~~30~~25. The Ligand-Drug Conjugate compound of claim 2, wherein p is an integer ranging from 1 to 8.

~~31~~26. The Ligand-Drug Conjugate compound of claim ~~29 or 30~~ 24 or 25, wherein the Ligand Unit is an antibody.

~~32~~27. The Ligand-Drug Conjugate Compound of claim ~~31~~26, wherein the Drug Unit corresponds in structure to free drug having hydroxyl functional group whose oxygen heteroatom is capable of incorporation into a methylene carbamate unit, wherein free drug is capable of binding to FKBP to inhibit mTOR or calcineurin effector function.

~~33~~28. The Ligand-Drug Conjugate compound of claim ~~32~~27, wherein the FKBP binding free drug is everolimus, tacrolimus or sirolimus.

~~34~~29. The Ligand-Drug Conjugate compound of claim ~~32~~27, wherein the Drug Unit corresponds in structure to free drug having a hydroxyl functional group whose oxygen heteroatom is capable of incorporation into a methylene carbamate unit, wherein free drug is an auristatin.

~~35~~30. The Ligand-Drug Conjugate compound of claim ~~34~~29, wherein the auristatin is MMAE or auristatin T.

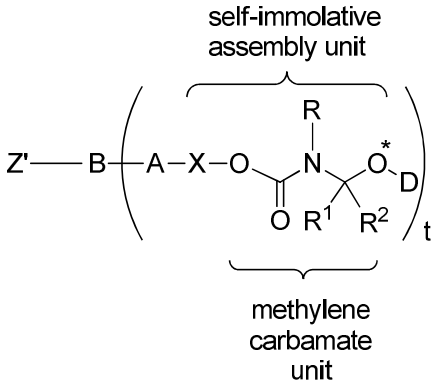
~~36~~31. A Ligand-Drug Conjugate composition comprising a plurality of Conjugate compounds, wherein each independently has the structure of a Ligand-Drug Conjugate compound of claim 1, wherein the integer range of subscript p is replaced by a number ranging from 1 to 16, and a pharmaceutically acceptable carrier.

~~37~~32. The Ligand-Drug Conjugate composition of claim ~~36~~31, wherein the Stretcher Unit (Z) of each of the Conjugate compounds independently comprises a succinimide moiety or an succinic acid-amide moiety, wherein that moiety is attached to a sulfur atom of the Ligand Unit.

~~38~~33. The Ligand-Drug Conjugate composition of claim ~~37~~32, wherein there is an average of 2 to 10 drug-linkers per Ligand Unit.

~~39~~34. The Ligand-Drug Conjugate composition of claim ~~37~~32, wherein there is an average of 2 to 8 drug-linkers per Ligand Unit.

~~40~~35. A Drug-Linker compound having the structure of:



or a pharmaceutically acceptable salt thereof, wherein

Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) and comprises a maleimide functional group that provides for covalent attachment of a Ligand Unit to Z;

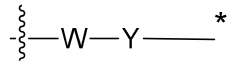
B is an optional Branching Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or polyamine residues or combinations thereof and is present when subscript t is greater than 1 and is absent when subscript t is 1;

A is an optional Connector Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or diamino residues or combinations thereof;

D is a Drug Unit having a hydroxyl functional group incorporated into the indicated methylene carbamate unit;

O* is the oxygen atom from said hydroxyl functional group;

X is an activateable self-immolative moiety, wherein the activateable self-immolative moiety is of formula (i):



(i)

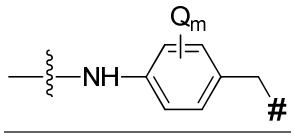
wherein the wavy line indicates covalent attachment of W to A, B, or Z depending on the presence or absence of A or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit;

W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

wherein the Activation Unit comprises a sequence of 1 to 12 amino acids having an amide linkage to the self-immolative Spacer Unit wherein the amide linkage is cleavable by the action of a tumor associated protease to initiate release of free drug, and

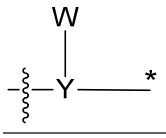
the self-immolative Spacer Unit is a PAB group having the structure of:



wherein the wavy line indicates the site of covalent attachment to the Activation Unit and the hashtag (#) indicates the site of covalent attachment to the benzylic carbon atom of the PAB group to the methylene carbamate unit; and

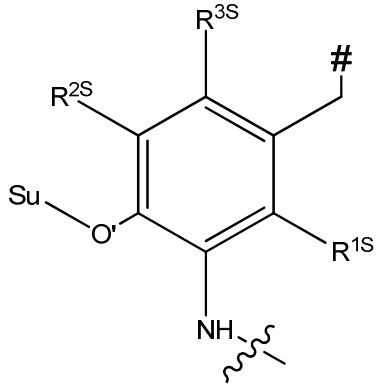
Q is independently -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), or other electron donating group and subscript m is 0, 1 or 2, or

the activateable self-immolative moiety is of formula (ii):



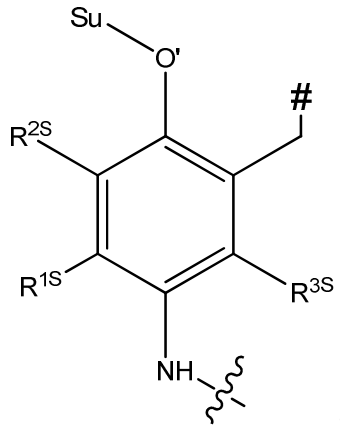
(ii)

wherein the wavy line indicates covalent attachment of Y to A, B, or Z, depending on the presence or absence of A or B, and the asterisk (*) indicates the site of covalent attachment of Y to the oxygen atom of the methylene carbamate unit, wherein formula (ii) is a Glucuronide Unit having the structure of formula XIXa or XIXb:



(XIXa)

or



(XIXb)

;

wherein Su is a Sugar moiety; -O'-represents the oxygen atom of glycosidic bond cleavable by a glycosidase;

R^{1S}, R^{2S} and R^{3S} are independently selected from the group consisting of hydrogen, halogen, -CN and $-NO_2$;

the wavy line indicates the site of covalent attachment to the Stretcher Unit precursor (Z'), either directly or indirectly through the Connector Unit (A); and

# indicates the site of attachment to the oxygen atom of the methylene carbamate unit

~~, wherein activation of the activateable self-immolative moiety in the Drug-Linker compound or in a Ligand-Drug Conjugate prepared from the Drug-Linker compound is by a protease or a glucosidase and results in release of D as free drug having said hydroxyl functional group~~;

R is ~~a Basic Unit (BU), or R is~~ hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted C_{6-14} aryl;

R^1 is hydrogen, and R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or

both R and R^1 together with the nitrogen and carbon atoms to which they are attached define an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety and R^2 is hydrogen; and

subscript t ranges from 1 to 4;

subscript p is an integer ranging from 1 to 16; and

wherein optional substituents are selected from the group consisting of -X, $-R^{op}$, -OH, $-OR^{op}$, $-N(R^{op})_2$, $-N(R^{op})_3$, $-NR^{op}C(=O)R^{op}$, $-C(=O)N(R^{op})_2$, $-S(=O)_2R^{op}$, $-S(=O)_2NR^{op}$, $-S(=O)R^{op}$, $-C(=O)R^{op}$, $-C(=O)N(R^{op})_2$, and $-C(=NR^{op})N(R^{op})_2$, wherein X is –F,

and each R^{op} is independently selected from the group consisting of hydrogen, $-C_1$-C_{20} alkyl, $-C_6$-C_{20} aryl, $-C_3$-C_{14} heterocycle, and a protecting group~~, and a prodrug moiety~~.

~~41~~36. The Drug-Linker compound of claim ~~40~~35, wherein R is a Basic Unit, wherein the basic functional group of the Basic Unit is a basic amine or a basic nitrogen-containing 3-, 4-, 5-, or 6-membered heterocycle that is C-linked or N-linked to 2-6 contiguous carbon atoms connecting

the carbamate nitrogen of the indicated methylene carbamate unit to the basic functional group and is optionally substituted.

~~42~~37. The Drug-Linker compound of claim ~~40~~35, wherein R is a Basic Unit, wherein the basic functional group of the Basic Unit is $–N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and C_{1-6} alkyl.

~~43~~38. The Drug-Linker compound of claim ~~40~~35, wherein R is a Basic Unit, wherein the basic functional group of the Basic Unit is $–N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and methyl.

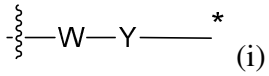
~~44~~39. The Drug-Linker compound of claim ~~40~~35, wherein R is a Basic Unit, wherein the Basic Unit is $–(CH_2)_xNH_2$, $–(CH_2)_xNHR^{op}$, or $–(CH_2)_xN(R^{op})_2$, wherein x is an integer ranging from 2-4 and R^{op} is C_{1-6} alkyl.

~~45~~40. The Drug-Linker compound of claim ~~40~~35, wherein R is a Basic Unit, wherein the Basic Unit is $–CH_2CH_2N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and methyl.

~~46~~41. The Drug-Linker compound of claim ~~40~~35, wherein the hydroxyl functional group is that of an aliphatic alcohol-containing free drug, so that O* represents the oxygen atom from that functional group.

~~47~~42. The Drug-Linker compound of claim ~~40~~35, wherein B is absent and subscript t is 1 or B is present and subscript t is 2.

~~48~~43. The Drug-Linker compound of claim ~~40~~35, wherein the structure of the indicated activateable self-immolative moiety (X) is represented by formula (i):



(i)

wherein the wavy line indicates covalent attachment of W to A, B or Z depending on the presence or absence of A and/or B and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit; and wherein

W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

wherein activation of self-immolation of Y in the Drug-Linker compound or in a Ligand-Drug Conjugate prepared from the Drug-Linker compound results in release of D as free drug.

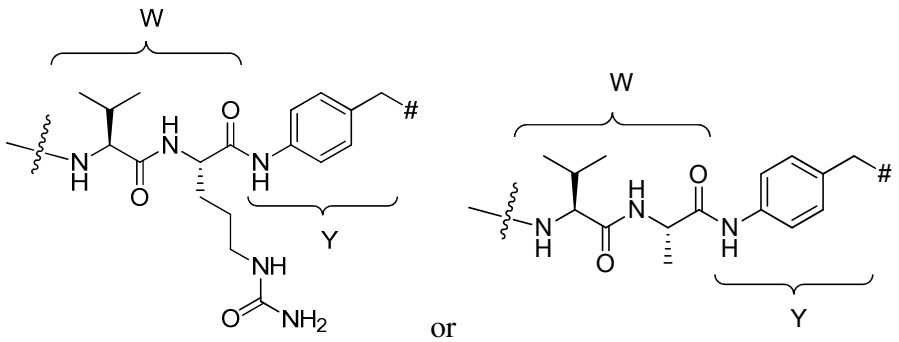
~~49.The Drug-Linker compound of claim 48, wherein activation for self-immolation of Y is by enzymatic cleavage of a covalent bond between W and Y.~~

~~50.The Drug-Linker compound of claim 49, wherein enzymatic cleavage is by a tumor associated protease.~~

~~51~~44. The Drug-Linker compound of claim ~~50~~43, wherein the tumor associated protease is cathepsin B.

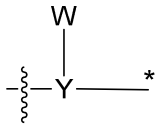
~~52~~45. The Drug-Linker compound of claim ~~46~~41, wherein W is -Val-Cit-, -Phe-Lys- or –Val-Ala-.

~~53~~46. The Drug-Linker compound of claim ~~49~~43, wherein –W-Y- is represented by the structure of:



wherein the wavy bond to the nitrogen of W indicates covalent attachment to Z, A or B, depending on the presence or absence of A and/or B, and the hash mark (#) indicates covalent attachment of the benzylic carbon of Y to the oxygen atom of the methylene carbamate unit.

~~54~~47. The Drug-Linker compound of claim ~~40~~35, wherein the structure of the indicated activateable self-immolative moiety (X) is represented by formula (ii):



(ii)

wherein the wavy line indicates covalent attachment of Y to A, B or Z depending on the presence or absence of A and/or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate moiety~~, and wherein~~;

W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

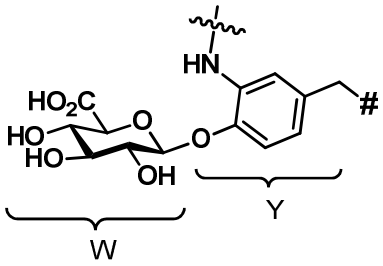
wherein activation of self-immolation of Y in the Drug-Linker compound or in a Ligand-Drug Conjugate prepared from the Drug-Linker compound results in release of D as free drug.

~~55.The Drug-Linker compound of claim 54, wherein activation for self-immolation of Y is by enzymatic cleavage of the covalent bond between W and Y, wherein enzymatic cleavage is by a glycosidase.~~

~~56~~48. The Drug-Linker compound of claim ~~55~~47, wherein the glycosidase is a glucuronidase.

~~57. The Drug-Linker compound of claim 54, wherein W is a sugar moiety connected to Y via a glycosidic bond capable of cleavable by a glycosidase for activation of self-immolation of Y.~~

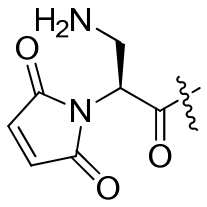
~~58~~49. The Drug-Linker compound of claim ~~57~~47, wherein –Y(W)- is represented by the structure of:



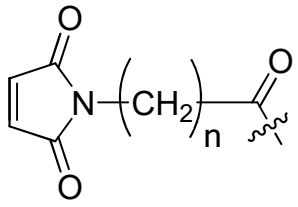
wherein the wavy bond adjacent to the nitrogen of Y indicates covalent attachment to Z', A or B, depending on the presence or absence of A and/or B, and the hash mark (#) indicates covalent attachment of the benzylic carbon of Y to the oxygen atom of the methylene carbamate unit.

~~59.The Drug-Linker compound of claim 40, wherein Z' comprises a maleimide moiety.~~

~~60~~50. The Drug-Linker compound of claim ~~59~~35, wherein Z' has the structure of:



or

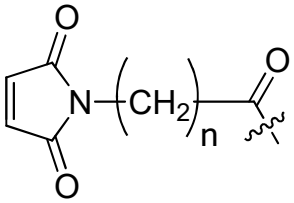


,

or an acid addition salt thereof,

or

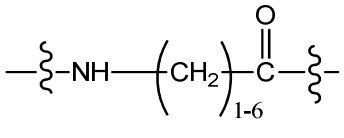
wherein Z' has the structure of:



and

wherein the wavy line adjacent to the carbonyl indicates covalent attachment of Z' to A, B or X, depending on the presence or absence of A and/or B, wherein n is an integer ranging from 2 to 5.

~~61~~51. The Drug-Linker compound of claim ~~40~~35, wherein A is present and has the formula

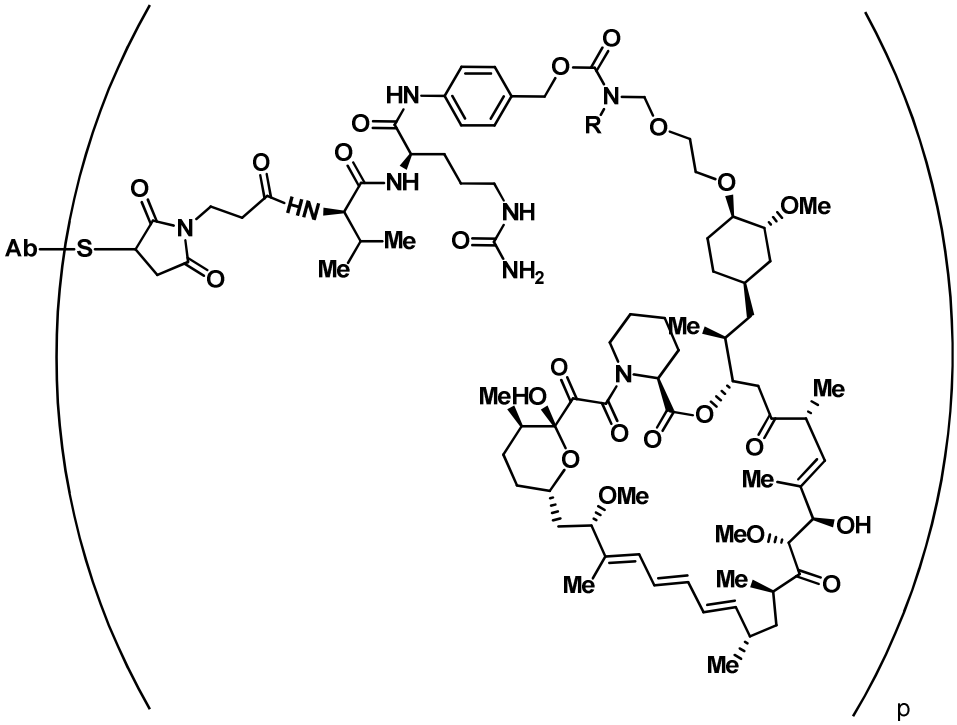


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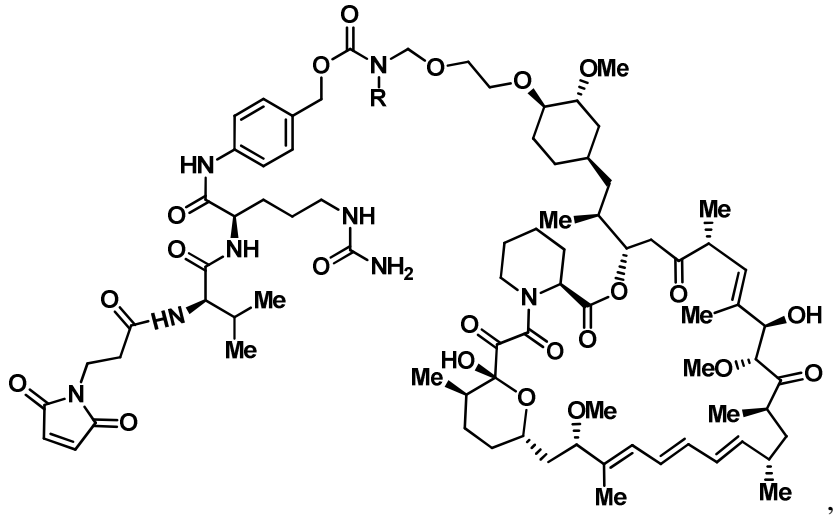
wherein the wavy lines indicate covalent attachments within the Drug-Linker compound structure.

~~62~~52. The Drug-Linker compound of claim ~~40~~35, wherein B is absent and subscript t is 1 or B is present and subscript t is 2.

~~63~~53. A Ligand-Drug Conjugate compound of claim 1, or composition thereof of claim ~~36~~31, or a Drug-Linker compound of claim ~~40~~35, wherein the hydroxyl functional group is that of an aliphatic alcohol-containing free drug so that O* represents the oxygen atom from that functional group, wherein the aliphatic alcohol-containing drug is capable of binding to FKBP for inhibition of mTOR or calcineurin effector function, wherein the Ligand-Drug Conjugate compound ~~and composition~~ and Drug-Linker compound~~,~~ have structures of:



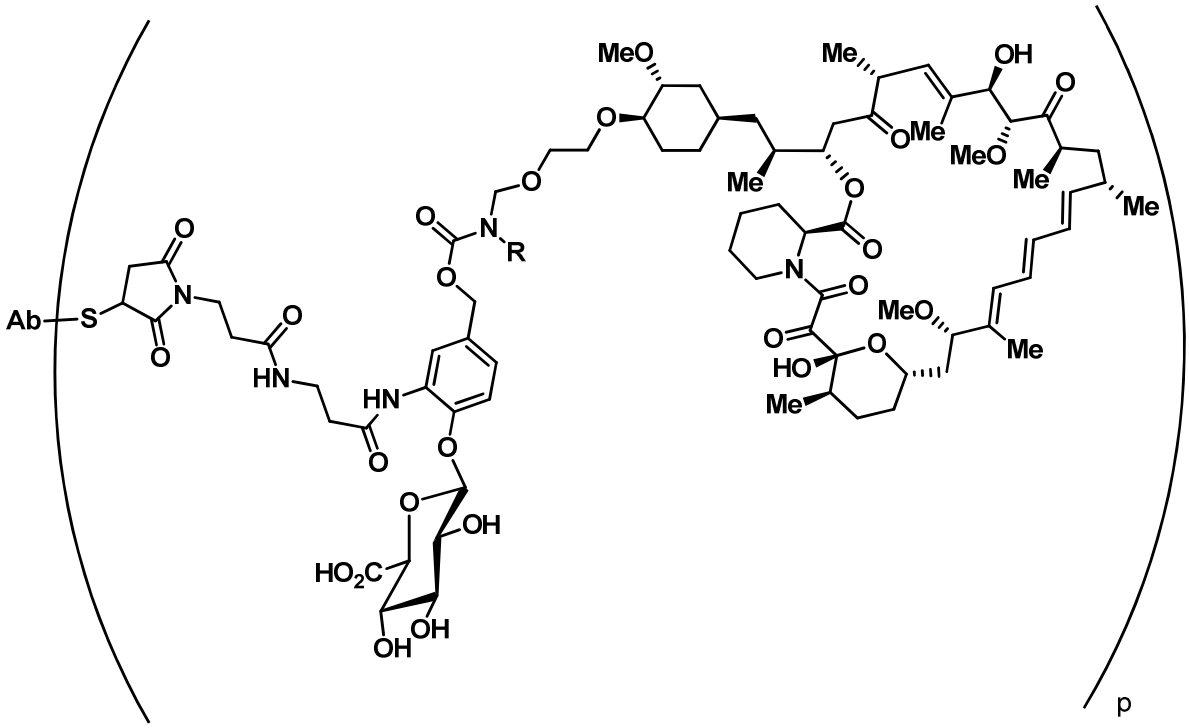
p and



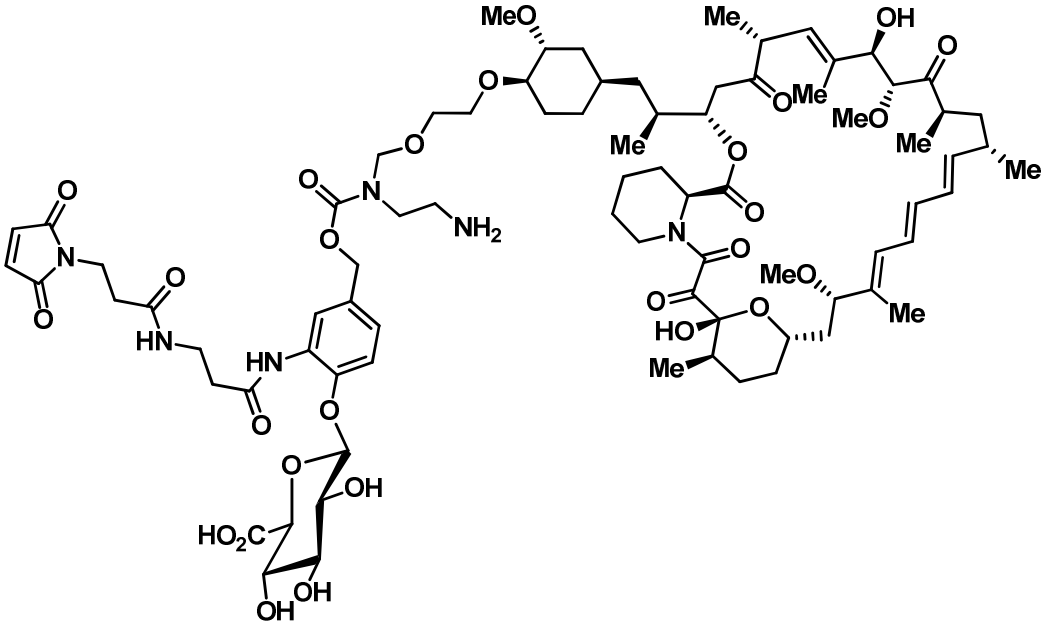
,

respectively, wherein Ab is an antibody and S is a sulfur atom from the antibody; R is hydrogen, ethyl or $–CH_2CH_2N(CH_3)_2$; and subscript p is a number or an integer ranging from 1 to 16 or 1 to 8.

~~64~~54. The Ligand-Drug Conjugate compound of claim 1, or composition thereof of claim 31, or a Drug-Linker compound of claim 35, wherein the hydroxyl functional group is that of an aliphatic alcohol-containing free drug so that O* represents the oxygen atom from that functional group, wherein the aliphatic alcohol-containing drug is capable of binding to FKBP for inhibition of mTOR or calcineurin effector function~~Ligand-Drug Conjugate compound and Ligand-Drug Conjugate composition or Drug-Linker compound of claim 63~~, wherein the Ligand-Drug Conjugate compound ~~and composition~~ and Drug-Linker compound~~,~~ have structures of:



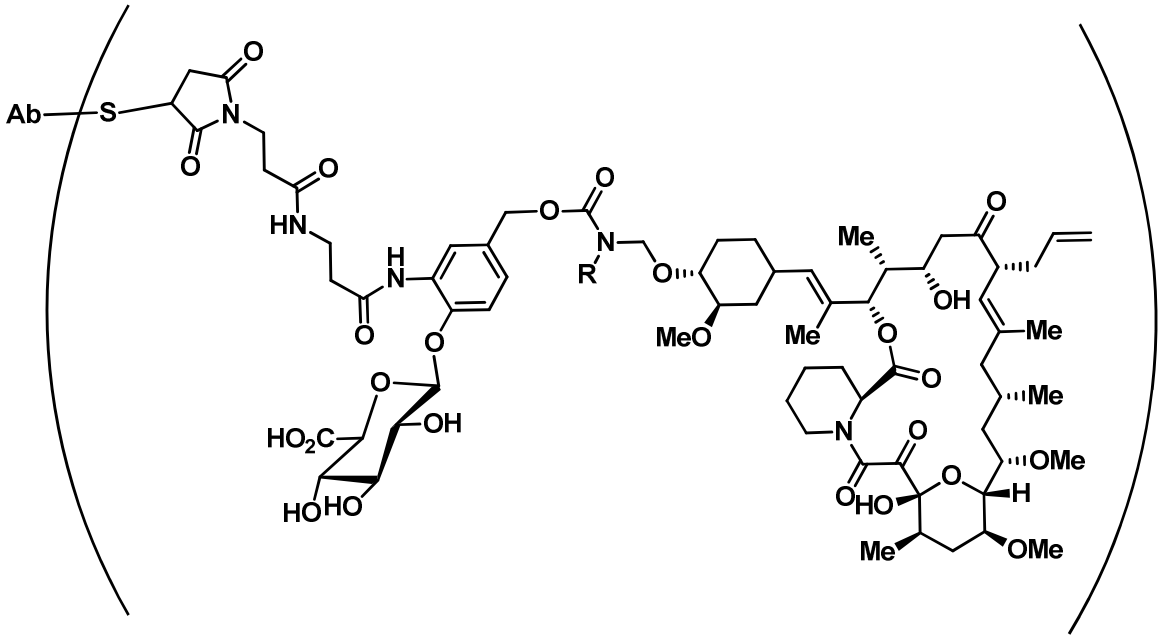
p and



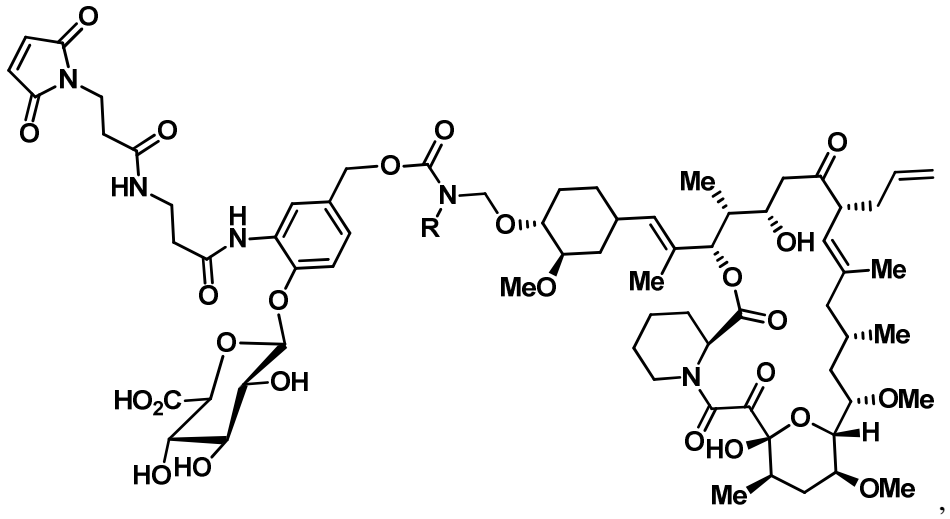
,

respectively, wherein Ab is an antibody and S is a sulfur atom from the antibody; R is hydrogen, ethyl or $–CH_2CH_2N(CH_3)_2$, and subscript p is a number or an integer ranging from 1 to 16 or 1 to 8.

~~65~~55. The Ligand-Drug Conjugate compound of claim 1, or composition thereof of claim 31, or a Drug-Linker compound of claim 35, wherein the hydroxyl functional group is that of an aliphatic alcohol-containing free drug so that O* represents the oxygen atom from that functional group, wherein the aliphatic alcohol-containing drug is capable of binding to FKBP for inhibition of mTOR or calcineurin effector function~~Ligand-Drug Conjugate compound and Ligand-Drug Conjugate composition or Drug-Linker compound of claim 63~~, wherein the Ligand-Drug Conjugate compound and ~~composition and~~ Drug-Linker compound~~,~~ have structures of:



p and



,

respectively, wherein Ab is an antibody and S is a sulfur atom from the antibody; R is hydrogen, ethyl or $–CH_2CH_2N(CH_3)_2$; and subscript p is a number or an integer ranging from 1 to 16 or 1 to 8.

~~66~~56. A method of preparing an Antibody Drug Conjugate compound of claim ~~21~~1, or a composition thereof of claim ~~37~~32, in which Stretcher Unit (Z) comprises a succinimide moiety

or an succinic acid-amide moiety; and wherein the Ligand Unit is an antibody, the method comprising the step of:

contacting a Drug-Linker compound of claim ~~59~~35 in which Stretcher Unit precursor (Z') comprises a maleimide moiety with an antibody having a reactive cysteine thiol functional group obtained from interchain disulfide bond reduction and/or from an engineered cysteine residue,

wherein said contacting converts Z' to Z by formation of a covalent bond between the reactive cysteine sulfur atom of the antibody and the succinimide moiety of Z, optionally followed by spontaneous hydrolysis of the succinimide moiety to an acid amide moiety, whereby the Antibody Drug Conjugate compound or composition thereof is obtained.

~~67~~57. The Ligand-Drug Conjugate compound of claim 1, wherein the Drug Unit is a cytotoxic drug.

~~68~~58. Use of a Ligand-Drug Conjugate compound of claim 1, or a composition thereof of claim ~~36~~31, for preparing a medicament.

~~69~~59. Use of a Ligand-Drug Conjugate compound of claim ~~67~~57, or composition thereof of claim ~~36~~31, in the manufacture of a medicament for treating a cancer.

~~70~~60. The use according to claim ~~69~~59, wherein the cancer is a hematological cancer.

~~71~~61. The use according to claim ~~69~~59, wherein the cancer is in the form of a solid tumor.