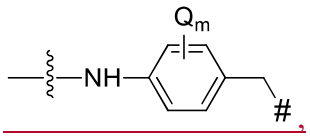
Z' is a stretcher unit precursor to a Stretcher Unit (Z) in a Ligand-Drug Conjugate and comprises a functional group capable of conjugation to a targeting ligand;

A is an optional Connector Unit;

X is an activeatable self-immolative moiety comprising an Activation Unit (W) and a self-immolative Spacer Unit (Y), ~~wherein X is activateable by a protease or glycosidase~~;

W comprises one amino acid or one or more contiguous or non-contiguous sequences of amino acids, or W comprises a sugar moiety linked via an oxygen bond to the self-immolative Spacer Unit;

Y is:



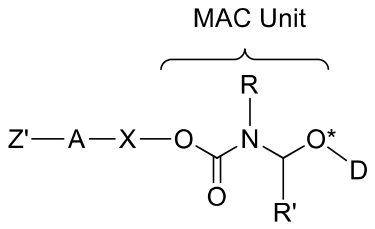
wherein the wavy line indicates covalent attachment to the Activation Unit and the hashtag (#) indicates covalent attachment of the benzylic carbon to the methylene carbamate unit, Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano; and m is an integer ranging from 0-4;

X' is a self-immolative moiety precursor to X, wherein X' has a hydroxyl functional group that participates in the Curtius rearrangement~~, and X' is otherwise inert to the Curtius rearrangement reaction conditions~~;

R is hydrogen; and

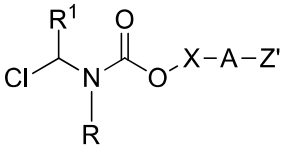
R^1 is hydrogen, or C_1-C_6 alkyl, C_6-C_{14} aryl or C-linked heteroaryl, optionally substituted with suitable protection as required.

[0006b] In another aspect, the present disclosure provides a method of preparing a Drug-Linker compound, wherein the Drug-Linker compound has the structure of:



said method comprising the step of:

contacting a drug having a free hydroxyl functional group with a N-chloromethylamine having the structure of:



under conditions sufficient for substitution of the chlorine atom with the oxygen heteroatom from said free drug functional group,

wherein

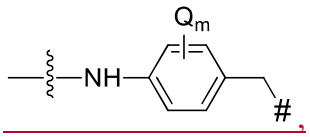
Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) of the Drug-Linker Compound and comprises a functional group for attachment of a targeting ligand;

A is an optional Connector Unit;

X is an activateable self-immolative moiety comprising an Activation Unit (W) and a self-immolative Spacer Unit (Y), ~~wherein X is inert to the chlorine substitution reaction conditions, and X is activateable by a protease or glycosidase~~;

W comprises one amino acid or one or more contiguous or non-contiguous sequences of amino acids, or W comprises a sugar moiety linked via an oxygen bond to the self-immolative Spacer Unit;

Y is:



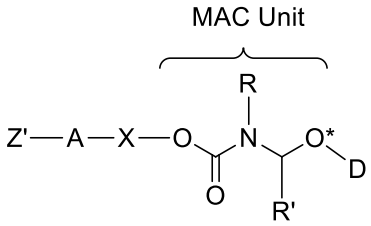
,

wherein the wavy line indicates covalent attachment to the Activation Unit and the hashtag (#) indicates covalent attachment of the benzylic carbon to the methylene carbamate unit, Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano; and m is an integer ranging from 0-4;

R is hydrogen, or C_1-C_6 alkyl, C_6-C_{14} aryl or C-linked heteroaryl, optionally substituted with suitable protection; and

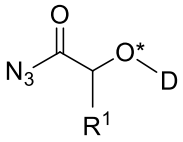
WHAT IS CLAIMED IS:

1. A method of preparing a Drug-Linker Compound, wherein the Drug-Linker compound has the structure of:



said method comprising the step of:

contacting a modified free drug having the structure of:



with an intermediate linker moiety represented by: Z'-A-X'-OH,

under conditions sufficient for providing the indicated MAC unit through Curtius rearrangement,

wherein D is a Drug Unit having a hydroxyl functional group that has been incorporated into the indicated MAC Unit, the oxygen atom from which is designated by O^*;

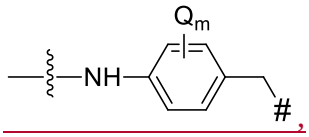
Z' is a stretcher unit precursor to a Stretcher Unit (Z) in a Ligand-Drug Conjugate and comprises a functional group capable of conjugation to a targeting ligand;

A is an optional Connector Unit;

X is an activeatable self-immolative moiety comprising an Activation Unit (W) and a self-immolative Spacer Unit (Y)~~, wherein X is activateable by a protease or glycosidase~~;

W comprises one amino acid or one or more contiguous or non-contiguous sequences of amino acids, or W comprises a sugar moiety linked via an oxygen bond to the self-immolative Spacer Unit;

Y is:



wherein the wavy line indicates covalent attachment to the Activation Unit and the hashtag (#) indicates covalent attachment of the benzylic carbon to the methylene carbamate

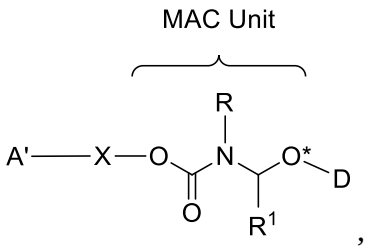
unit, Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano; and m is an integer ranging from 0-4;

X' is a self-immolative moiety precursor to X, wherein X' has a hydroxyl functional group that participates in the Curtius rearrangement~~, and X' is otherwise inert to the Curtius rearrangement reaction conditions~~;

R is hydrogen; and

R^1 is hydrogen, or C_1-C_6 alkyl, C_6-C_{14} aryl or C-linked heteroaryl, optionally substituted with suitable protection as required.

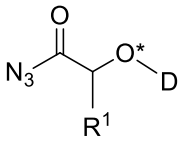
2. A method of preparing an intermediate of a Drug-Linker compound having the structure of claim 1, wherein the intermediate has the structure of:



,

said method comprising the step of:

contacting a modified free drug having the structure of:



with a self-immolative intermediate represented by: A'-X-OH,

under conditions sufficient for providing the indicated MAC Unit through Curtius rearrangement,

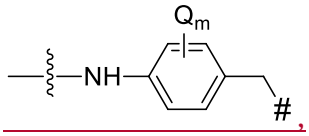
wherein D is a Drug Unit having a hydroxyl functional group that has been incorporated into the indicated MAC Unit, the oxygen atom from which is designated by O^*;

A' is a Connector Unit precursor to a Connector Unit (A) and comprises a functional group for bond formation to the remainder of the Linker Unit of the Drug-Linker compound;

X is an activeatable self-immolative moiety comprising an Activation Unit (W) and a self-immolative Spacer Unit (Y), ~~wherein X is inert to the Curtius rearrangement reaction conditions, and X is activateable by a protease or glycosidase~~;

W comprises one amino acid or one or more contiguous or non-contiguous sequences of amino acids, or W comprises a sugar moiety linked via an oxygen bond to the self-immolative Spacer Unit;

Y is:

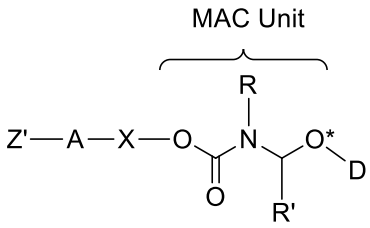


wherein the wavy line indicates covalent attachment to the Activation Unit and the hashtag (#) indicates covalent attachment of the benzylic carbon to the methylene carbamate unit, Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano; and m is an integer ranging from 0-4;

R is hydrogen; and

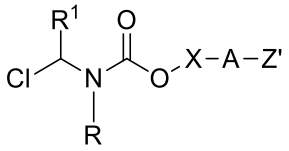
R^1 is hydrogen, or C_1-C_6 alkyl, C_6-C_{14} aryl or C-linked heteroaryl, optionally substituted with suitable protection as required.

3. A method of preparing a Drug-Linker compound, wherein the Drug-Linker compound has the structure of:



said method comprising the step of:

contacting a drug having a free hydroxyl functional group with a N-chloromethylamine having the structure of:



under conditions sufficient for substitution of the chlorine atom with the oxygen heteroatom from said free drug functional group,

wherein

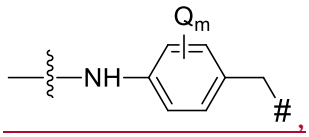
Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) of the Drug-Linker Compound and comprises a functional group for attachment of a targeting ligand;

A is an optional Connector Unit;

X is an activateable self-immolative moiety comprising an Activation Unit (W) and a self-immolative Spacer Unit (Y)~~, wherein X is inert to the chlorine substitution reaction conditions, and X is activateable by a protease or glycosidase~~;

W comprises one amino acid or one or more contiguous or non-contiguous sequences of amino acids, or W comprises a sugar moiety linked via an oxygen bond to the self-immolative Spacer Unit;

Y is:



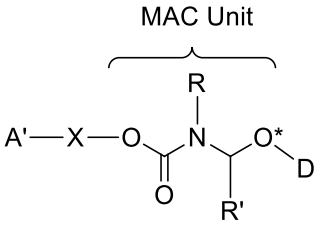
wherein the wavy line indicates covalent attachment to the Activation Unit and the hashtag (#) indicates covalent attachment of the benzylic carbon to the methylene carbamate unit, Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano; and m is an integer ranging from 0-4;

R is hydrogen, or C_1-C_6 alkyl, C_6-C_{14} aryl or C-linked heteroaryl, optionally substituted with suitable protection; and

R^1 is hydrogen, or C_1-C_6 alkyl, C_6-C_{14} aryl or C-linked heteroaryl, optionally substituted with suitable protection as required,

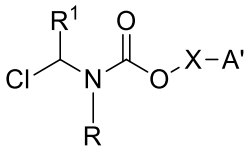
or R and R^1 together with the nitrogen and carbon atoms to which they are attached comprise a pyrrolodinyl or piperidinyl moiety.

4. A method of preparing an intermediate of a Drug-Linker Compound having the structure of claim 1, wherein the intermediate has the structure of:



said method comprising the step of:

contacting a drug having a free hydroxyl functional group with a N-chloromethylamine having the structure of:



under conditions sufficient for substitution of the chlorine atom with the oxygen heteroatom from said free drug functional group,

wherein

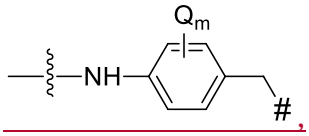
Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) of the Drug-Linker Compound and comprises a functional group for attachment of a targeting ligand;

A’ is a Connector Unit precursor to a Connector Unit (A) and comprises a functional group for bond formation to the remainder of the Linker Unit of the Drug-Linker compound;

X is an activatable self-immolative moiety comprising an Activation Unit (W) and a self-immolative Spacer Unit (Y)~~, wherein X is inert to the chlorine substitution reaction conditions, and X is activateable by a protease or glycosidase~~;

W comprises one amino acid or one or more contiguous or non-contiguous sequences of amino acids, or W comprises a sugar moiety linked via an oxygen bond to the self-immolative Spacer Unit;

Y is:



,

wherein the wavy line indicates covalent attachment to the Activation Unit and the hashtag (#) indicates covalent attachment of the benzylic carbon to the methylene carbamate unit, Q is -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -halogen, -nitro, or -cyano; and m is an integer ranging from 0-4;

R is hydrogen, or C_1-C_6 alkyl, C_6-C_{14} aryl or C-linked heteroaryl, optionally substituted with suitable protection; and

R^1 is hydrogen, or C_1-C_6 alkyl, C_6-C_{14} aryl or C-linked heteroaryl, optionally substituted with suitable protection as required,

or R and R^1 together with the nitrogen and carbon atoms to which they are attached comprise a pyrrolodinyl or piperidinyl moiety.