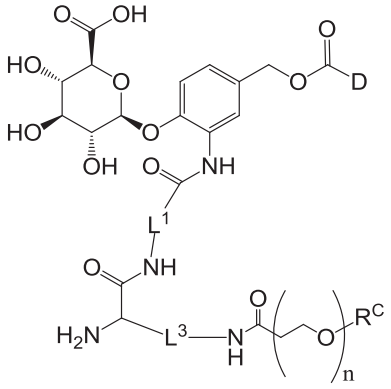
in yield. Therefore, there is a need for improved methods for preparing such Drug Linker compounds with reduced amounts of contaminating impurities, so as to improve purity and yields.

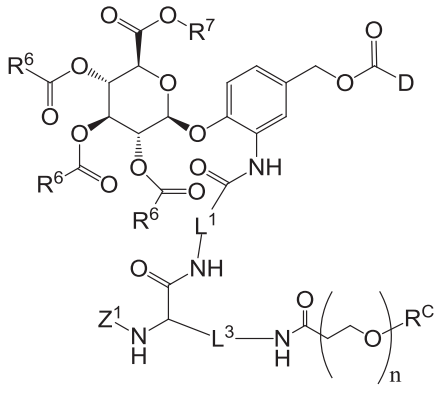
SUMMARY

[0010] The disclosure provides *inter alia,* improved processes in producing PEGylated Drug Linker compounds containing a Glucuronide Unit , as well as the intermediates thereof. Principal embodiments of the disclosure include methods for preparing Drug Linker intermediates of Formula **IE:**



[0011] (**IE**),

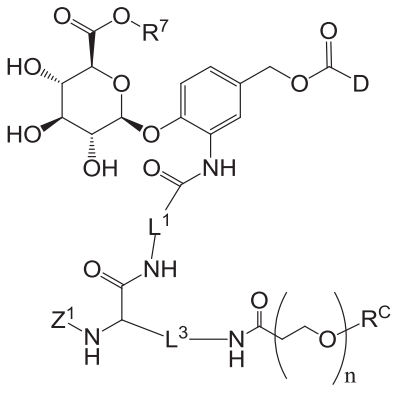
[0012] or a salt thereof, wherein D is an auristatin Drug Unit; each of L^1 and L^2 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo; R^7 is optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so–OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group; R^C is hydrogen or a PEG Capping Unit; and subscript n ranges from 2 to 24, the method comprising step (c) contacting a Drug Linker intermediate compound of Formula **IC** with either a Grignard reagent or an alkoxy magnesium halide in a suitable alcohol-containing solvent, wherein the Formula **IC** Drug Linker intermediate compound has the structure of:



(**IC**)

[0013] (d) contacting the product of step (c) with a first deprotecting agent, wherein said first deprotecting agent contacting removes the Z^1 amino and carboxylic acid protecting groups to provide the Formula **IE** Drug Linker intermediate compound.

[0013a] In one aspect, there is provided a method for preparing a Drug Linker intermediate compound of Formula **ID**:



(**ID**),

or a salt thereof,

wherein D is an auristatin Drug Unit,

each of L^1 and L_3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^7 is optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so–OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group;

Z^1 is a first suitable amino protecting group;

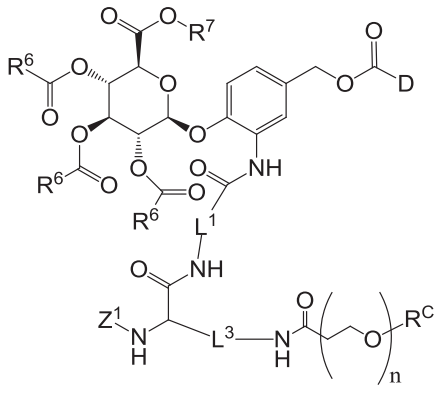
R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

the method comprising the step of:

(c) contacting a Drug Linker intermediate compound of Formula **IC** with either a Grignard reagent or an alkoxy magnesium halide in a suitable alcohol-containing solvent,

wherein the Formula **IC** Drug Linker intermediate compound has the structure of:

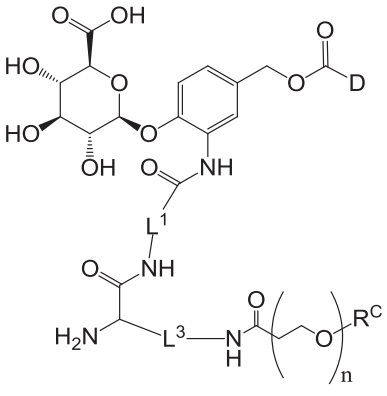


(**IC**)

wherein each of R^6 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group; and the the remaining variable groups are as previously described; and

wherein said Grignard reagent or an alkoxy magnesium halide contacting selectively removes the hydroxyl protecting groups to provide the Formula **ID** compound.

[0013b] In another aspect, there is provided a method for preparing a Drug Linker intermediate of Formula **IE:**



(**IE**),

or a salt thereof,

wherein D is an auristatin Drug Unit,

each of L^1 and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally

substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^7 is optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so–OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group;

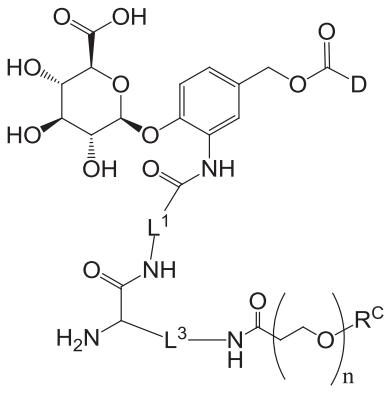
R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

the method comprising step (c) disclosed herein, further comprising the subsequent step of:

(d) contacting the product of step (c) with a first deprotecting agent, wherein said first deprotecting agent contacting removes the Z^1 amino and carboxylic acid protecting groups to provide the Formula **IE** Drug Linker intermediate compound.

[0013c] In another aspect, there is provided a method for preparing a Drug Linker intermediate compound of Formula **IE**:



(**IE**)

or a salt thereof,

wherein D is an auristatin Drug Unit,

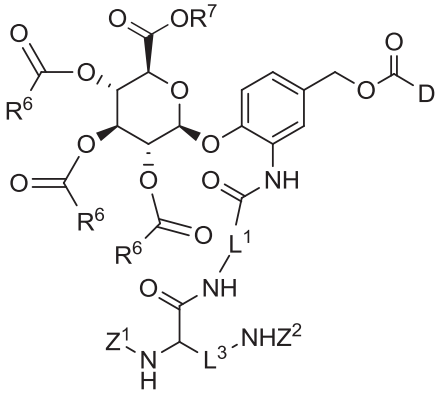
each of L^1 and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

the method comprising the steps disclosed herein, further comprising prior to steps (c) and (d) the steps of:

(a) contacting a Drug Linker intermediate of Formula **IA** with a second deprotecting agent, wherein the Formula **IA** Drug Linker intermediate compound has the structure of :



(**IA**),

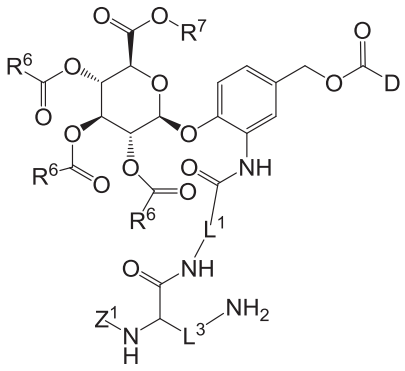
or a salt thereof, wherein

each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group;

each of Z^1 and Z^2 is independently a first and second suitable amino protecting group, respectively; and

the remaining variable groups as previously defined,

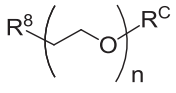
wherein said second deprotecting agent contacting selectively removes the Z^2 amino protecting group to provide a Drug Linker intermediate compound of Formula **IB**:



(**IB**)

or a salt thereof, wherein the variable groups are as previously defined;

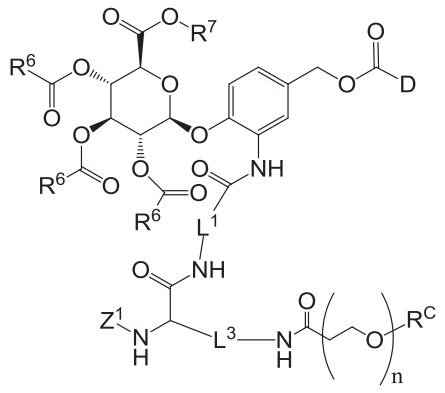
(b) contacting the Formula **IB** compound in a suitable solvent with a compound of Formula **iv**:



(**iv**),

wherein R^8 is an activated ester group; and the remaining variable groups are as previously defined, or

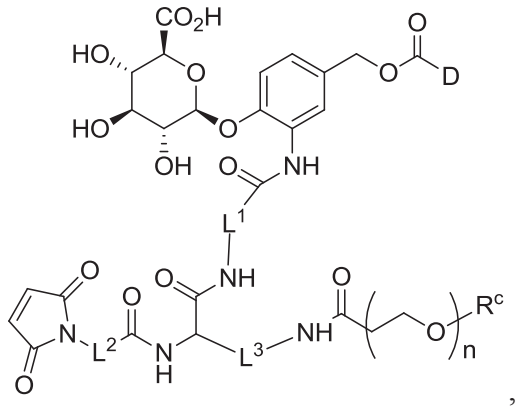
(b') contacting the Formula **IB** Drug Linker intermediate compound in a suitable solvent with a Formula **iv** compound in which R^8 is –COOH and the remaining variable groups are as previously defined in the presence of a first activating agent, wherein said contacting step (b) or (b') provides the Formula **IC** Drug Linker intermediate compound of:



(**IC**),

or a salt thereof, wherein the variable groups are as previously defined.

[0013d] In another aspect, there is provided a method for preparing a Drug Linker compound or intermediate thereof of Formula **I**:



,

or a salt thereof,

wherein D is an auristatin Drug Unit,

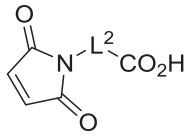
each of L^1, L^2, and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

the method comprising steps (a)-(d) disclosed herein, followed by the step of:

(e) contacting the Formula **IE** Drug Linker intermediate compound in a suitable solvent with a compound of Formula **v**:

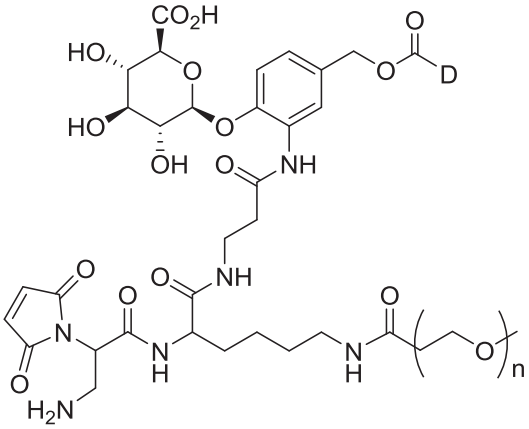


(**v**),

or a salt thereof, wherein L^2 is as previously defined, in the presence of a second activating agent; and

wherein said Formula **v** contacting provides the Formula **I** Drug Linker or Drug Linker intermediate compound or salt thereof.

[0013e] In another aspect, there is provided a method for preparing a Drug Linker compound of Formula **II**:



(**II**)

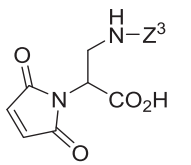
or a salt thereof,

wherein D is an auristatin Drug Unit; and

subscript n ranges from 2 to 24,

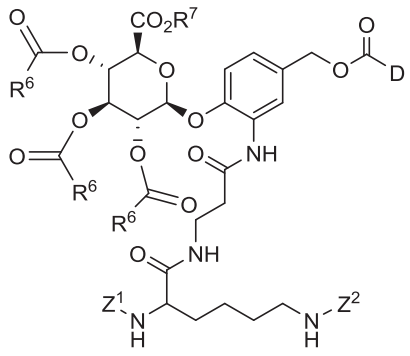
the method comprising steps (a)-(e) disclosed herein,

wherein the Formula **v** compound has the structure of:

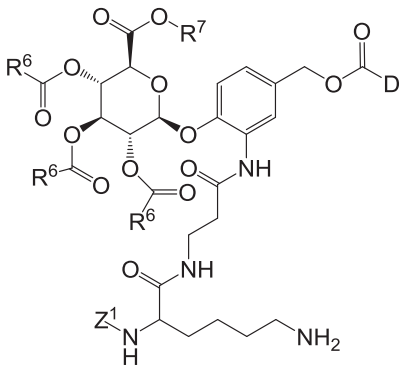


(**v**),

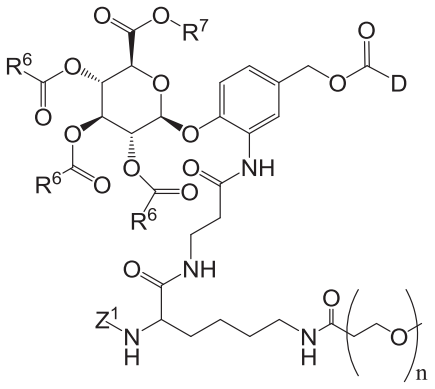
and wherein the Formula **IA**, Formula **IB**, Formula **IC**, Formula **ID** and Formula **IE** Drug Linker intermediate compounds, optionally in salt form, have the structures of Formula **IIA**, Formula **IIB**, Formula **IIC**, Formula **IID**, Formula **IIE**, Formula **IIF**:



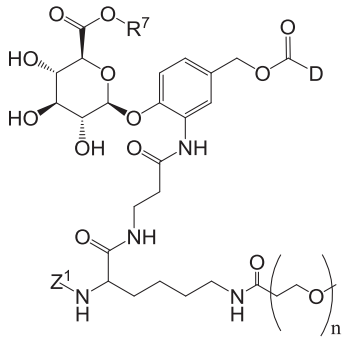
(**IIA**),



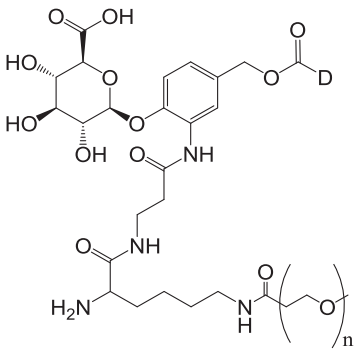
(**IIB**)



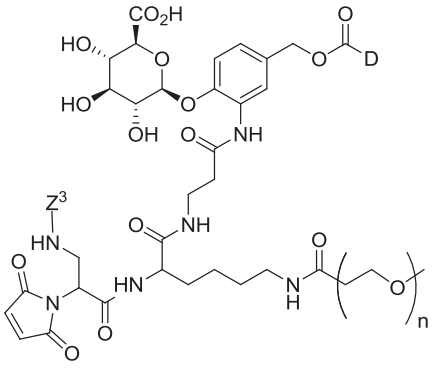
(**IIC**)



(**IID**)



(**IIE**)



(**IIF**),

wherein

each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group;

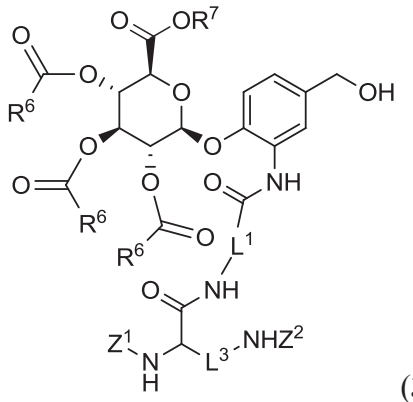
Z^1, Z^2 and Z^3 are independently a first, second and third suitable amino protecting group, respectively, or

Z_1 and Z_2 are independently a first and second suitable amino protecting group, respectively and Z^3 is an acid-labile amino protecting group, or Z_1 and Z_2 are independently a first and second suitable amino protecting group, respectively, and Z_3 is –C(=O)O-t-Bu,

the method further comprising the step of:

(f) contacting the Formula **IF** Drug Linker intermediate compound of with a third deprotecting agent, wherein said third deprotecting reagent contacting removes the Z^3 amino protecting group whereby the Formula **II** Drug Linker compound or salt thereof is provided.

[0013f] In another aspect, there is provided a compound of Formula **3** having the structure of:



(**3**)

or a salt thereof, wherein

L^1 and L^3 are independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo, or L^1 and L^3 independently are C_1-C_4 alkylene;

each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group,

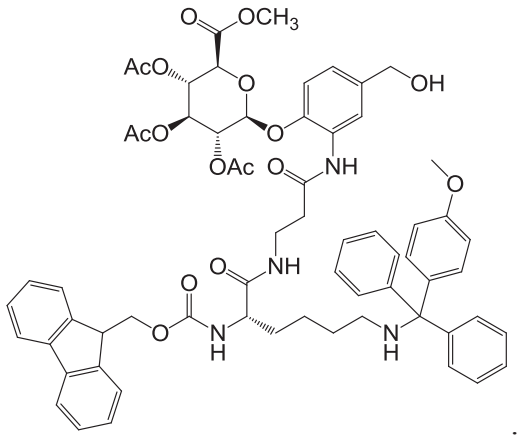
or each R^6 is C_1-C_4 alkyl or optionally substituted phenyl and/or R^7 is methyl or ethyl or R^6 and R^7 are each methyl and the remaining variable

groups are as defined in the claim, or

Formula **3** has the structure of:

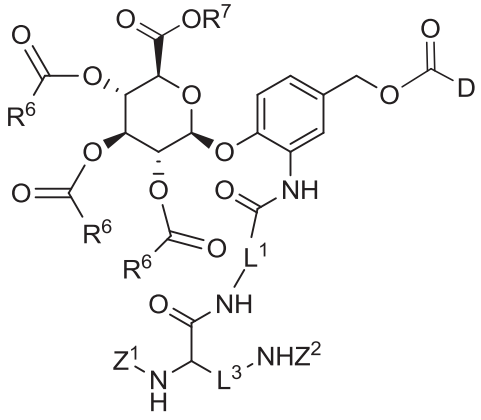
wherein Z^1 and Z^2 independently are a first and second suitable amino protecting group,

Z^1 fluorenylmethyloxy carbonyl (FMOC) and Z^2 is 4-methoxy trityl (MMTr), or the Formula **3** compound has the structure of:



.

[0013g] In another aspect, there is provided a Drug Linker intermediate compound having the structure of Formula **4** of:



(**4**),

or a salt thereof, wherein

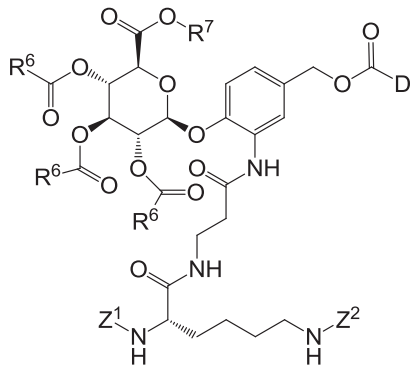
D is an auristatin Drug Unit;

L^1 and L^3 are independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group; and

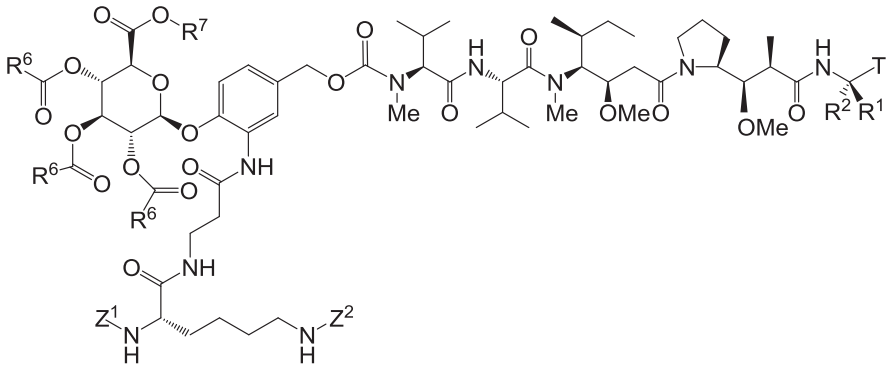
Z^1 and Z^2 independently are a first and second suitable amino protecting group, or

the Formula **4** compound, or salt thereof, has the structure of:



,

wherein Z_2 is MMTr, or the Formula **4** Drug Linker intermediate compound, optionally in salt form, has the structure of:



,

wherein

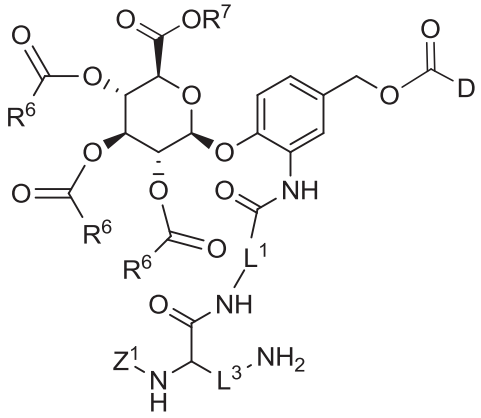
R^1 is H or C_1-C_4 alkyl;

R^2 is H, C_1-C_4 alkyl, or $–CH_2$-R^3;

R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl; and

T is selected from the group consisting of $–CH(OR^4)$-R^5 and -C(=O)-OR^4, wherein R^4 is H, C_1-C_4 alkyl and R^5 is C_6-C_{10} aryl or C_3-C_6 heteroaryl.

[0013h] In another aspect, there is provided a Drug Linker intermediate compound, wherein the Drug Linker intermediate compound has the structure of Formula **5** of:



(**5**),

or a salt thereof, wherein

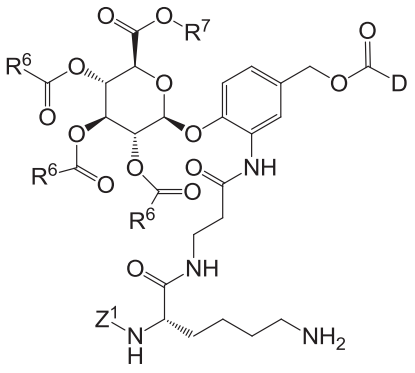
D is an auristatin Drug Unit;

L^1 and L^3 are independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group; and

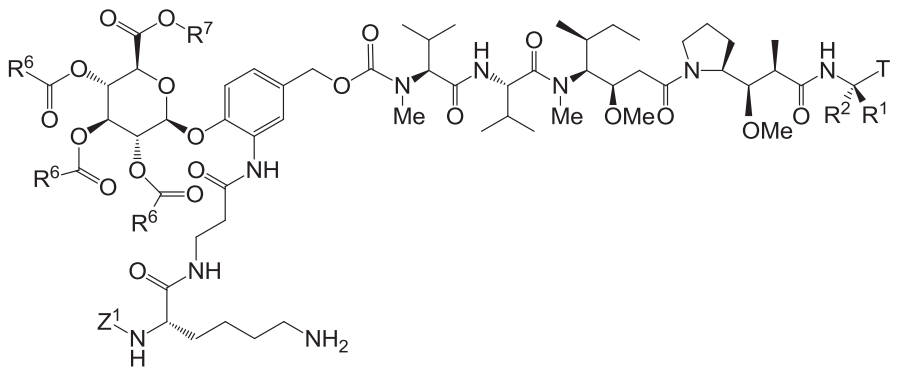
Z^1 is a first suitable amino protecting group,

or the Formula **5** Drug Linker intermediate compound, optionally in salt form, has the structure of:



, or

the Formula **5** Drug Linker intermediate compound, optionally in salt form, has the structure of:



,

wherein

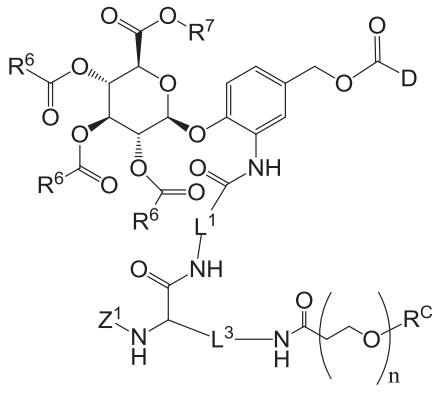
R^1 is H or C_1-C_4 alkyl;

R^2 is H, C_1-C_4 alkyl, or $–CH_2$-R^3;

R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl; and

T is selected from the group consisting of $–CH(OR^4)$-R^5 and -C(=O)-OR^4, wherein R^4 is H, C_1-C_4 alkyl and R^5 is C_6-C_{10} aryl or C_3-C_6 heteroaryl.

[0013i] In another aspect, there is provided a Drug Linker intermediate compound, wherein the Drug Linker intermediate compound has the structure of Formula **6** of:



(**6**),

or a salt thereof, wherein

D is an auristatin Drug Unit;

L^1 and L^3 are independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

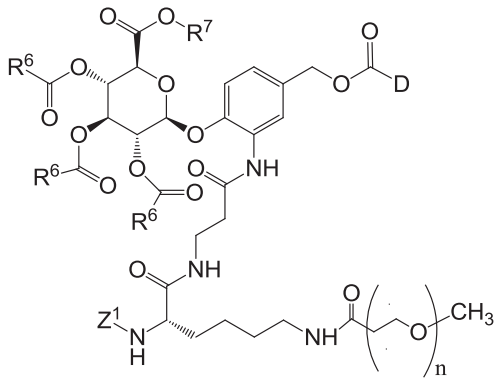
each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group;

Z^1 is a first suitable amino protecting group;

R^C is a PEG Capping Unit; and

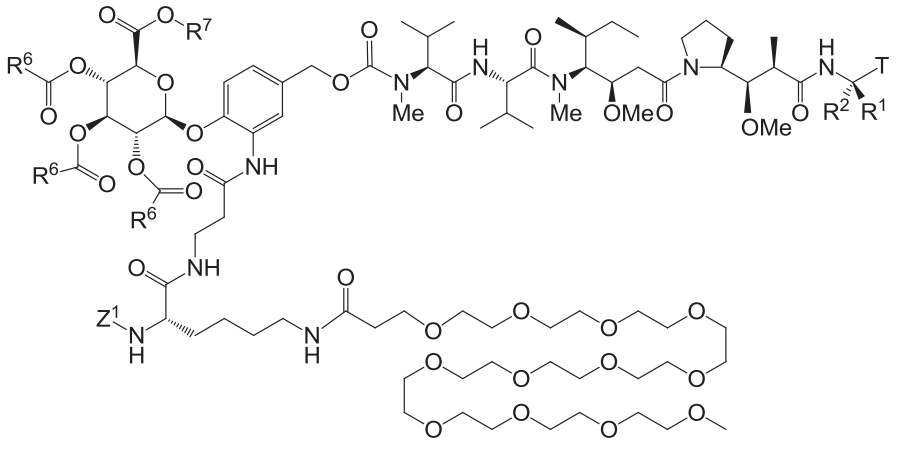
subscript n ranges from 1 to 24**, or**

subscript n is 8 or 12, or the Formula **6** Drug Linker intermediate compound, optionally in salt form, has the structure of:



,

or the Formula **6** Drug Linker intermediate compound, optionally in salt form, has the structure of:



,

wherein

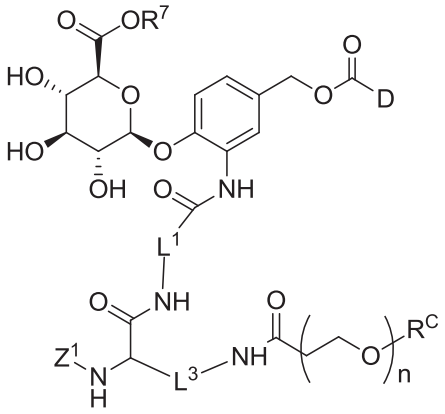
R^1 is H or C_1-C_4 alkyl;

R^2 is H, C_1-C_4 alkyl, or $–CH_2$-R^3;

R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl; and

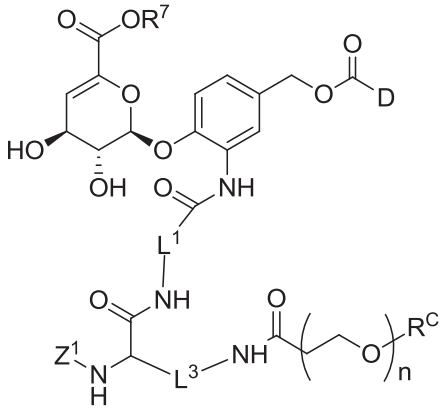
T is selected from the group consisting of –CH(OR^4)-R^5 and -C(=O)-OR^4, wherein R^4 is H, C_1-C_4 alkyl and R^5 is C_6-C_{10} aryl or C_3-C_6 heteroaryl.

[0013j] In another aspect, there is provided a composition comprised of a Drug Linker intermediate compound of Formula **7** having the structure of:



(**7**)

or a salt thereof, and a compound of Formula **7A** having the structure of:



(**7A**)

or a salt thereof,

wherein in Formula **7** and Formula **7A**:

D is an auristatin Drug Unit,

each of L^1 and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^7 is optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so–OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group, or R^7 is methyl;

Z^1 is a first suitable amino protecting group;

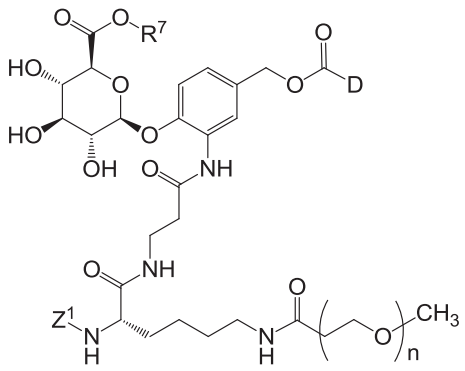
R^C is a PEG Capping Unit; and

subscript n is from 2 to 24,

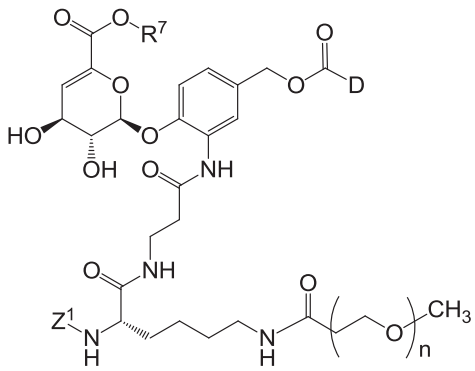
wherein the composition is comprised of no more than 5 wt.%, of the Formula **7A** compound:

or the composition is comprised of:

a Drug Linker intermediate compound of the Formula **7** and a compound of Formula **7A** optionally in salt forms, having the structures of:



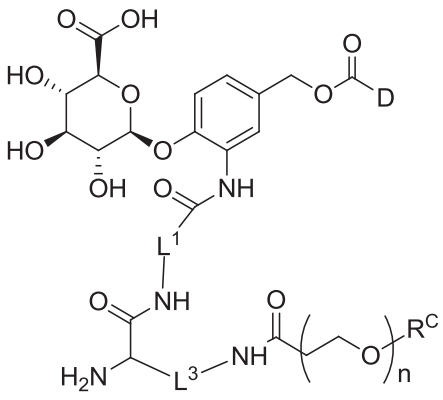
(**7**) and



(7**A**)

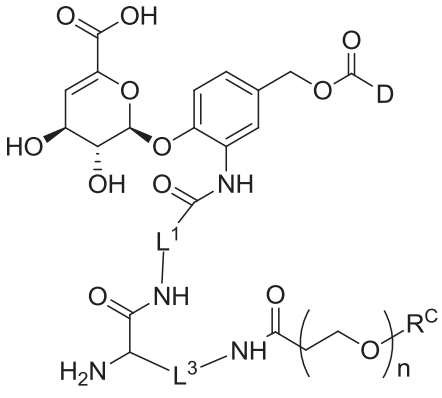
respectively, wherein Z_1 is FMOC and subscript n is from 2 to 24, and wherein the composition is comprised of no more than 5 wt.%, of the Formula **7A** compound.

[0013k] In another aspect, there is provided a composition comprised of a Drug Linker intermediate compound of Formula **8** having the structure of:



(**8**)

or a salt thereof, and a compound of Formula **8A** having the structure of:



(**8A**)

or a salt thereof,

wherein in Formula **8** and Formula **8A**:

D is an auristatin Drug Unit,

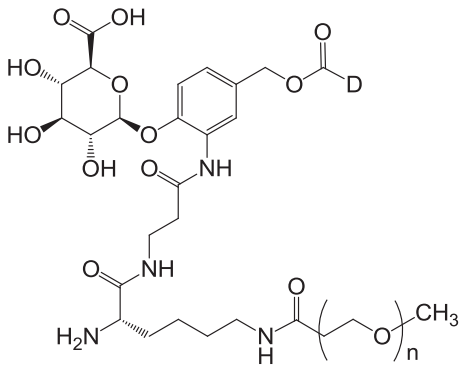
each of L^1 and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^C is a PEG Capping Unit; and

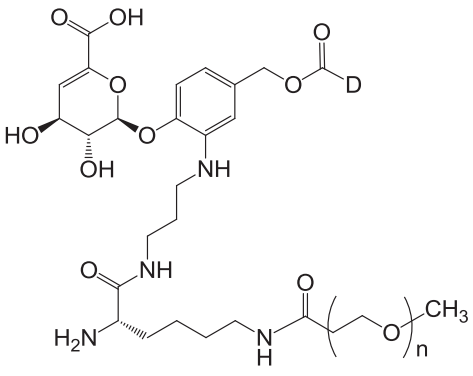
subscript n is from 2 to 24, and

wherein the composition is comprised of no more than about 5 wt.%, or no more than between 3 wt.% and 4 wt.%, of the Formula **8A** compound

or a composition comprised of a Drug Linker intermediate compound of Formula **8** and a compound Formula **8A** optionally in salt forms, having the structures of:



(**8**) and



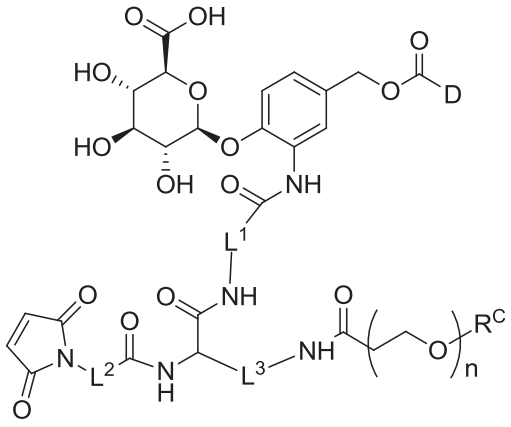
(8**A**)

respectively, wherein

subscript n is from 2 to 24; and

wherein the composition is comprised of no more than 5 wt.%, or no more than between 3 wt.% and 4 wt.%, of the Formula **8A** compound.

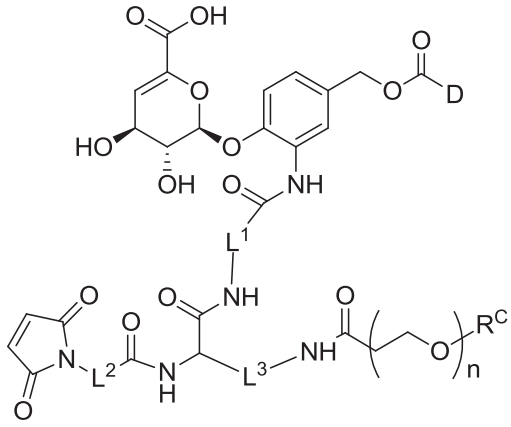
[0013l] In another aspect, there is provided a composition comprised of a compound of Formula **9** having the structure of:



(**9**)

or a salt thereof, and

a compound of Formula **9A** having the structure of:



(**9A**)

or a salt thereof,

wherein in Formula **9** and Formula **9A**:

D is an auristatin Drug Unit,

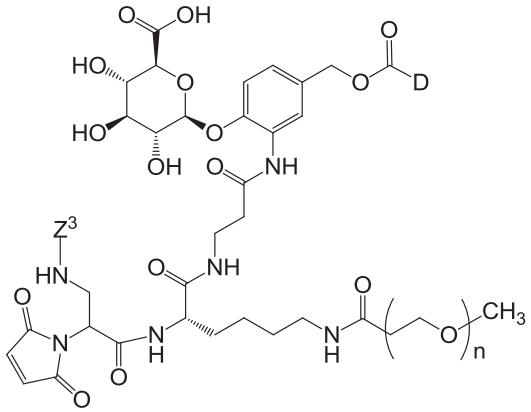
each of L^1, L^2 and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^C is a PEG Capping Unit; and

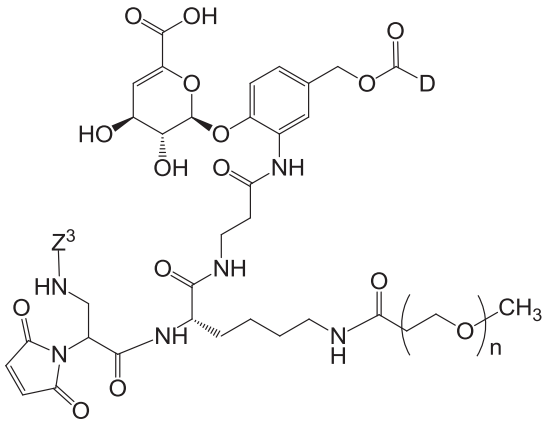
subscript n is from 2 to 24,

wherein the composition is comprised of no more than 5 wt.% of the Formula **9A** compound

or the composition is comprised of compound of the Formula **9** and a compound of Formula **9A** optionally in salt forms, having the structures of:



(**9**) and



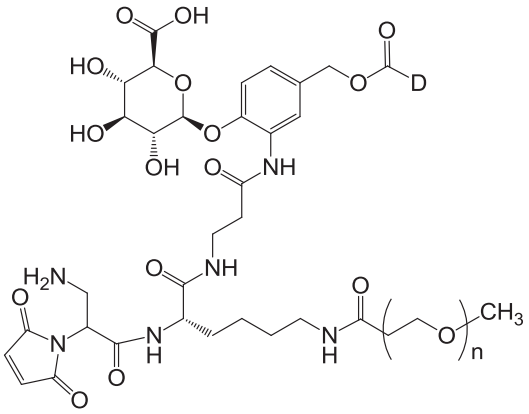
(**9A**),

respectively, wherein

subscript n is from 2 to 24; and

Z^3 is a third amino protecting group that is acid-labile, or is of formula –C(=O)O-R^8, wherein R^8 is C_1-C_4 alkyl or optionally substituted phenyl, and wherein the composition is comprised of no more than 5 wt.% of the Formula **9A**
compound.

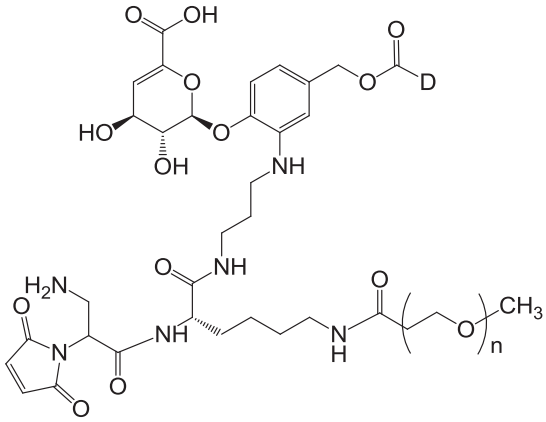
[0013m] In another aspect, there is provided a composition comprised of Drug Linker compound of Formula **10** having the structure of:



(**10**)

or a salt thereof,

and a compound of Formula **10A** having the structure of:



(**10A**),

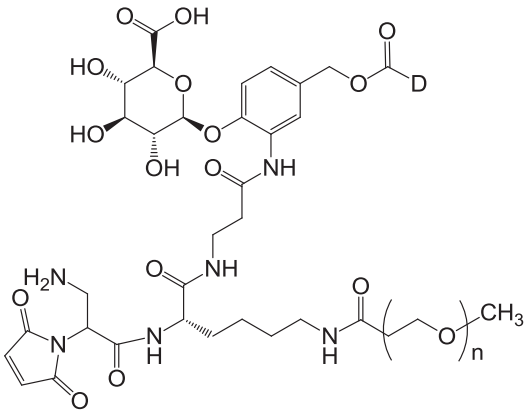
or a salt thereof, wherein in Formula **10** and Formula **10A**:

D is an auristatin Drug Unit; and

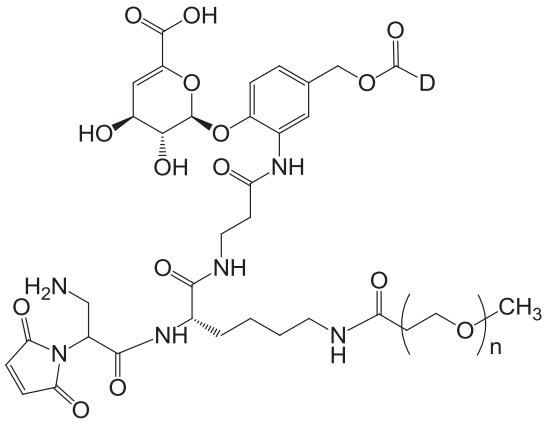
subscript n is from 2 to 24, and

wherein the composition is comprised of no more than 5 wt.%, of the Formula **10A** compound

or a composition comprised of a Drug Linker compound of Formula **10** and a compound of Formula **10A**, optionally in salt forms, having the structures of:



(**10**) and

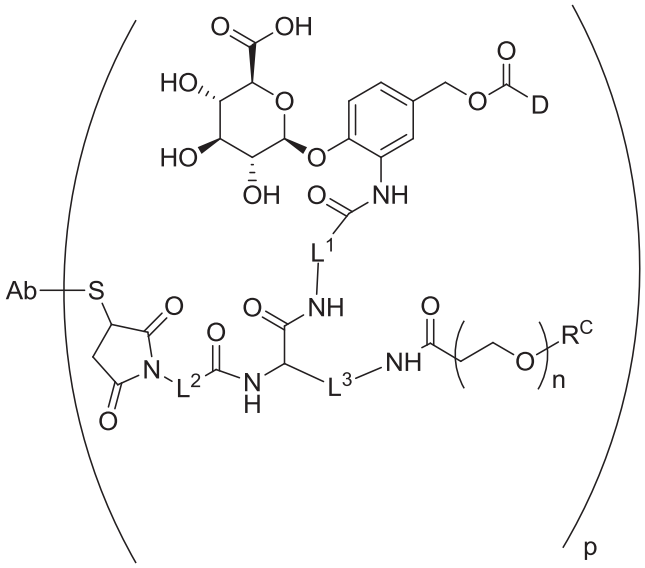


(**10A**)

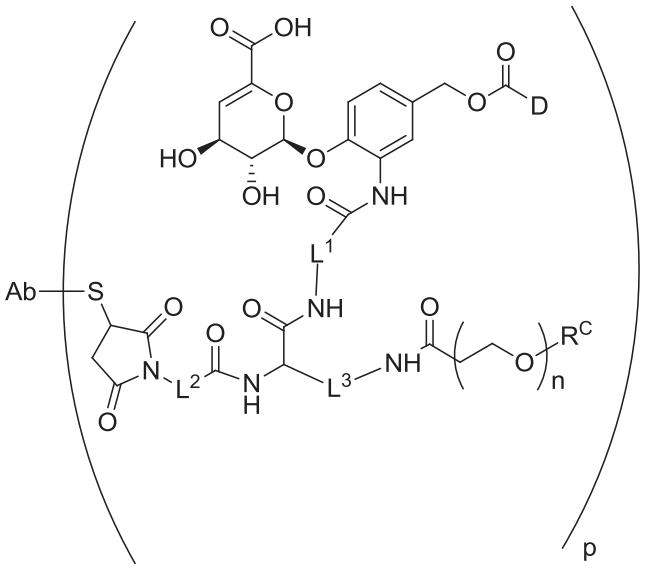
respectively, wherein subscript n is from 2 to 24; and

wherein the composition is comprised of no more than 5 wt.%, of the Formula **10A** compound.

[**0013n**] In another aspect, there is provided a composition comprising Antibody Drug Conjugates represented by Formula **11** and Formula **11A** having the structures of:



(**11**) and



(**11A**)

or pharmaceutically acceptable salts thereof, wherein in Formula 11 and Formula 11A:

Ab is an antibody;

S is a sulfur atom from the antibody;

D is an auristatin Drug Unit;

L^1, L^2 and L^3, independently are selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

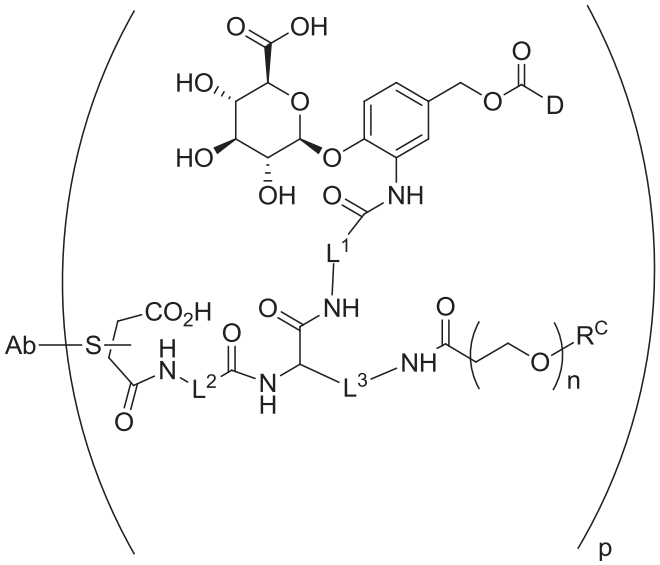
R^C is a PEG Capping Unit;

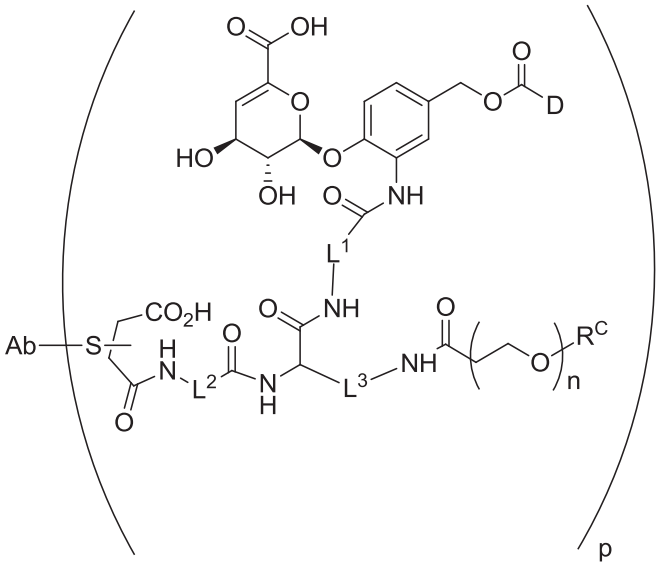
subscript n is from 2 to 24; and

subscript p is from 1 to 16,

wherein the composition contains no more than 5 wt.%, of Formula **11A** Antibody Drug Conjugate.

[0014] Other principle examples include Antibody Drug Conjugates compositions comprised of Antibody Drug Conjugatew of Formula **12** and Formula **12A**, optionally in pharmaceutically acceptable salt form, having the structures of:

[0015]  (**12**) and

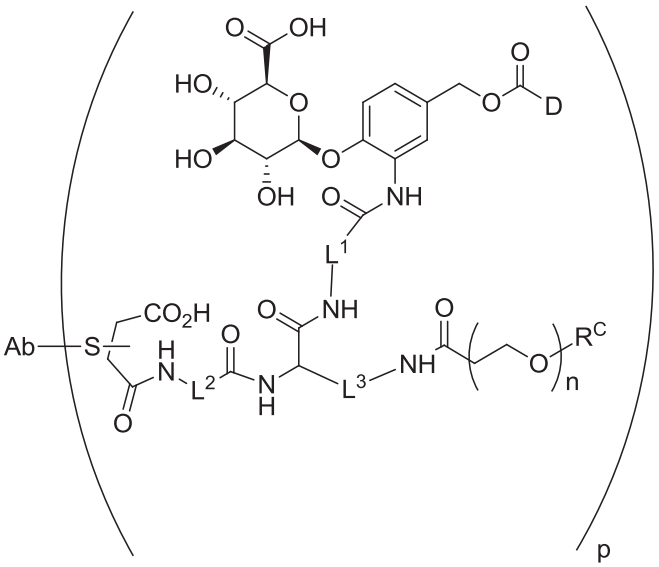
[0016] 

(**12A**)

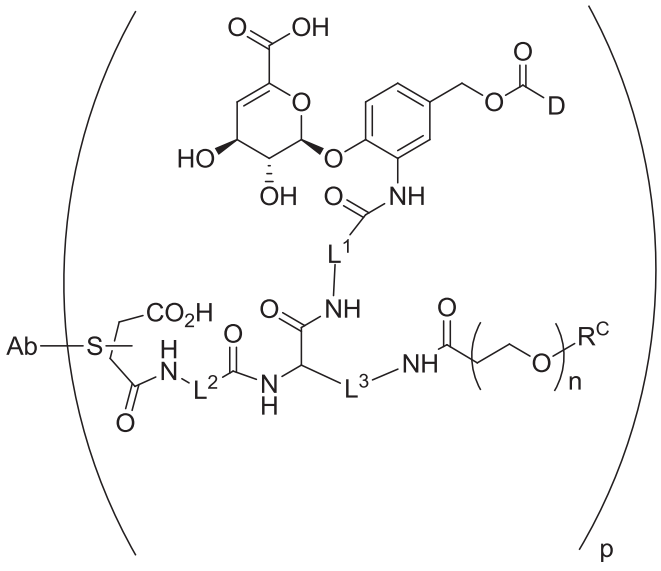
[0017] wherein Ab is an antibody; S is a sulfur atom from the antibody; the Ab-S-moeity is attached to the carbon atom α or β to the carboxylic acid functional group; D is an auristatin Drug Unit; L^1, L^2 and L^3, independently are selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;R^C is a hydrogen or a PEG Capping Unit; subscript n ranges from 2 to 24; and subscript p ranges from about 1 to about 16; and

[0018] wherein the composition contains no more than 10 wt.% or no more than 5 wt.% Formula **12A** Antibody Drug Conjugate.

[0018a] In another aspect, there is provided a composition comprising Antibody Drug Conjugates represented by Formula **12** and Formula **12A**, optionally in pharmaceutically acceptable salt form, having the structures of:



(**12**) and



(**12A**)

wherein in Formula 12 and Formula 12A:

Ab is an antibody;

S is a sulfur atom from the antibody;

the Ab-S- moeity is attached to the carbon atom α or β to the carboxylic acid functional group

D is an auristatin Drug Unit;

L^1, L^2 and L^3, independently are selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally

substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

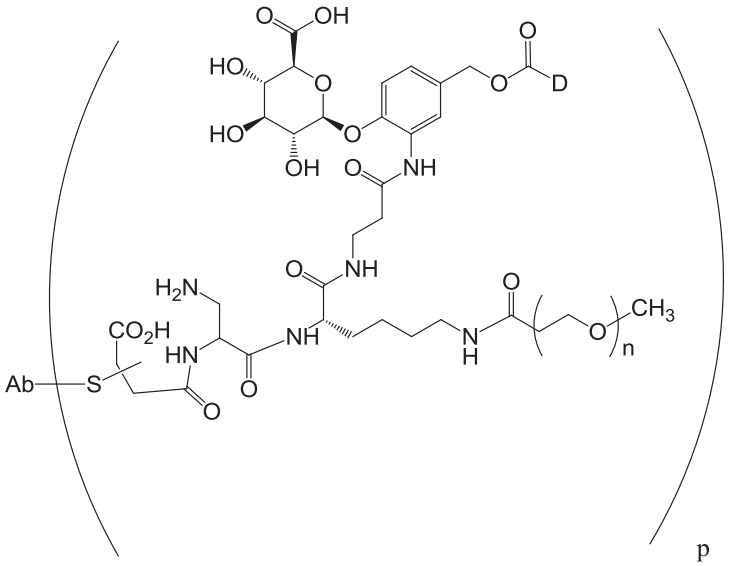
R^C is a PEG Capping Unit;

subscript n is from 2 to 24; and

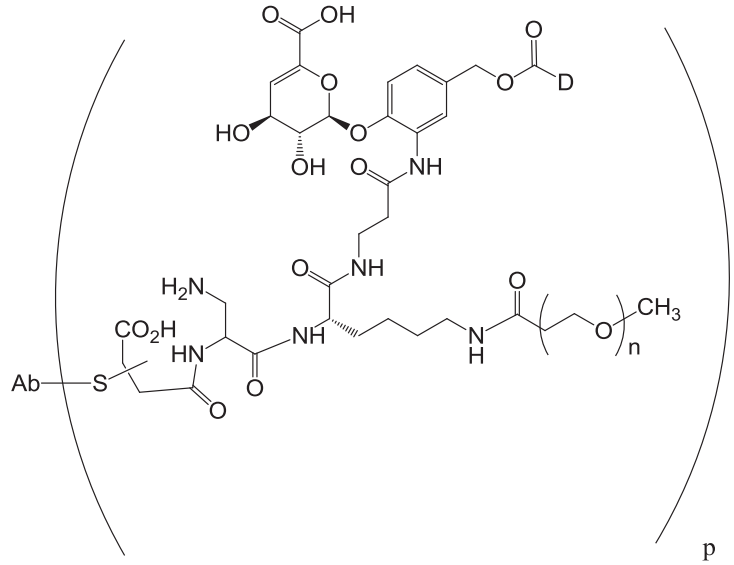
subscript p is from about 1 to about 16,

wherein the composition contains no more than 5 wt.% Formula **12A** Antibody Drug Conjugate, or

the Formula **12** and Formula **12A** Antibody Drug Conjugates, optionally in pharmaceutically acceptable salt forms, have the structures of:



p and



p

respectively, wherein Ab is an antibody;

S is a sulfur atom from the antibody;

the Ab-S- moeity is attached to the carbon atom α or β to the carboxylic acid functional group; and

the remaining variable groups are as previously defined by the claim,

wherein the composition contains no more than 5 wt.% Formula **12A** Antibody Drug Conjugate.

[0018b] In another aspect, there is provided use of a composition disclosed herein, in the manufacture of a medicament for the treatment of a haematological malignancy in a subject, or for treatment of a leukemia or for treatment of lymphoma, more particularly a B-cell malignancy.

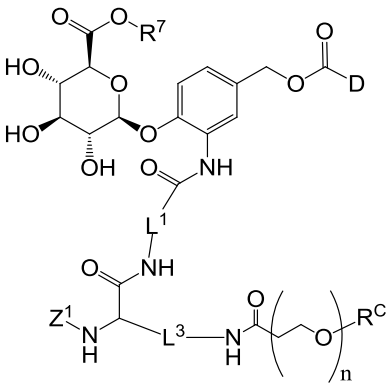
DESCRIPTION OF THE INVENTION

[0019] General

[0020] The present invention is based, in part, on the surprising discovery that the method of deprotection of a Glucuronide Unit in the synthesis of certain PEGylated Auristatin Drug Linker compounds can have a profound effect on the purity and yield of the desired product. Specifically, the present inventors have discovered that using an alkoxymagnesium halide in a solvent comprising an alcohol for removal of acyl protecting groups in the carbohydrate moeity of the Glucuronide Unit, instead of conventionally used reagents such as LiOH, leads to significant reduction of in an undesirable β-eliminated impurity (to below about 5% from about 20%). In some aspects, the alkoxymagnesium halide reagent is prepared *in situ* by contacting a Gringard reagent with the alcohol-

WHAT IS CLAIMED IS:

1. A method for preparing a Drug Linker intermediate compound of Formula **ID**:



(**ID**),

or a salt thereof,

wherein D is an auristatin Drug Unit,

each of L^1 and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^7 is optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so–OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group;

Z^1 is a first suitable amino protecting group;

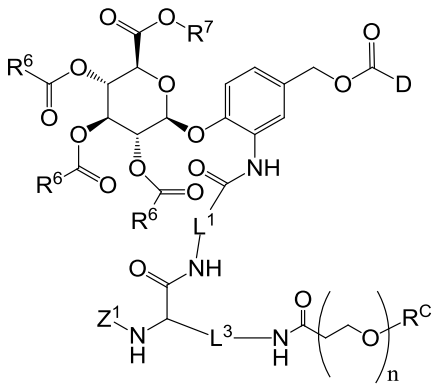
R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

the method comprising the step of:

(c) contacting a Drug Linker intermediate compound of Formula **IC** with either a Grignard reagent or an alkoxy magnesium halide in a suitable alcohol-containing solvent,

wherein the Formula **IC** Drug Linker intermediate compound has the structure of:

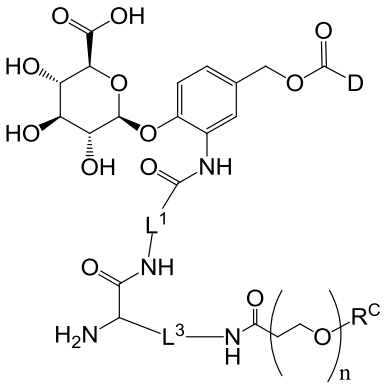


(**IC**)

wherein each of R^6 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group; and the the remaining variable groups are as previously described; and

wherein said Grignard reagent or an alkoxy magnesium halide contacting selectively removes the hydroxyl protecting groups to provide the Formula **ID** compound.

2. A method for preparing a Drug Linker intermediate of Formula **IE:**



(**IE**),

or a salt thereof,

wherein D is an auristatin Drug Unit,

each of L^1 and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^7 is optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so–OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group;

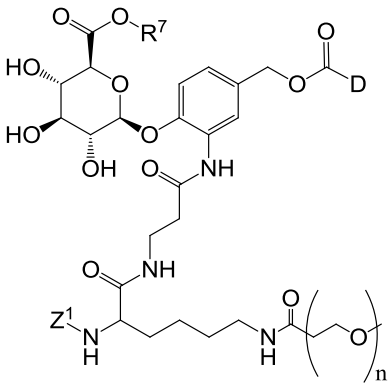
R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

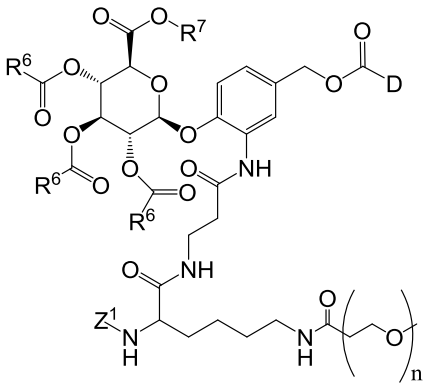
the method comprising step (c) of claim **1**, further comprising the subsequent step of:

(d) contacting the product of step (c) with a first deprotecting agent, wherein said first deprotecting agent contacting removes the Z^1 amino and carboxylic acid protecting groups to provide the Formula **IE** Drug Linker intermediate compound.

3. The method of claim **1**, wherein the Formula **IC** and Formula **ID** Drug Linker intermediate compounds have the structures of Formula **IIC** and Formula **IID**:

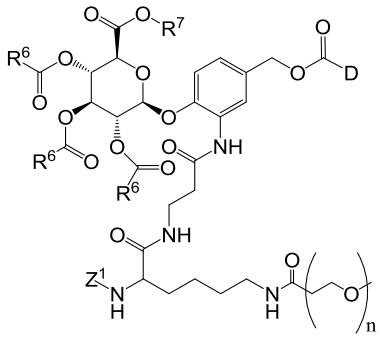


(**IIC**)

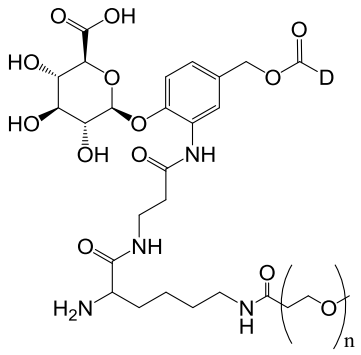


(**IID**).

4. The method of claim **2**, wherein the Formula **IC** and Formula **IE** Drug Linker intermediate compounds, or salts thereof, have the structures of Formula **IIC** and Formula **IIE**:

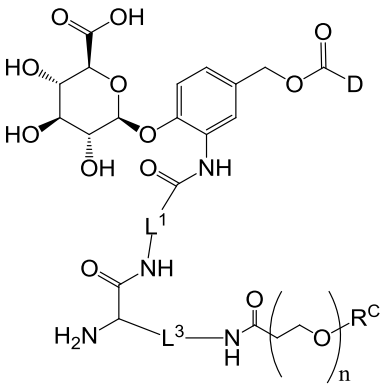


(**IIC**)



(**IIE**).

5. A method for preparing a Drug Linker intermediate compound of Formula **IE**:



(**IE**)

or a salt thereof,

wherein D is an auristatin Drug Unit,

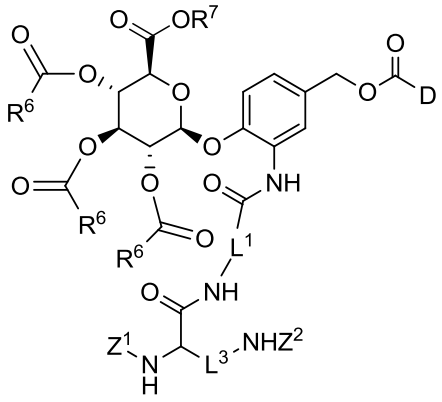
each of L^1 and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

the method comprising the steps of claim **2**, further comprising prior to steps (c) and (d) the steps of:

(a) contacting a Drug Linker intermediate of Formula **IA** with a second deprotecting agent, wherein the Formula **IA** Drug Linker intermediate compound has the structure of :



(**IA**),

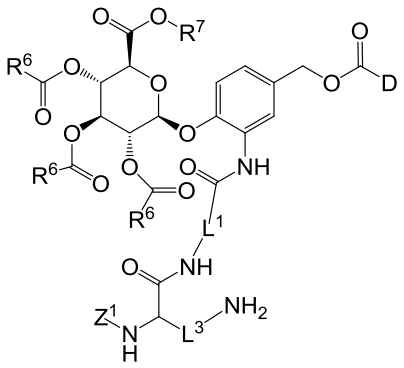
or a salt thereof, wherein

each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group;

each of Z^1 and Z^2 is independently a first and second suitable amino protecting group, respectively; and

the remaining variable groups as previously defined,

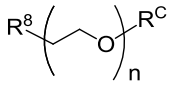
wherein said second deprotecting agent contacting selectively removes the Z^2 amino protecting group to provide a Drug Linker intermediate compound of Formula **IB**:



(**IB**)

or a salt thereof, wherein the variable groups are as previously defined;

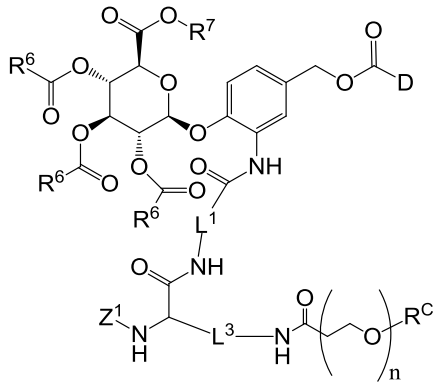
(b) contacting the Formula **IB** compound in a suitable solvent with a compound of Formula **iv**:



(**iv**),

wherein R^8 is an activated ester group; and the remaining variable groups are as previously defined, or

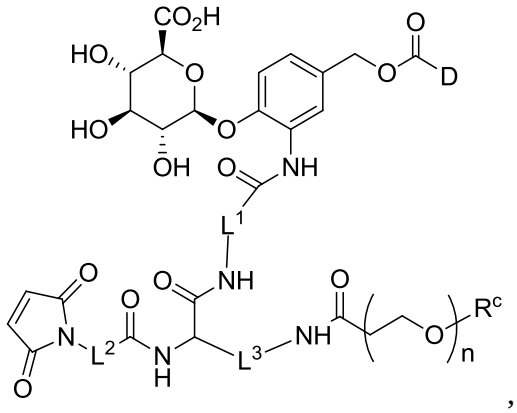
(b') contacting the Formula **IB** Drug Linker intermediate compound in a suitable solvent with a Formula **iv** compound in which R^8 is –COOH and the remaining variable groups are as previously defined in the presence of a first activating agent, wherein said contacting step (b) or (b') provides the Formula **IC** Drug Linker intermediate compound of:



(**IC**),

or a salt thereof, wherein the variable groups are as previously defined.

6. A method for preparing a Drug Linker compound or intermediate thereof of Formula **I**:



,

or a salt thereof,

wherein D is an auristatin Drug Unit,

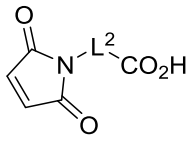
each of L^1, L^2, and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

the method comprising steps (a)-(d) of claim **5**, followed by the step of:

(e) contacting the Formula **IE** Drug Linker intermediate compound in a suitable solvent with a compound of Formula **v**:



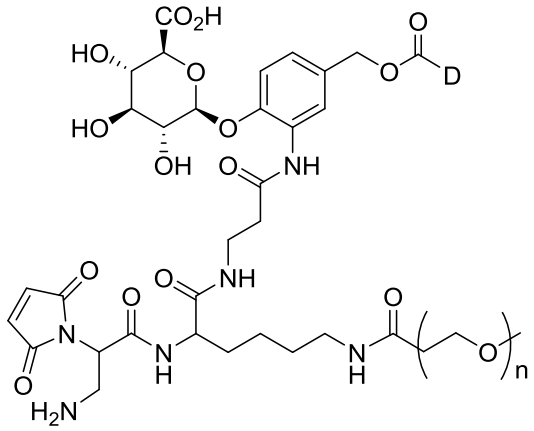
(**v**),

or a salt thereof, wherein L^2 is as previously defined, in the presence of a second activating agent; and

wherein said Formula **v** contacting provides the Formula **I** Drug Linker or Drug Linker intermediate compound or salt thereof.

7. The method of any one of claims **1**-7 wherein each of L^1 and L^3 is independently C_1-C_4 alkylene and L^2 is independently optionally substituted C_1-C_4 alkylene.

8. A method for preparing a Drug Linker compound of Formula **II**:



(**II**)

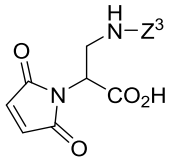
or a salt thereof,

wherein D is an auristatin Drug Unit; and

subscript n ranges from 2 to 24,

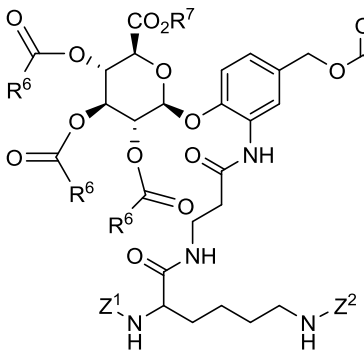
the method comprising steps (a)-(e) of claim **6**,

wherein the Formula **v** compound has the structure of:

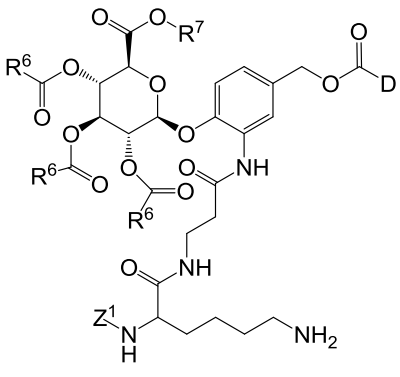


(**v**),

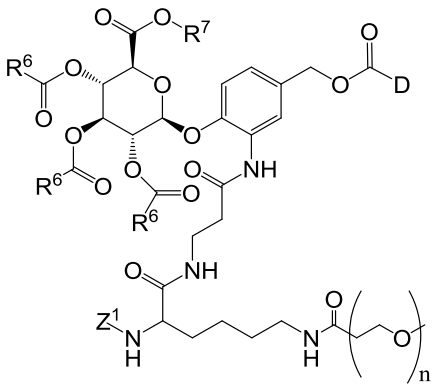
and wherein the Formula **IA**, Formula **IB**, Formula **IC**, Formula **ID** and Formula **IE** Drug Linker intermediate compounds, optionally in salt form, have the structures of Formula **IIA**, Formula **IIB**, Formula **IIC**, Formula **IID**, Formula **IIE**, Formula **IIF**:



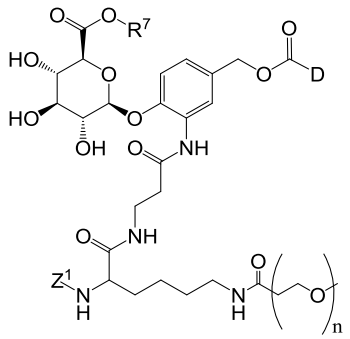
(**IIA**),



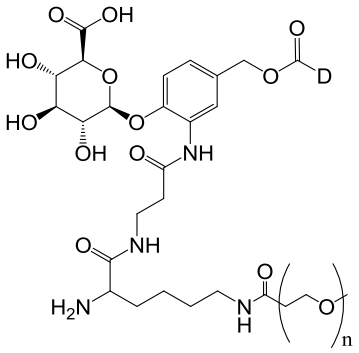
(**IIB**)



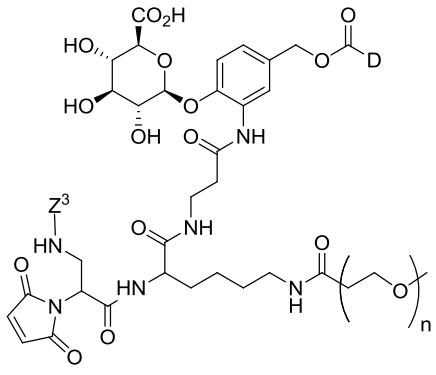
(**IIC**)



(**IID**)



(**IIE**)



(**IIF**),

wherein

each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group;

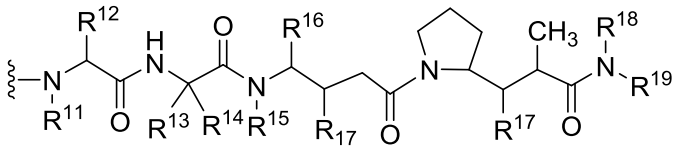
Z^1, Z^2 and Z^3 are independently a first, second and third suitable amino protecting group, respectively, or

Z^1 and Z^2 are independently a first and second suitable amino protecting group, respectively and Z^3 is an acid-labile amino protecting group,or Z^1 and Z^2 are independently a first and second suitable amino protecting group, respectively, and Z^3 is –C(=O)O-t-Bu,

the method further comprising the step of:

(f) contacting the Formula **IF** Drug Linker intermediate compound of with a third deprotecting agent, wherein said third deprotecting reagent contacting removes the Z^3 amino protecting group whereby the Formula **II** Drug Linker compound or salt thereof is provided.

9. The method of any one of claims **1**-**8**, wherein the auristatin Drug Unit (D) has the structure of:



(**D**),

wherein the wavy line indicates covalent bonding of D to the remainder of the Drug Linker or Drug Linker intermediate compound;

R^{11} is selected from the group consisting of H and C_1-C_8 alkyl, in particular methyl,

R^{12} is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle, and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

R^{13} is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle, and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

R^{14} is selected from the group consisting of H and methyl;

or R^{13} and R^{14} jointly form a carbocyclic ring and have the formula $-(CR^aR^b)_n-$ wherein R^a and R^b are independently selected from the group consisting of H, C_1-C_8 alkyl and C_3-C_8 carbocycle, and n is selected from the group consisting of 2, 3, 4, 5 and 6;

R^{15} is selected from the group consisting of H and C_1-C_8 alkyl;

R^{16} is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle, and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

each R^{17} is independently selected from the group consisting of H, OH, C_1-C_8 alkyl, C_3-C_8 carbocycle, and O-(C_1-C_8 alkyl);

R^{18} is selected from the group consisting of H and C_1-C_8 alkyl;

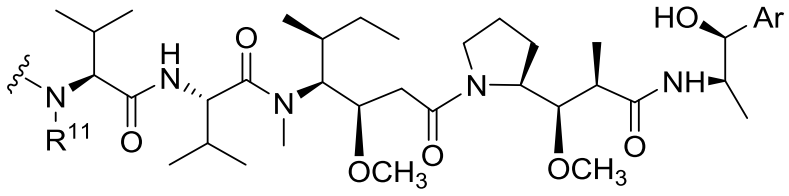
R^{19} is selected from the group consisting of $–C(R^{17})_2–C(R^{17})_2–$aryl, $–C(R^{17})_2–C(R^{17})_2–$($C_3$-$C_8$ heterocycle), $–C(R^{17})_2–C(O)–ZR^{20}$, and $–C(R^{17})_2–C(R^{17})_2–$($C_3$-$C_8$ carbocycle);

R^{20} is selected from the group consisting of H, C_1-C_8 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_5-C_{10} heteroaryl and C_3-C_8 heterocyclyl;

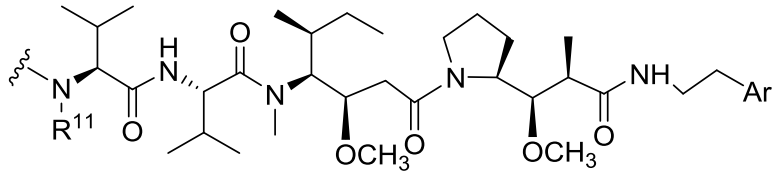
Z is –O-, or –NH-, or

Z- is –O- and R^{20} is C_1-C_4 alkyl or Z is –NH- and R^{20} is optionally substituted phenyl or optionally substituted C_5-C_6 heteroaryl, or

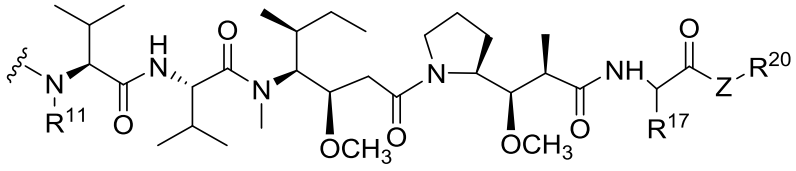
the auristatin Drug Unit (D) has the structure of Formula $\mathbf{D_{E\text{-}1}}$, $\mathbf{D_{E\text{-}2}}$, $\mathbf{D_{F\text{-}1}}$ or $\mathbf{D_{F/E\text{-}3}}$:



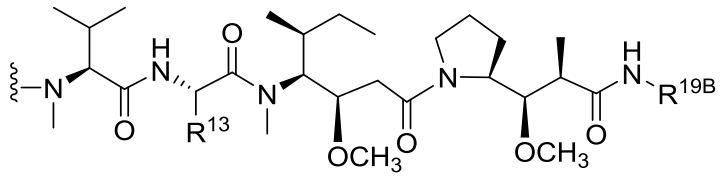
(**D**$_{E-1}$),



(**D**$_{E-2}$**)**,



(**D**$_{F-1}$),



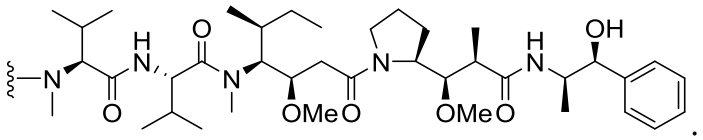
or (**D**$_{F/E-3}$),

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

R^{19B} is $–CH(CH_3)$-CH(OH)Ph, $-CH(CO_2H)CH_2Ph$, $-CH(CH_2Ph)$-2-thiazole, $-CH(CH_2Ph)$-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-3-quinolyl, or $-CH(CH_2Ph)C(=O)$NH-p-Cl-Ph;

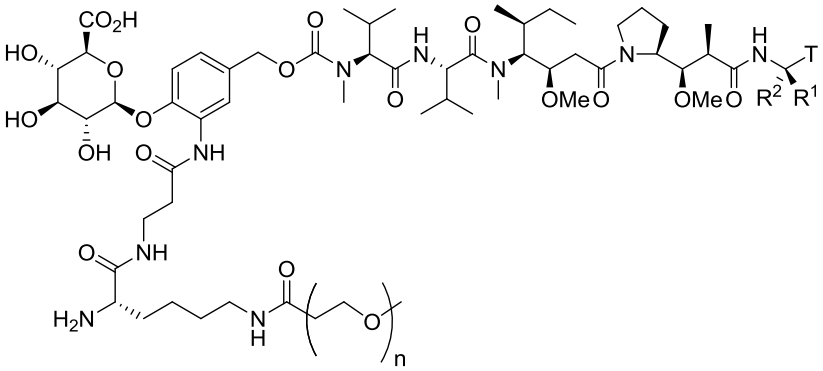
Ar is optionally substituted C_6-C_{10} aryl or optionally substituted C_3-C_8 heterocyclyl, in particular**,** or Ar is optionally substituted phenyl or optionally substituted 2-pyridyl, or

the auristatin Drug Unit (D) has the structure of:



.

10. The method of claim **5**, wherein the Formula **IE** Drug Linker intermediate has the structure of Formula **8**:



(**8**),

or a salt thereof, wherein

subscript n ranges from 2 to 24;

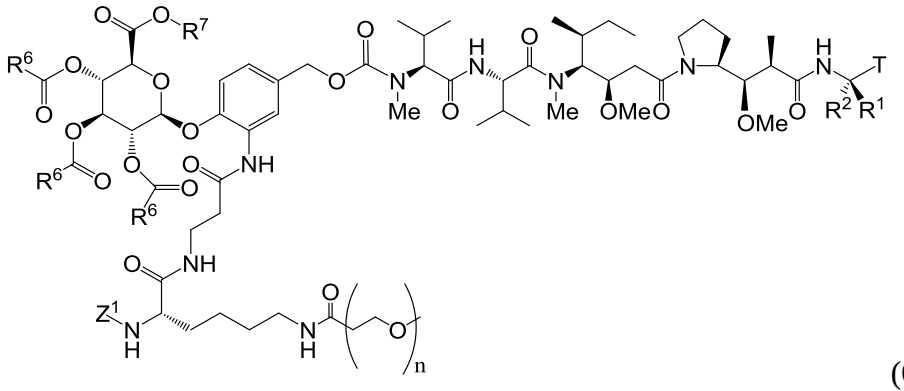
R^1 is H or C_1-C_4 alkyl;

R^2 is H, C_1-C_4 alkyl or $–CH_2$-R^3;

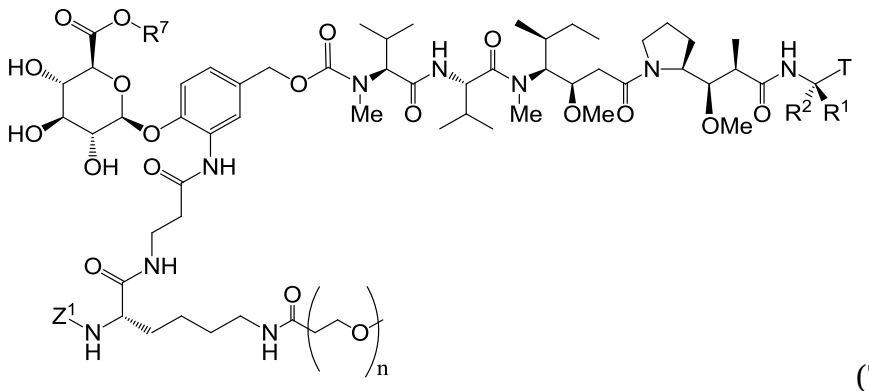
R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl; and

T is selected from the group consisting of $–CH(OR^4)$-R^5 and -C(=O)-OR^4, wherein R^4 is H or C_1-C_4 alkyl; and R^5 is C_6-C_{10} aryl or C_3-C_6 heteroaryl,

wherein the Formula **IC** and Formula **ID** Drug Linker intermediate compounds, optionally in salt form, have the structures of Formula **6** and Formula **7**:



(**6**),



(**7**)

wherein

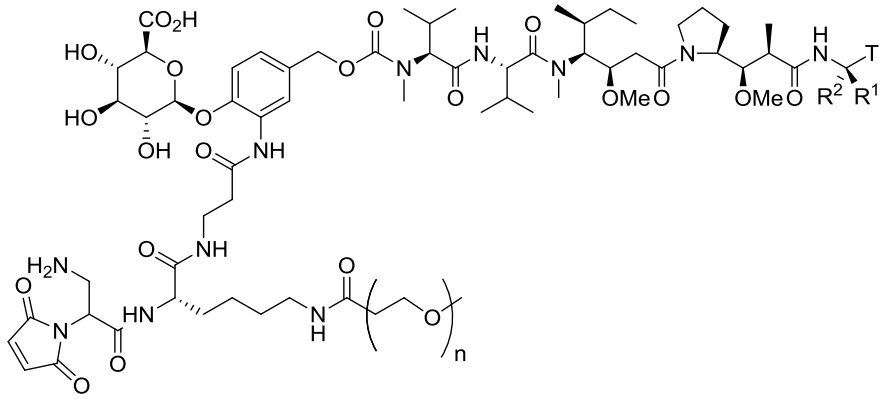
each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group;

Z^1 is a first suitable amino protecting group; and the remaining variable groups are as previously defined in the claim, or

R^1 is H or methyl, R^2 is H, and T is–$CH(OR^4)$-R^5, wherein R^4 is H or methyl and R^5 is C_6-C_{10} aryl, and the remaining variable groups are as previously defined in the claim, or

R^1 is methyl, R^2 is H, and T is–CH(OH)Ph and the remaining variable groups are as previously defined in the claim.

11. The method of claim **8**, wherein the Formula **II** Drug Linker compound has the structure of Formula **10:**



(**10**),

or a salt thereof, wherein

subscript n ranges from 2 to 24;

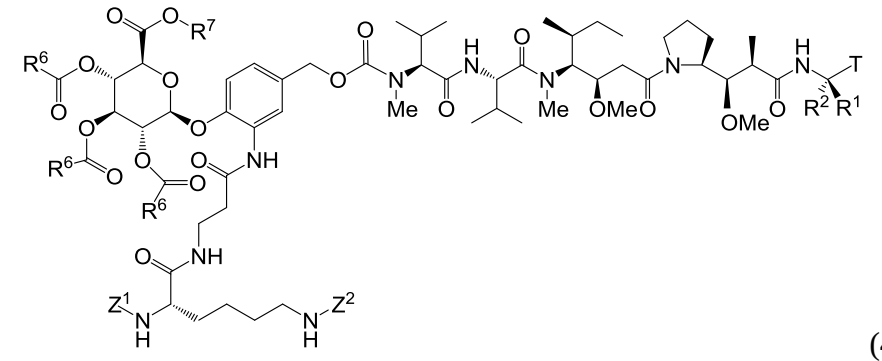
R^1 is H or C_1-C_4 alkyl;

R^2 is H, C_1-C_4 alkyl or –CH_2-R^3;

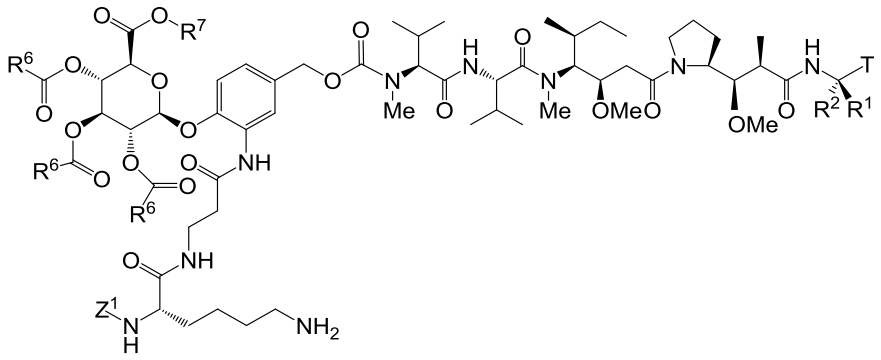
R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl; and

T is selected from the group consisting of –$CH(OR^4)$-R^5 and -C(=O)-OR^4, wherein R^4 is H or C_1-C_4 alkyl; and R^5 is C_6-C_{10} aryl or C_3-C_6 heteroaryl; and

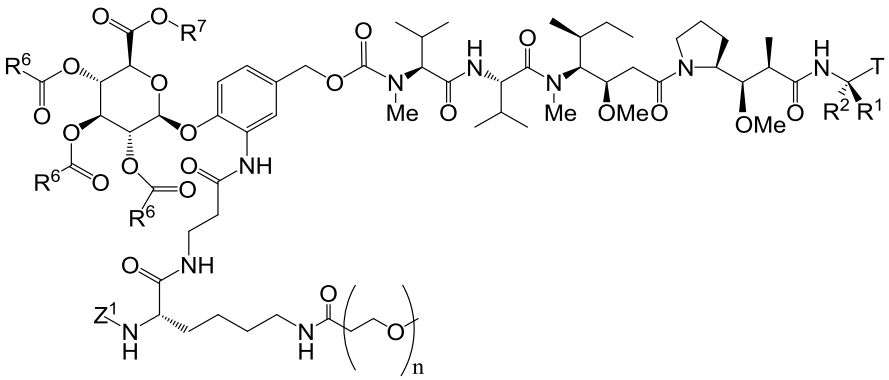
wherein the Drug Linker intermediate compounds, optionally in salt form, of Formula **IA**, Formula **IB**, Formula **IC**, Formula **ID**, Formula **IE** and Formula **IF** have the structure of Formula **4**, Formula **5,** Formula **6**, Formula **7**, Formula **8**, and Formula **9**, respectively:



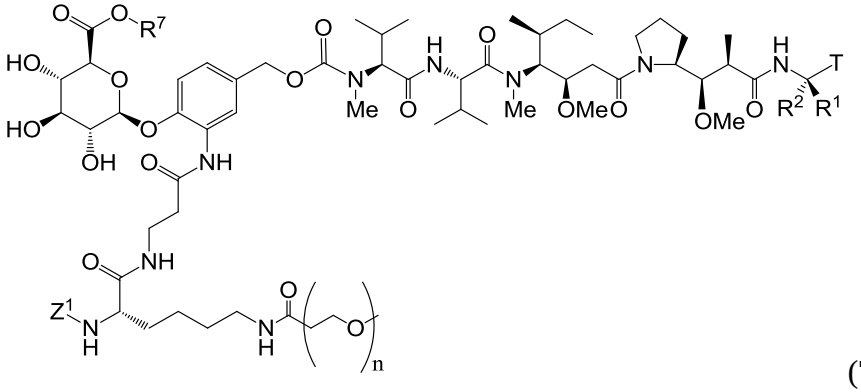
(**4**)



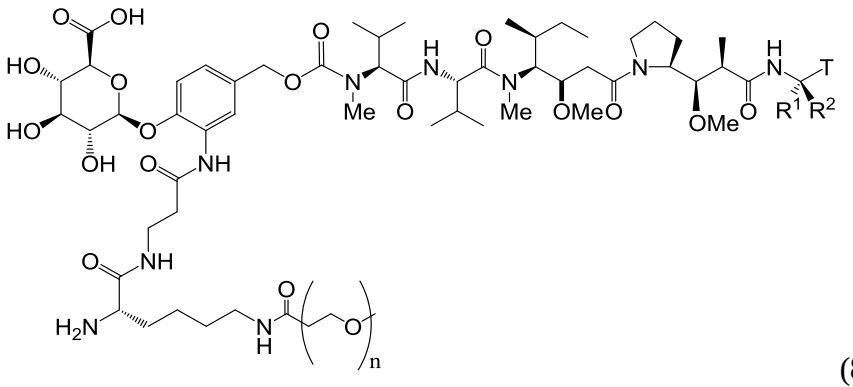
(**5**),



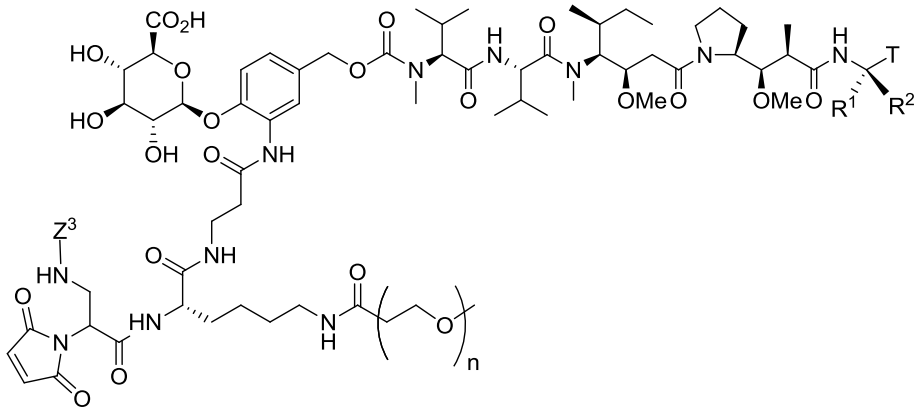
(**6**),



(**7**)

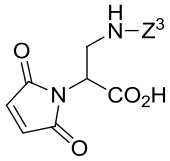


(**8**),



(**9**),

and the Formula **v** compound has the structure of:



or salt thereof, wherein

each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and $–OR^7$ provides an ester functional group that is a suitable carboxylic acid protecting group; and

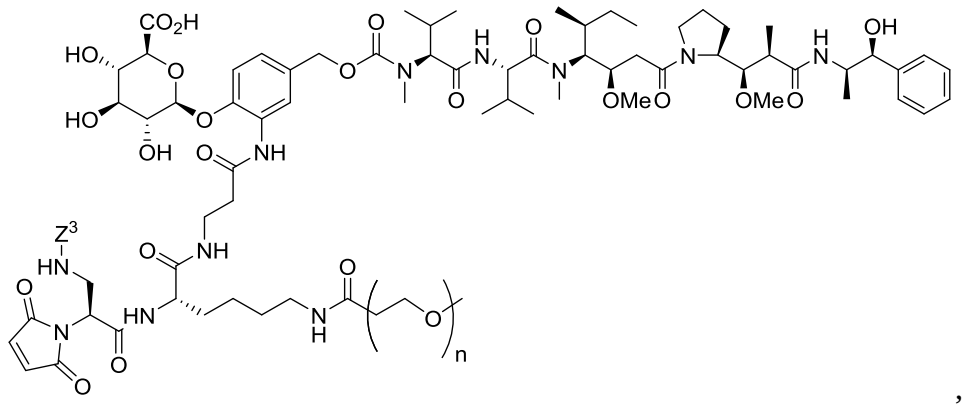
Z^1, Z^2 and Z^3 are independently a suitable amino protecting group, or

R^1 is H or methyl, R^2 is H, and T is–$CH(OR^4)$-R^5, wherein R^4 is H or methyl and R^5 is C_6-C_{10} aryl, and the remaining variable groups are as previously defined in the claim, or

R^1 is methyl, R^2 is H, and T is–CH(OH)Ph, and the remaining variable groups are as previously defined in the claim.

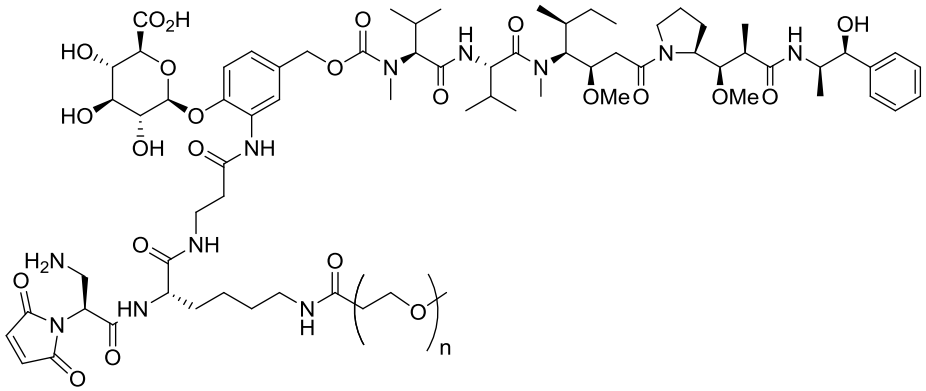
12. The method of any one of claims **1**-**11**, wherein Z^1 is FMOC, or the method of any one of claims **6**-**11**, wherein Z^1 is FMOC and/or Z^2 is optionally substituted trityl, or Z^1 is FMOC and Z^2 is 4-methoxy-trityl (MMT).

13. The method of claim **11**, wherein the Formula **10** Drug linker compound has the structure of:

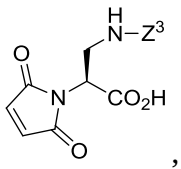


,

the Formula **9** Drug Linker intermediate and Formula **v** compounds, or salts thereof, have structures of:

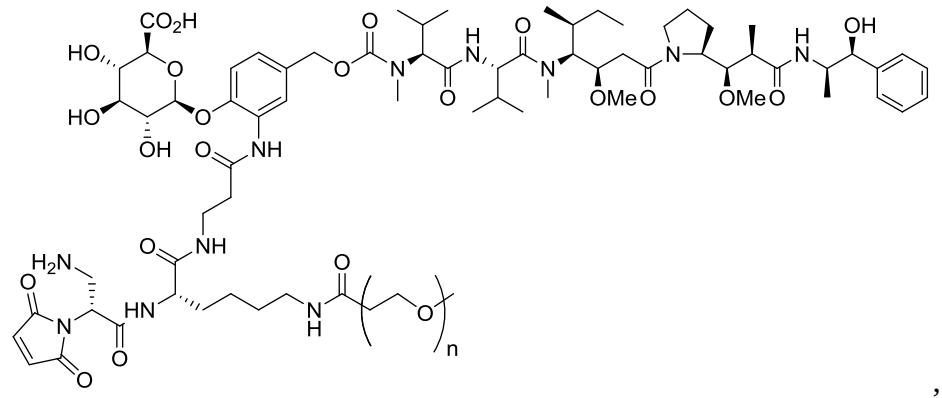


,



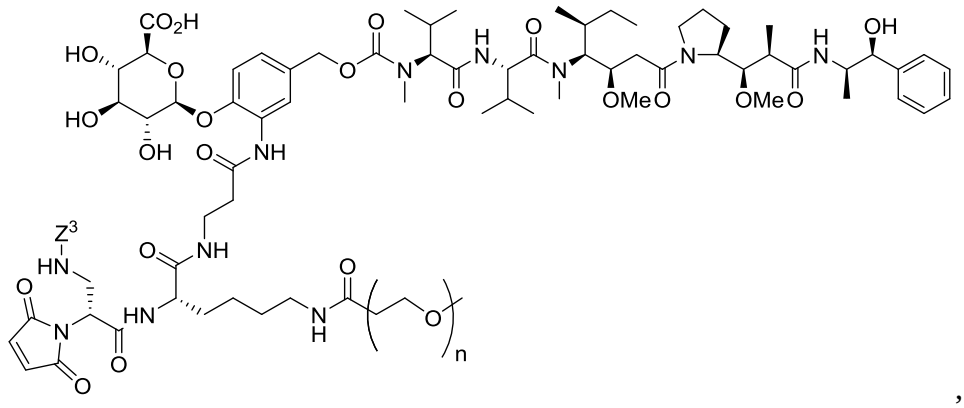
, or

the Formula **10** Drug Linker compound has the structure of:

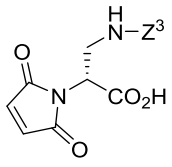


,

or a salt thereof, wherein the Formula **9** Drug Linker intermediate and Formula **v** compounds, optionally in salt form, have the structures of:



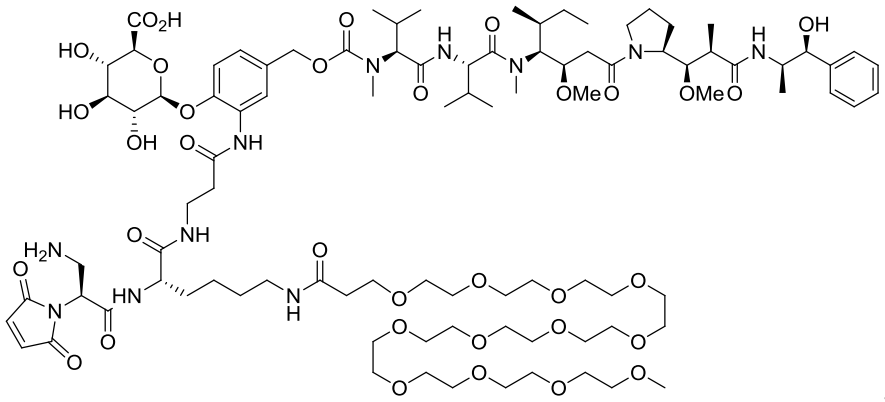
,



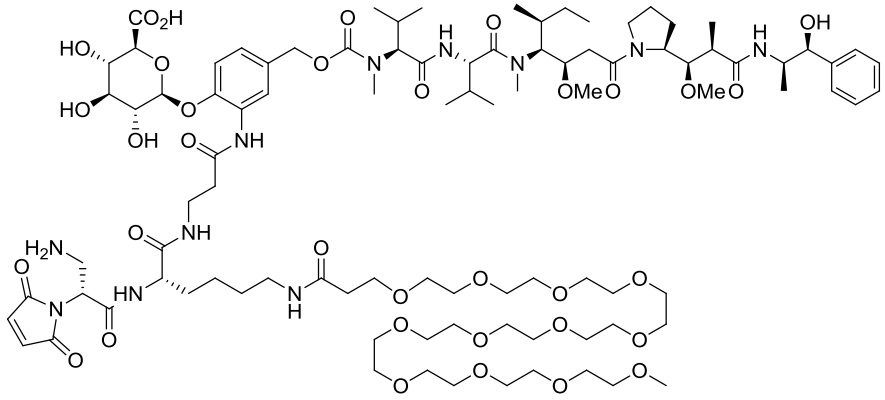
;

and wherein the other Drug Linker intermediate compounds of Formula **4**, Formula **5,** Formula **6**, Formula **7** and Formula **8** are those of claim **22**,

or the Formula **10** Drug Linker compound has the structure of:



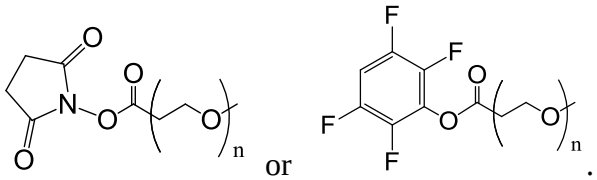
, or



14. The method of claim **13**, wherein Z^3 is –C(=O)O-t-Bu and/or R^6 and R^7 are independently C_1-C_4 alkyl, or

Z^3 is –C(=O)O-t-Bu; and R^6 and R^7 are independently methyl or ethyl, or R^6 and R^7 are each methyl.

15. The method of any one of claims **6**-**14**, wherein the Formula **iv** compound has the structure of:



or

.

16. The method of any one of claims **1**-**14**, wherein subscript n ranges from 8 to 16, or wherein subscript n is 12.

17. The method of any one of claims **6**-**16**, wherein the second or third deprotecting agent for removal of Z^2 or Z^3 is an aqueous-containing acid solution having a pKa ranging from 0-3, or

the aqueous-containing acid solution is that of or is an aqueous solution of trifluoroacetic acid or trichloroacetic acid.

18. The method of any one of claims **1**-**17**, wherein the Grignard reagent in a suitable alcohol-containing solvent has the formula of R^gMgX and the alkoxy magnesium halide in a suitable alcohol-containing has the formula of R^gOMgX, wherein R^g is C_1-C_4 alkyl or phenyl; and X is I, Br, or Cl, or

the Grignard reagent in a suitable alcohol-containing solvent is MeMgI or MeMgCl, the alkoxy magnesium halide is MeOMgI or MeOMgCl and the alcohol-containing solvent comprises a C_1-C_4 alcohol, or the alcohol-containing solvent is a1:1 (v/v) mixture of methanol and THF.

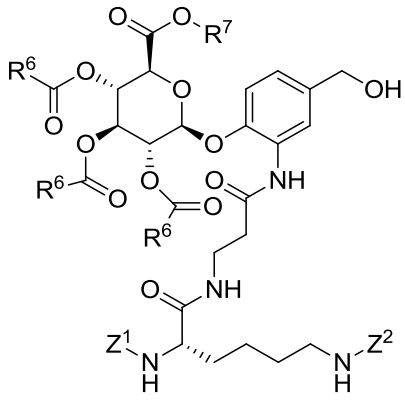
19. The method any one of claims **1**-**18**, wherein the first deprotecting agent for removal of Z^1 is an aqueous-containing solution of LiOH.

20. The method of any one of claims **6**-**19**, wherein the first activating agent for said Formula **iv** contacting is a solution of: N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC·HCl), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), (1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride/N-Hydroxysuccinimide, O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), Diphenyl phosphoryl azide (DPPA), Chloro-N,N,N',N'-bis(tetramethylene)formamidinium tetrafluoroborate, Fluoro-N,N,N',N'-bis(tetramethylene)formamidinium hexafluorophosphate, N,N'-Dicyclohexylcarbodiimide, N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, 1,1'-Carbonyldiimidazole, 2-Chloro-1,3-dimethylimidazolidinium tetrafluoroborate, (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 2-Chloro-1-methylpyridinium iodide, or Propylphosphonic anhydride, or

the first activating agent for said Formula **iv** contacting is a solution of EDC·HCl, EEDQ or COMU, or a solution of COMU.

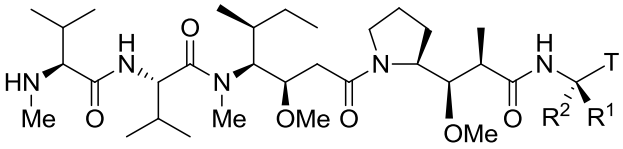
21. The method of claim **11**, wherein the Drug Linker intermediate compound of Formula **4** or salt thereof is prepared by the method comprising the step of:

contacting a compound of Formula **3** having the structure of:



(**3**),

or a salt thereof, in a suitable solvent with a auristatin compound of Formula **iii** having the structure of:



(**iii**),

in the presence of a carbamate coupling agent, or

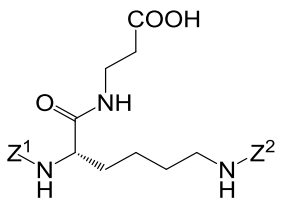
a solution of phosgene, trichloromethyl chloroformate (Diphosgene) and bis(trichloromethyl) carbonate (Triphosgene), 1,1'-Carbonyldiimidazole (CDI), or 1,1′-Carbonyl-di-(1,2,4-triazole) (CDT), or a solution of 1,1′-carbonyl-di-(1,2,4-triazole) (CDT),

wherein said Formula **3** contacting provides the Formula **4** Drug Linker intermediate compound or salt thereof.

22. The method of claim **21**, wherein the Formula **3** compound is prepared by a method comprising the step of:

contacting a Parallel Connector Unit precursor (L_P') of Formula **1,** or salt thereof, and a compound of Formula **2** in a suitable solvent in the presence of a claim **32** activating agent,

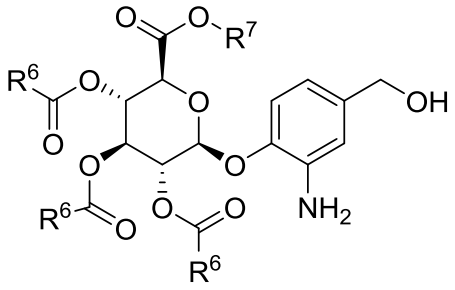
wherein the Formula **1** L_P' compound has the structure of:



(**1**)

or a salt hereof, wherein each of Z^1 and Z^2 is independently a suitable amino protecting group; and

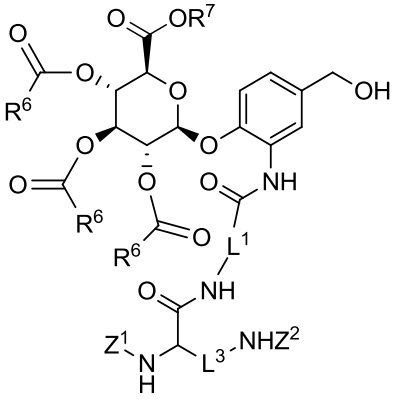
the Formula **2** compound has the structure of:



(**2**),

wherein said contacting provides the Formula **3** compound or salt thereof.

23. A compound of Formula **3** having the structure of:



(**3**)

or a salt thereof, wherein

L^1 and L^3 are independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo, or L^1 and L^3 independently are C_1-C_4 alkylene;

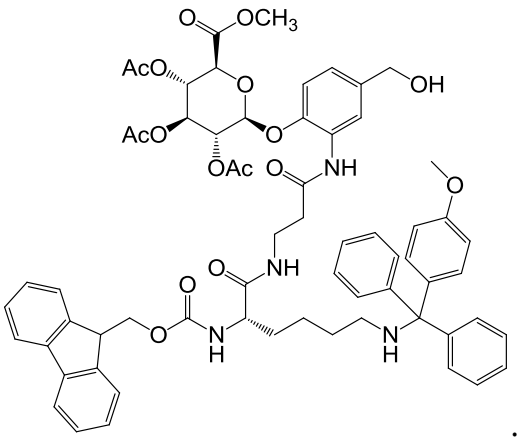
each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group,

or each R^6 is C_1-C_4 alkyl or optionally substituted phenyl and/or R^7 is methyl or ethylor R^6 and R^7 are each methyl and the remaining variable groups are as defined in the claim, or

Formula **3** has the structure of:

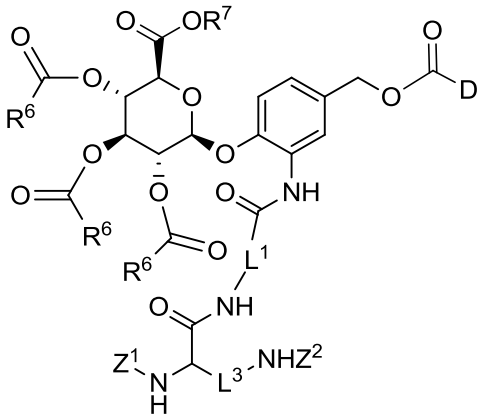
wherein Z^1 and Z^2 independently are a first and second suitable amino protecting group,

Z^1 fluorenylmethyloxy carbonyl (FMOC) and Z^2 is 4-methoxy trityl (MMTr), or the Formula **3** compound has the structure of:



.

24. A Drug Linker intermediate compound having the structure of Formula **4** of:



(**4**),

or a salt thereof, wherein

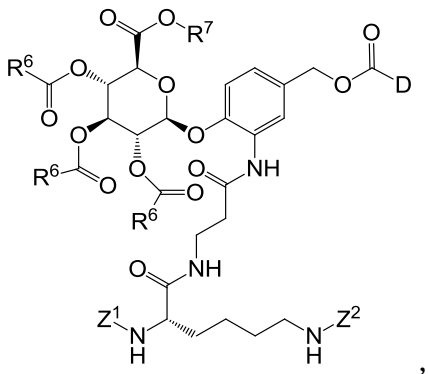
D is an auristatin Drug Unit;

L^1 and L^3 are independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group; and

Z^1 and Z^2 independently are a first and second suitable amino protecting group**,** or

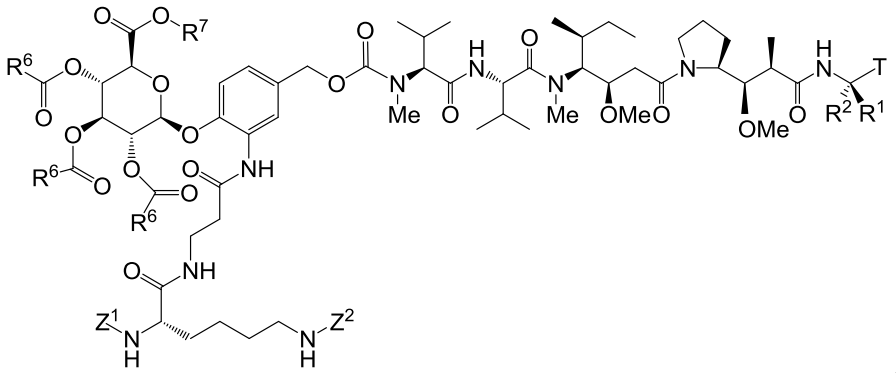
the Formula **4** compound, or salt thereof, has the structure of:



,

wherein Z^2 is MMTr, or

the Formula **4** Drug Linker intermediate compound, optionally in salt form, has the structure of:



,

wherein

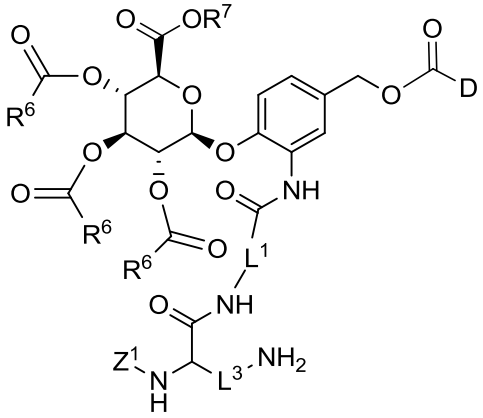
R^1 is H or C_1-C_4 alkyl;

R^2 is H, C_1-C_4 alkyl, or $–CH_2$-R^3;

R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl; and

T is selected from the group consisting of $–CH(OR^4)$-R^5 and -C(=O)-OR^4, wherein R^4 is H, C_1-C_4 alkyl and R^5 is C_6-C_{10} aryl or C_3-C_6 heteroaryl.

25. A Drug Linker intermediate compound, wherein the Drug Linker intermediate compound has the structure of Formula **5** of:



(**5**),

or a salt thereof, wherein

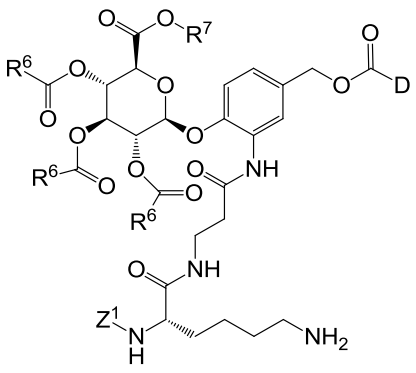
D is an auristatin Drug Unit;

L^1 and L^3 are independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$- provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group; and

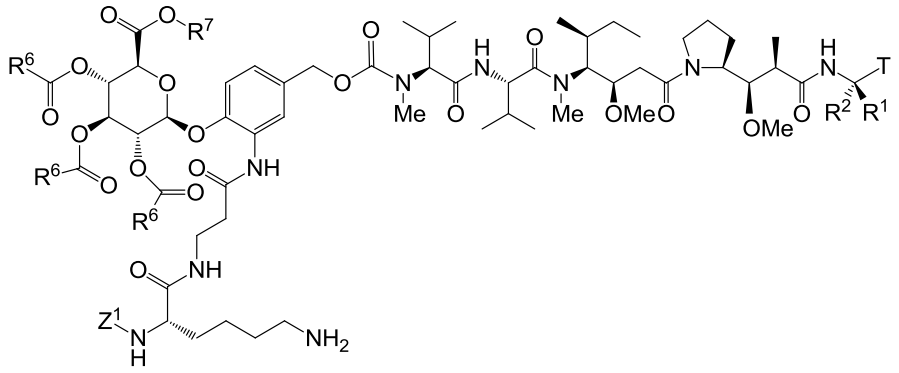
Z^1 is a first suitable amino protecting group,

or the Formula **5** Drug Linker intermediate compound, optionally in salt form, has the structure of:



, or

the Formula **5** Drug Linker intermediate compound, optionally in salt form, has the structure of:



,

wherein

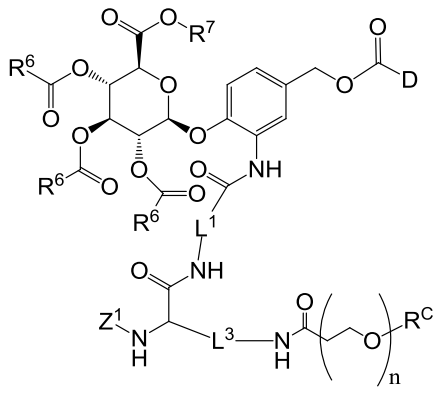
R^1 is H or C_1-C_4 alkyl;

R^2 is H, C_1-C_4 alkyl, or $–CH_2$-R^3;

R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl; and

T is selected from the group consisting of $–CH(OR^4)$-R^5 and -C(=O)-OR^4, wherein R^4 is H, C_1-C_4 alkyl and R^5 is C_6-C_{10} aryl or C_3-C_6 heteroaryl.

26. A Drug Linker intermediate compound, wherein the Drug Linker intermediate compound has the structure of Formula **6** of:



(**6**),

or a salt thereof, wherein

D is an auristatin Drug Unit;

L^1 and L^3 are independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

each of R^6 and R^7 is independently optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so that $R^6C(=O)$-

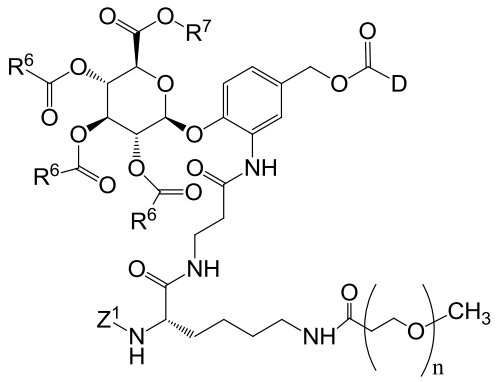
provides for an ester functional group that is a suitable hydroxyl protecting group and –OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group;

Z^1 is a first suitable amino protecting group;

R^C is a PEG Capping Unit; and

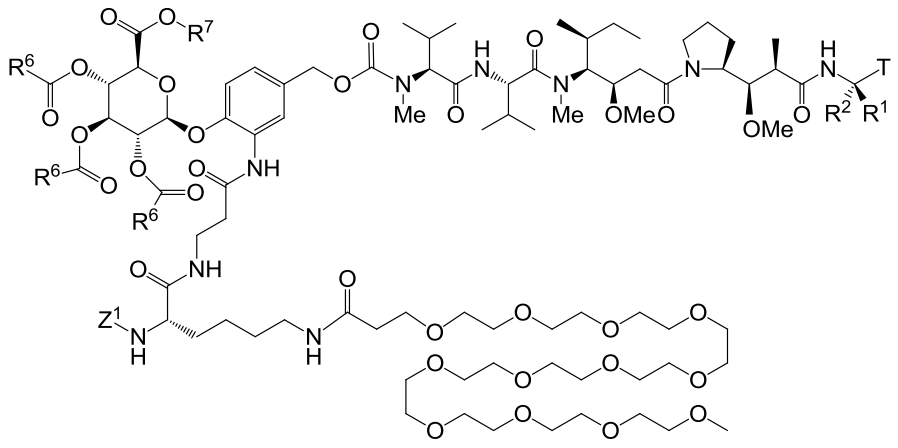
subscript n ranges from 1 to 24, orsubscript n is 8 or 12, or

the Formula **6** Drug Linker intermediate compound, optionally in salt form, has the structure of:



,

or the Formula **6** Drug Linker intermediate compound, optionally in salt form, has the structure of:



,

wherein

R^1 is H or C_1-C_4 alkyl;

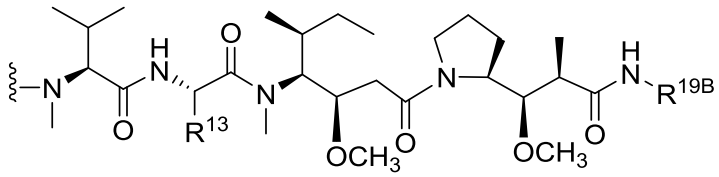
R^2 is H, C_1-C_4 alkyl, or –CH_2-R^3;

R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl; and

T is selected from the group consisting of –CH(OR^4)-R^5 and -C(=O)-OR^4, wherein R^4 is H, C_1-C_4 alkyl and R^5 is C_6-C_{10} aryl or C_3-C_6 heteroaryl.

27. The compound of any one of claims **24-26**, wherein the auristatin Drug Unit (D) has any one of the structures of claim **9**, or

wherein the auristatin Drug Unit (D) has the structure of Formula $\mathbf{D_{F/E-3}}$:



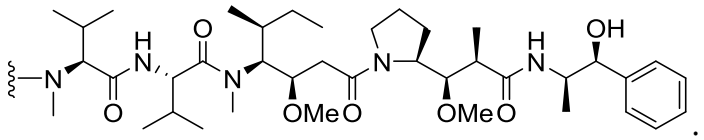
($\mathbf{D_{F/E-3}}$),

wherein

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

R^{19B} is $–CH(CH_3)$-CH(OH)Ph, -$CH(CO_2H)CH_2$Ph, -$CH(CH_2Ph)$-2-thiazole, -$CH(CH_2Ph)$-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-3-quinolyl, or -$CH(CH_2Ph)$C(=O)NH-p-Cl-Ph, or

wherein the auristatin Drug Unit (D) has the structure of:

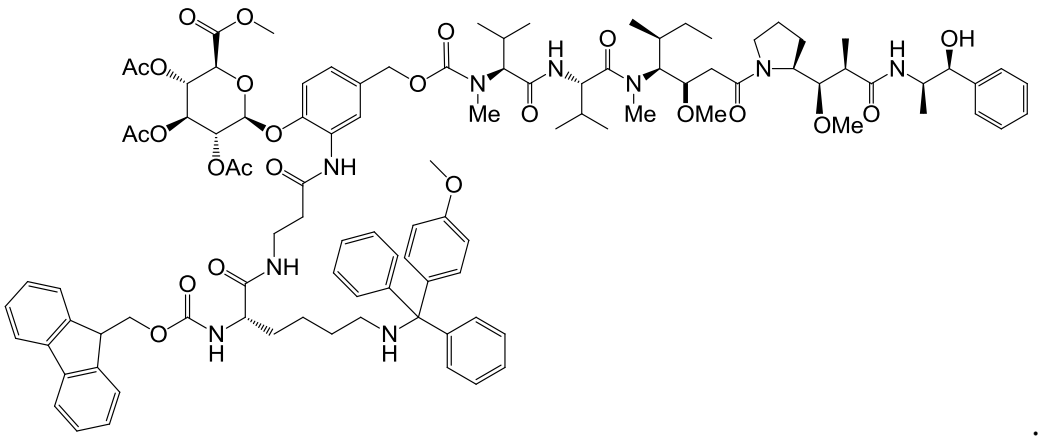


.

28. The Drug Linker intermediate compound of any one of claims **24-27** wherein each of R^6 and R^7 is independently C_1-C_4 alkyl, or each of R^6 and R^7 is methyl or each of R^6 and R^7 is ethyl.

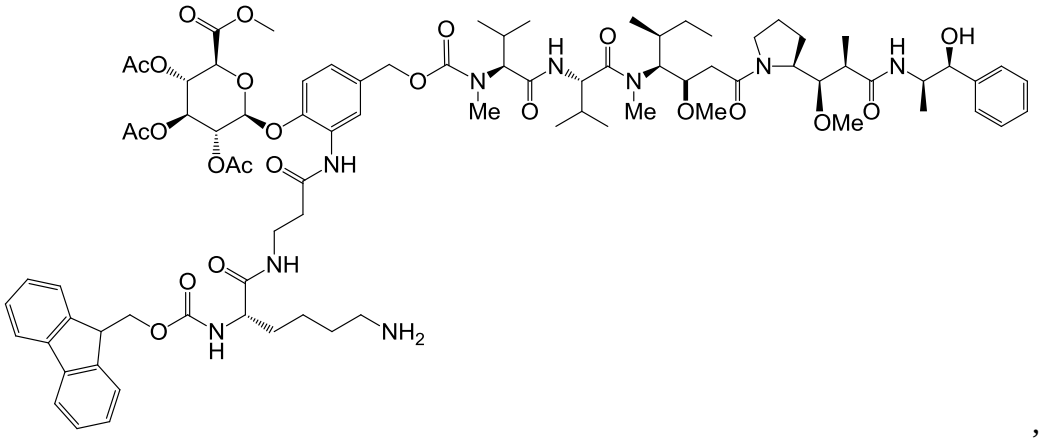
29. The Drug Linker intermediate compound of claim **24**, **25** or **26**, wherein R^1 is hydrogen or methyl; R^2 is hydrogen; and T is–$CH(OR^4)$-R^5; wherein R^4 is hydrogen or methyl and R^5 is C_6-C_{10} aryl and Z^1 is FMOC, or R^1 is methyl, R^2 is H, and T is–CH(OH)-Ph, and Z^1 is FMOC.

30. The Drug Linker intermediate compound of claim **24**, wherein the Formula **4** Drug Linker intermediate compound has the structure of:



.

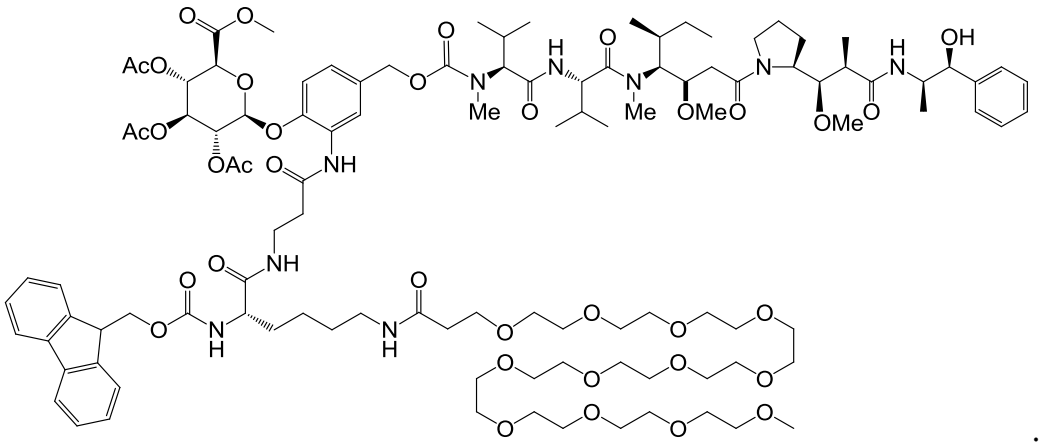
31. The Drug Linker intermediate compound of claim **25**, wherein the Formula **5** Drug Linker intermediate compound has the structure of:



,

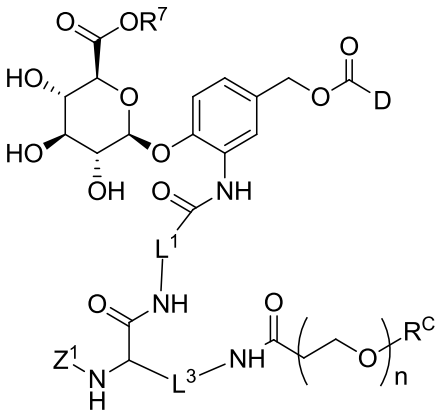
or a salt thereof.

32. The Drug Linker intermediate compound of claim **26**, wherein the Formula **6** compound has the structure of:



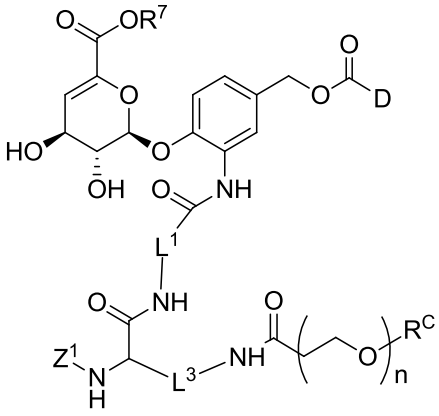
.

33. A composition comprised of a Drug Linker intermediate compound of Formula **7** having the structure of:



(**7**)

or a salt thereof, and a compound of Formula **7A** having the structure of:



(**7A**)

or a salt thereof,

wherein in Formula **7** and Formula **7A**:

D is an auristatin Drug Unit,

each of L^1 and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

R^7 is optionally substituted C_1-C_8 alkyl, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene so–OR^7 provides an ester functional group that is a suitable carboxylic acid protecting group, or R^7 is methyl;

Z^1 is a first suitable amino protecting group;

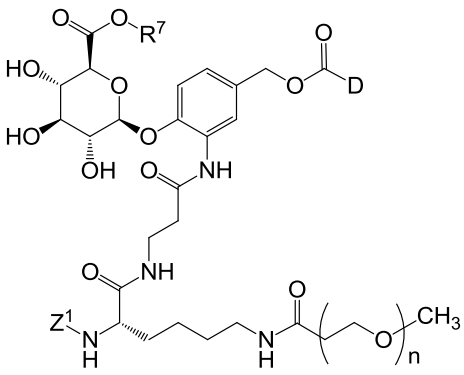
R^C is a PEG Capping Unit; and

subscript n is from 2 to 24,

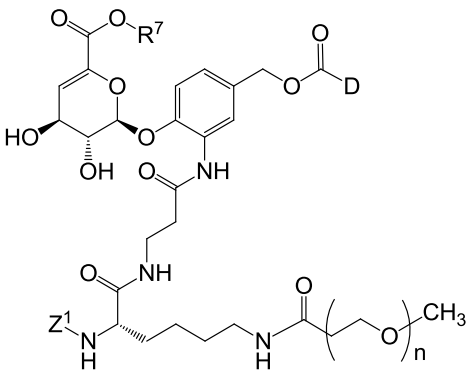
wherein the composition is comprised of no more than 5 wt.%, of the Formula **7A** compound:

or the composition is comprised of:

a Drug Linker intermediate compound of Formula **7** and a compound of Formula **7A** optionally in salt forms, having the structures of:



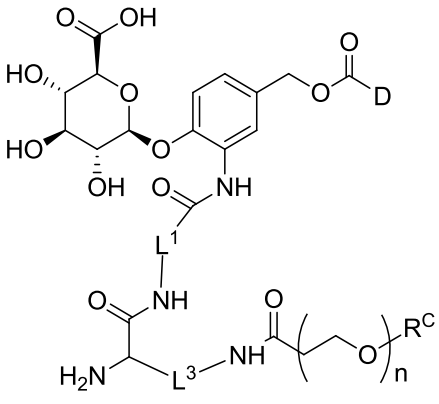
(**7**) and



(**7A**).

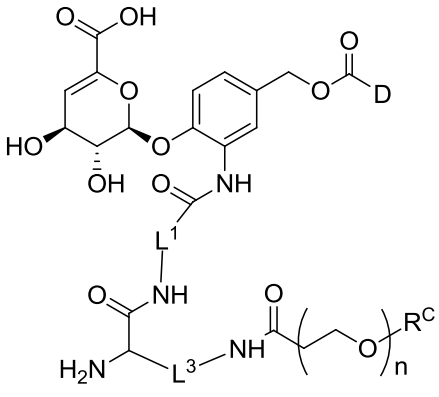
respectively, wherein Z^1 is FMOC and subscript n is from 2 to 24, and wherein the composition is comprised of no more than 5 wt.%, of the Formula **7A** compound.

34. A composition comprised of a Drug Linker intermediate compound of Formula **8** having the structure of:



(**8**)

or a salt thereof, and a compound of Formula **8A** having the structure of:



(**8A**)

or a salt thereof,

wherein in Formula **8** and Formula **8A**:

D is an auristatin Drug Unit,

each of L^1 and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

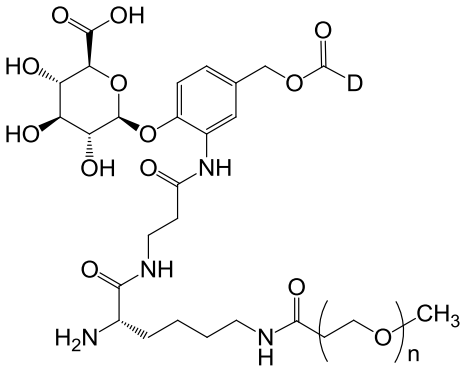
R^C is a PEG Capping Unit; and

subscript n is from 2 to 24, and

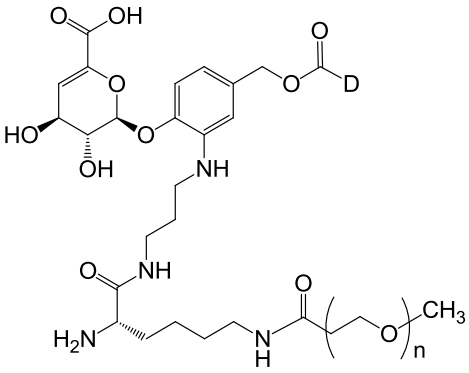
wherein the composition is comprised of no more than about 5 wt.%, or no more than between 3 wt.% and 4 wt.%, of of the Formula **8A** compound

, or

a composition comprised of a Drug Linker intermediate compound of Formula **8** and a compound of Formula **8A**, optionally in salt forms, having the structures of:



(**8**) and



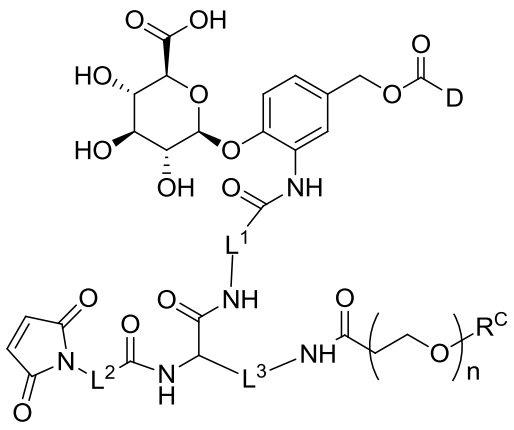
(**8A**) .

respectively, wherein

subscript n is from 2 to 24; and

wherein the composition is comprised of no more than 5 wt.%, or no more than between 3 wt.% and 4 wt.%, of the Formula **8A** compound.

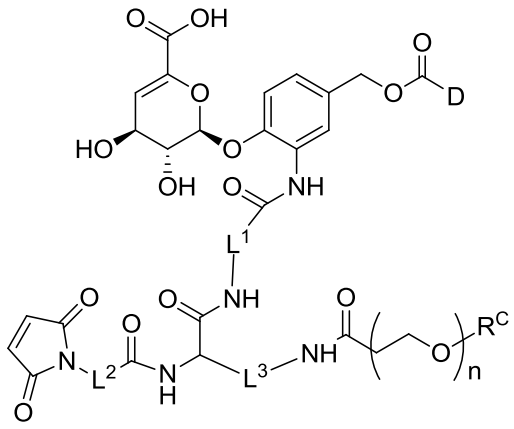
35. A composition comprised of a compound of Formula **9** having the structure of:



(**9**)

or a salt thereof, and

a compound of Formula **9A** having the structure of:



(**9A**)

or a salt thereof,

wherein in Formula **9** and Formula **9A**:

D is an auristatin Drug Unit,

each of L^1, L^2 and L^3 is independently selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

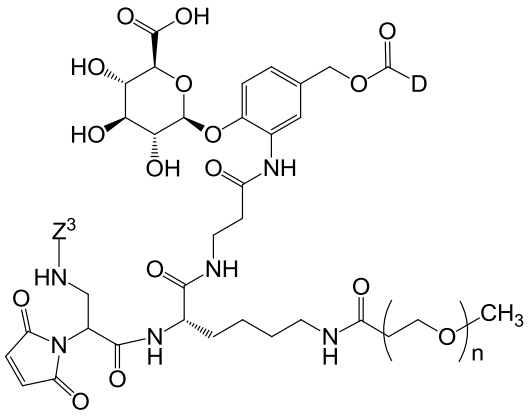
R^C is a PEG Capping Unit; and

subscript n is from 2 to 24,

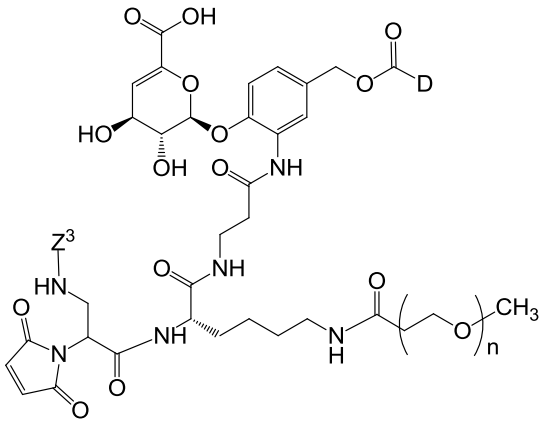
wherein the composition is comprised of no more than 5 wt.% of the Formula **9A** compound

or

the composition is comprised of compound of the Formula **9** and a compound of Formula **9A**, optionally in salt forms, having the structures of:



(**9**) and



(**9A**),

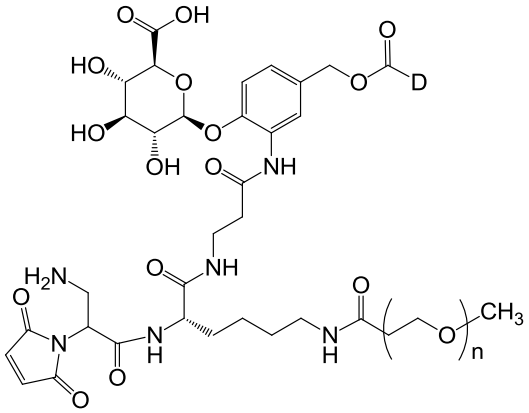
respectively, wherein

subscript n is from 2 to 24; and

Z^3 is a third amino protecting group that is acid-labile, or is of formula –C(=O)O-R^8, wherein R^8 is C_1-C_4 alkyl or optionally substituted phenyl, and

wherein the composition is comprised of no more than 5 wt.% of the Formula **9A** compound.

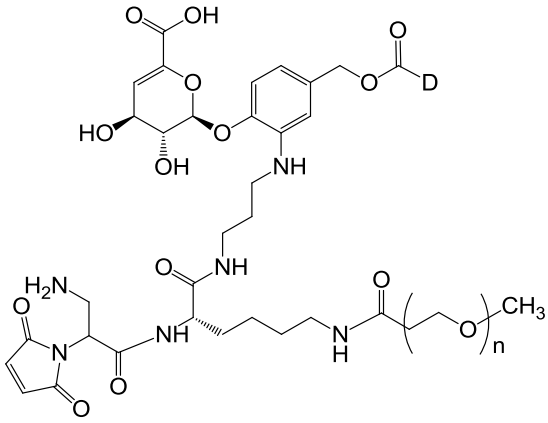
36. A composition comprised of Drug Linker compound of Formula **10** having the structure of:



(**10**)

or a salt thereof,

and a compound of Formula **10A** having the structure of:



(**10A**),

or a salt thereof, wherein in Formula **10** and Formula **10A**:

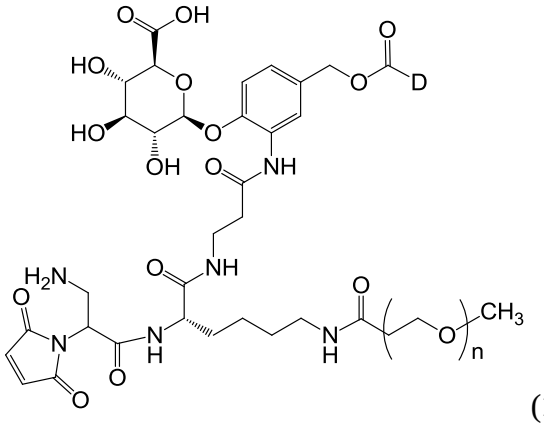
D is an auristatin Drug Unit; and

subscript n is from 2 to 24, and

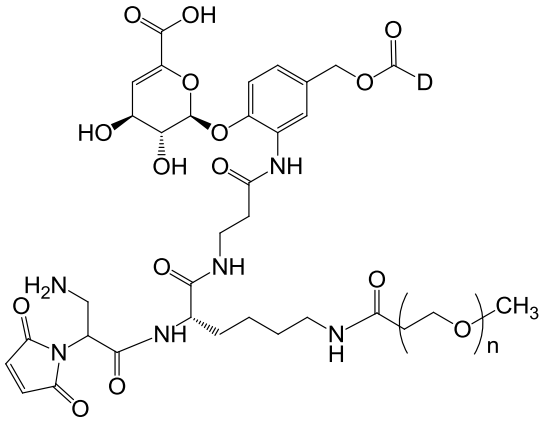
wherein the composition is comprised of no more than 5 wt.%, of the Formula **10A** compound:

or

a composition comprised of a Drug Linker compound of Formula **10** and a compound of Formula **10A**, optionally in salt forms, having the structures of:



(**10**) and

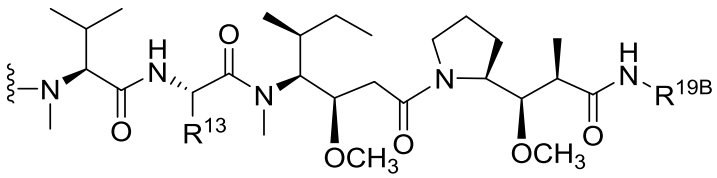


(**10A**)

respectively, wherein subscript n is from 2 to 24; and

wherein the composition is comprised of no more than 5 wt.%, of the Formula **10A** compound.

37. The composition of any one of claims **33-36**, wherein the auristatin Drug Unit (D) has any one of the structures of claim **9**, or the auristatin Drug Unit (D) has the structure of Formula $\mathbf{D_{F/E\text{-}3}}$:



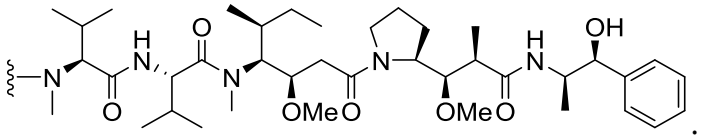
($\mathbf{D_{F/E\text{-}3}}$),

wherein

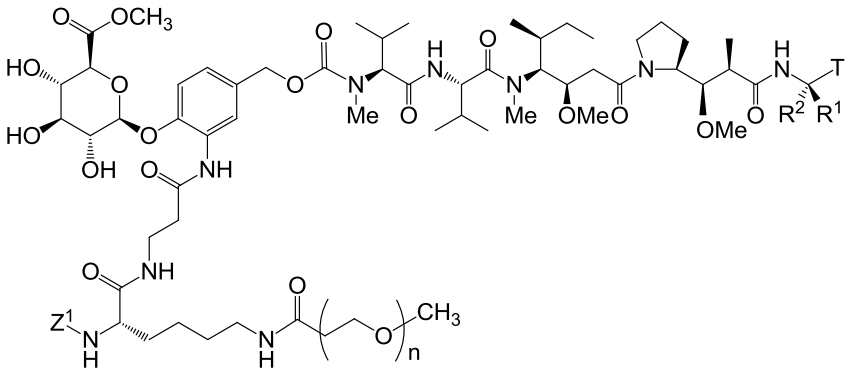
R^{13} is isopropyl or $–CH_2\text{-}CH(CH_3)_2$; and

R^{19B} is $–CH(CH_3)\text{-}CH(OH)Ph$, $-CH(CO_2H)CH_2Ph$, -CH(CH2Ph)-2-thiazole, -CH(CH2Ph)-2-pyridyl, -CH(CH2-p-Cl-Ph), $-CH(CO_2Me)\text{-}CH_2Ph$, $-CH(CO_2Me)\text{-}CH_2CH_2SCH_3$, $CH(CH_2CH_2SCH_3)C(=O)$NH-3-quinolyl, or $-CH(CH_2Ph)C(=O)$NH-p-Cl-Ph, or

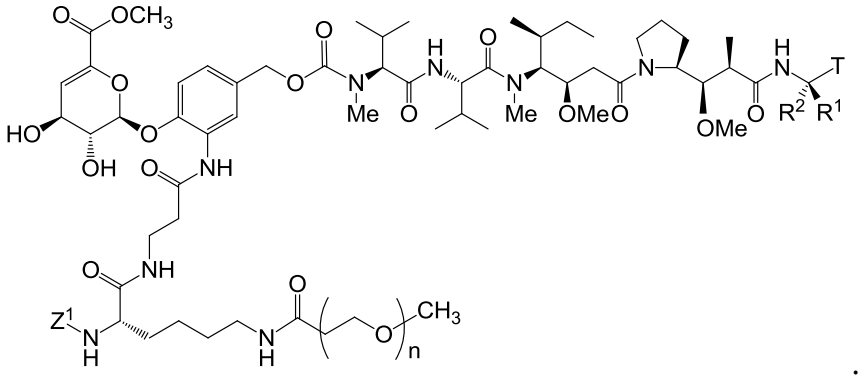
wherein the auristatin Drug Unit has the structure of:



38. The composition of claim **33**, wherein the Formula **7** Drug Linker intermediate compound and the Formula **7A** compound optionally in salt forms, have the structures of:



and



respectively wherein in both structures:

Z^1 is FMOC;

R^1 is H or C_1-C_4 alkyl;

R^2 is H, C_1-C_4 alkyl, or $–CH_2$-R^3;

R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl; and

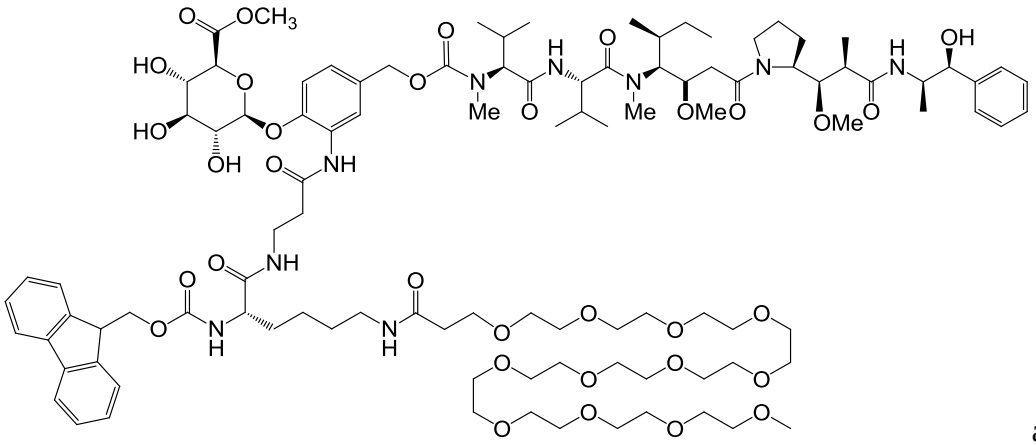
T is selected from the group consisting of $–CH(OR^4)$-R^5 and -C(=O)-OR^4, wherein R^4 is H, C_1-C_4 alkyl and R^5 is C_6-C_{10} aryl or C_3-C_6 heteroaryl, and

subscript n is from 2 to 24, or

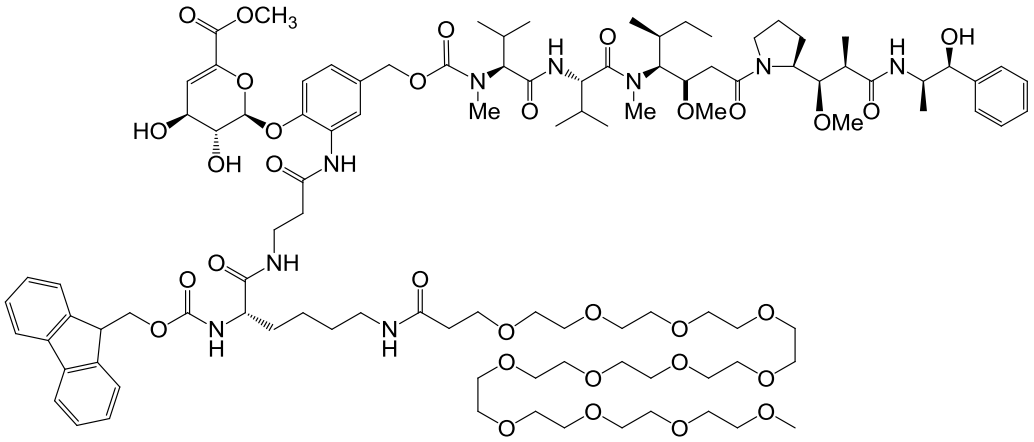
wherein in both structures R^2 is hydrogen; and T is$–CH(OR^4)$-R^5; wherein R^4 is hydrogen or methyl and R^5 is C_6-C_{10} aryl, and the remaining variable groups are as defined in the claim, or

R^2 is H, and T is–CH(OH)-Ph and subscript n is 8 or 12; and the remaining variable groups are as previously defined by the claim, or

the Formula **7** Drug linker intermediate compound and the Formula **7A** compound, optionally in salt forms, have the structures of:

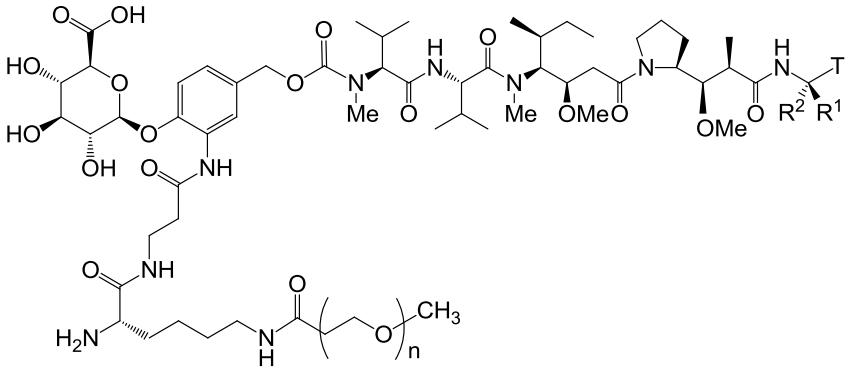


and

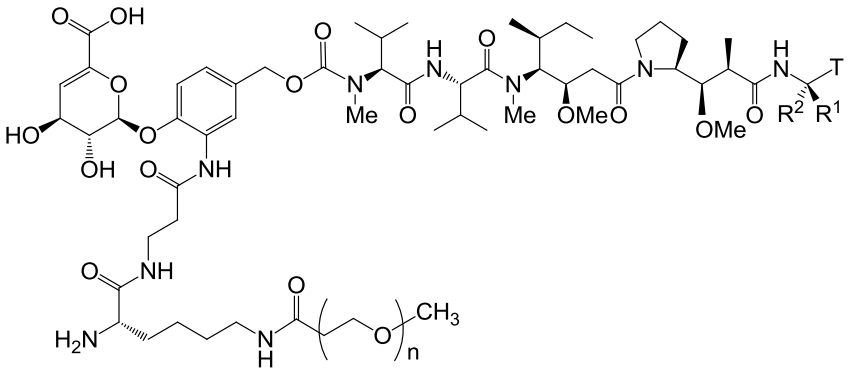


respectively.

39. The composition of claim **34**, wherein the Formula **8** Drug Linker intermediate compound and the Formula **8A** compound, optionally in salt forms, have the structures of:



and



respectively, wherein

R^1 is H or C_1-C_4 alkyl;

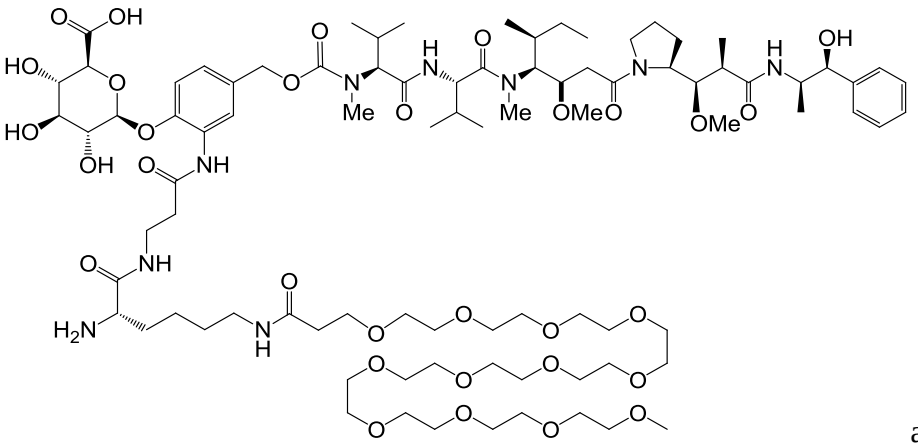
R^2 is H, C_1-C_4 alkyl, or $–CH_2$-R^3;

R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl;

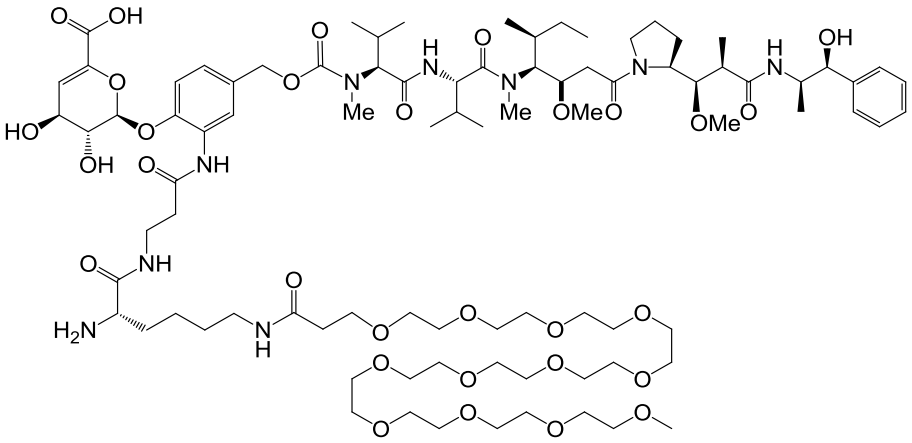
T is selected from the group consisting of $–CH(OR^4)$-R^5 and -C(=O)-OR^4, wherein R^4 is H, C_1-C_4 alkyl and R^5 is C_6-C_{10} aryl or C_3-C_6 heteroaryl, and subscript n ranges from 2 to 24, or

R^2 is hydrogen; and T is$–CH(OR^4)$-R^5; wherein R^4 is hydrogen or methyl and R^5 is C_6-C_{10} aryl, or R^2 is H, and T is–CH(OH)-Ph and subscript n is 8 or 12, and the remaining variable groups are as defined in the claim, or

the Formula **8** Drug Linker intermediate compound and the Formula **8A** compound, optionally in salt forms, have the structures of:

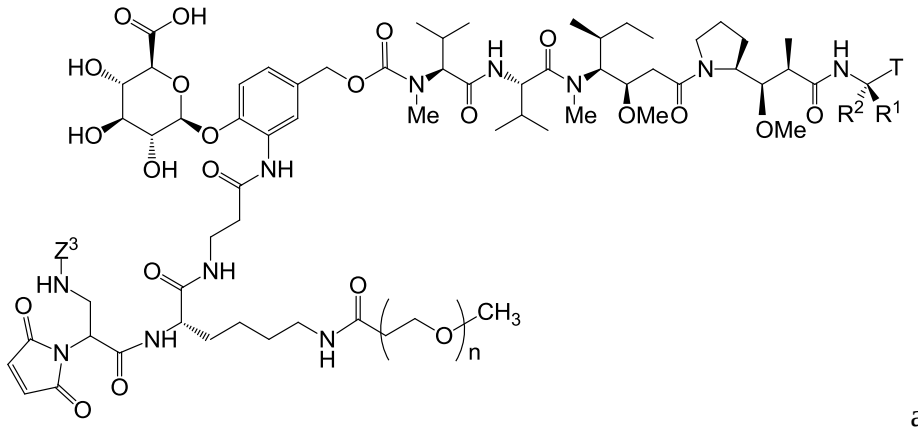


and

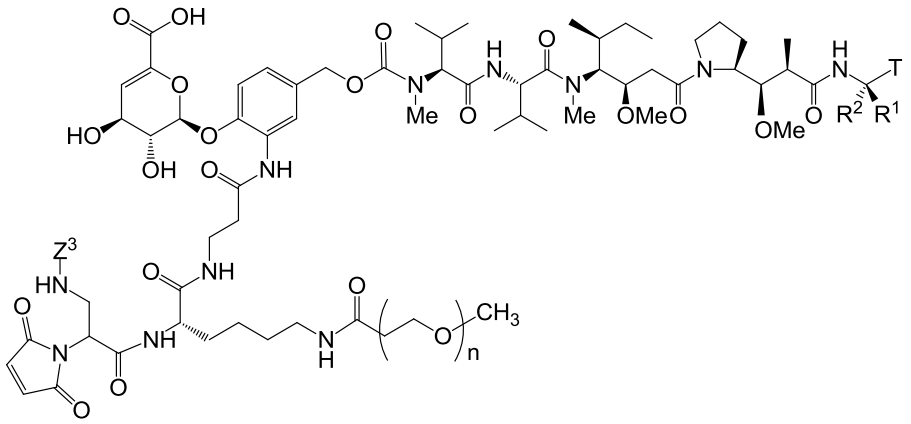


respectively.

40. The composition of claim **35**, wherein the Formula **9** and Formula **9A** compound, optionally in salt forms, have the structures of:



and



,

wherein in both structures:

Z^3 is –C(=O)O-t-Bu;

R^1 is H or C_1-C_4 alkyl;

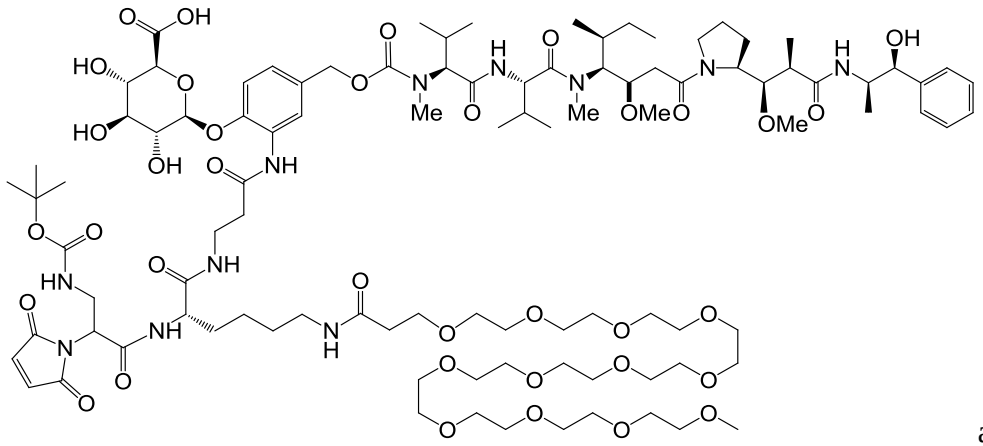
R^2 is H, C_1-C_4 alkyl, or $–CH_2$-R^3;

R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl; and

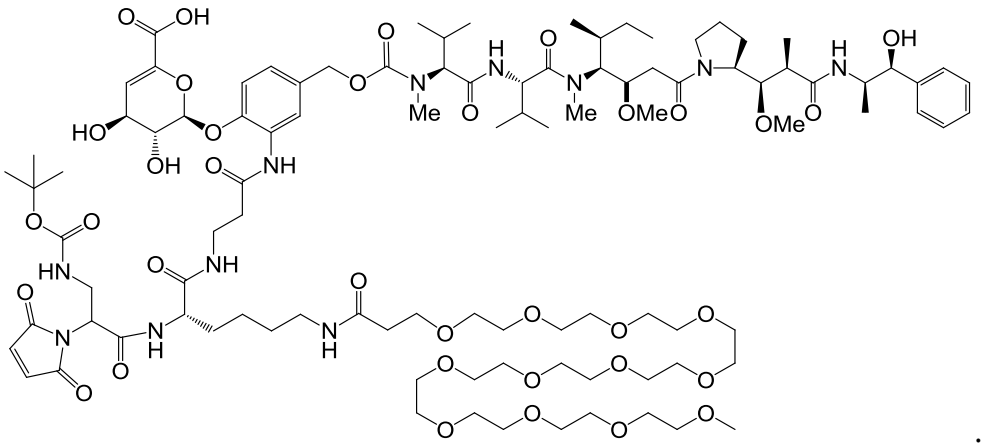
T is selected from the group consisting of $–CH(OR^4)$-R^5 and -C(=O)-OR^4, wherein R^4 is H, C_1-C_4 alkyl and R^5 is C_6-C_{10} aryl or C_3-C_6 heteroaryl, and

subscript n is from 2 to 24, or R^2 is hydrogen; and T is$–CH(OR^4)$-R^5; wherein R^4 is hydrogen or methyl and R^5 is C_6-C_{10} aryl, more particularly R^2 is H, and T is–CH(OH)-Ph, and/or subscript n is 8 or 12, and the remaining variable groups are as previously described, or

the Formula **9** Drug Linker intermediate compound and the Formula **9A** compound, optionally in salt forms, have the structures of:

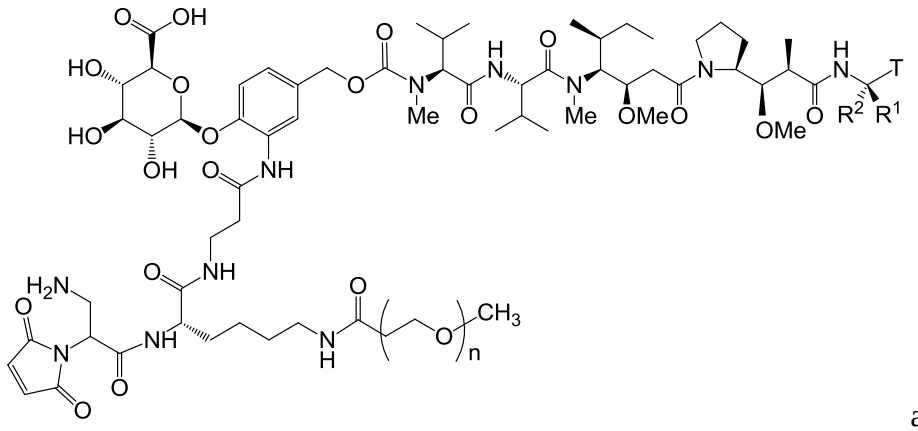


and

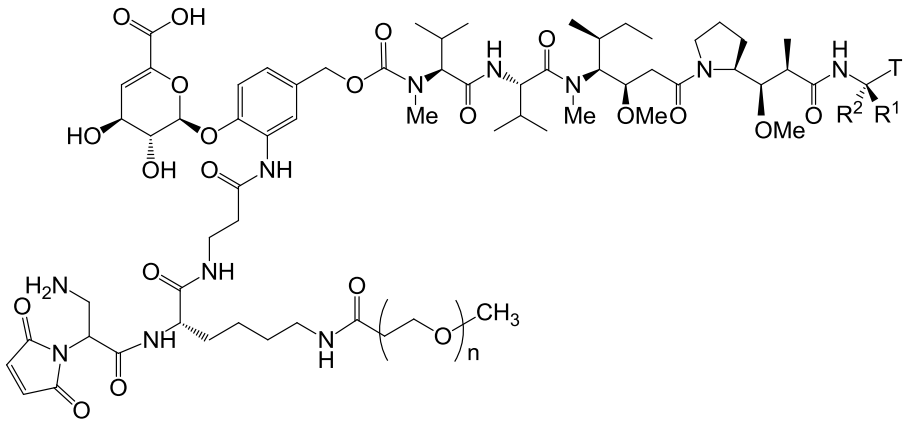


.

41. The composition of claim **36**, wherein the Formula **10** Drug Linker compound and the Formula **10A** compound, optionally in salt forms, have the structures of:



and



,

wherein

R^1 is H or C_1-C_4 alkyl;

R^2 is H, C_1-C_4 alkyl, or $–CH_2$-R^3;

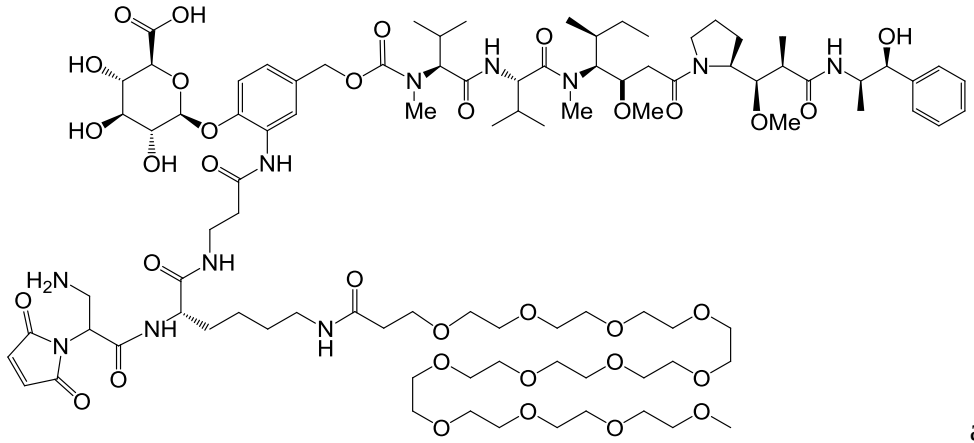
R^3 is C_6-C_{10} aryl or C_3-C_8 heterocyclyl; and

T is selected from the group consisting of –CH(OR^4)-R^5 and -C(=O)-OR^4, wherein R^4 is H, C$_1$-C$_4$ alkyl and R^5 is C$_6$-C$_{10}$ aryl or C$_3$-C$_6$ heteroaryl, and

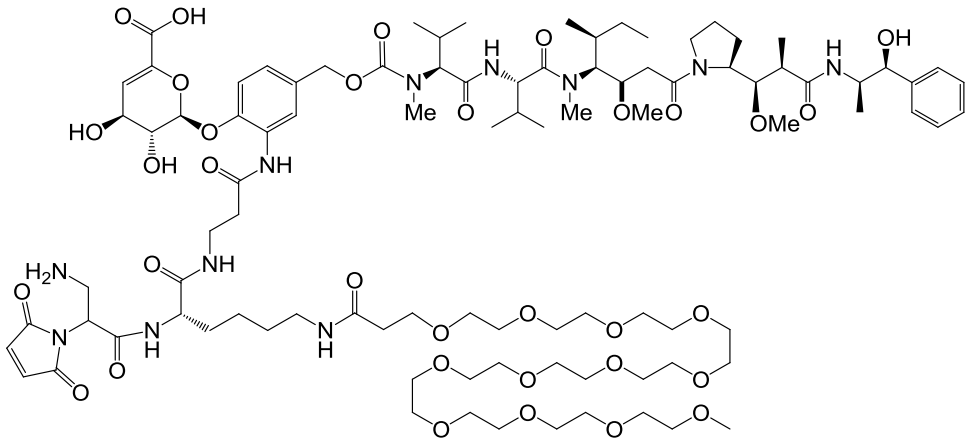
subscript n is from 2 to 24, or

R^2 is hydrogen; and T is–CH(OR^4)-R^5; wherein R^4 is hydrogen or methyl and R^5 is C$_6$-C$_{10}$ aryl, R^2 is H, and T is–CH(OH)-Ph and subscript n is 8 or 12, and the remaining variable groups are as previously defined in the claim, or

the Formula **10** Drug Linker compound and the Formula **10A** compound, optionally in salt forms, have the structures of:



and

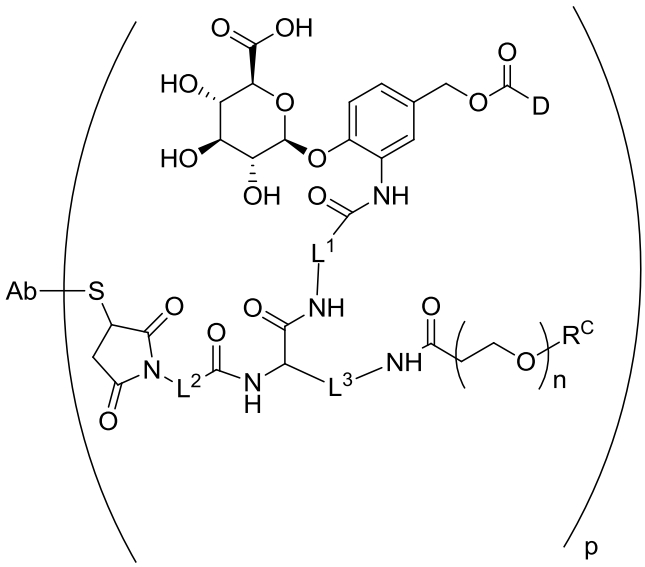


respectively.

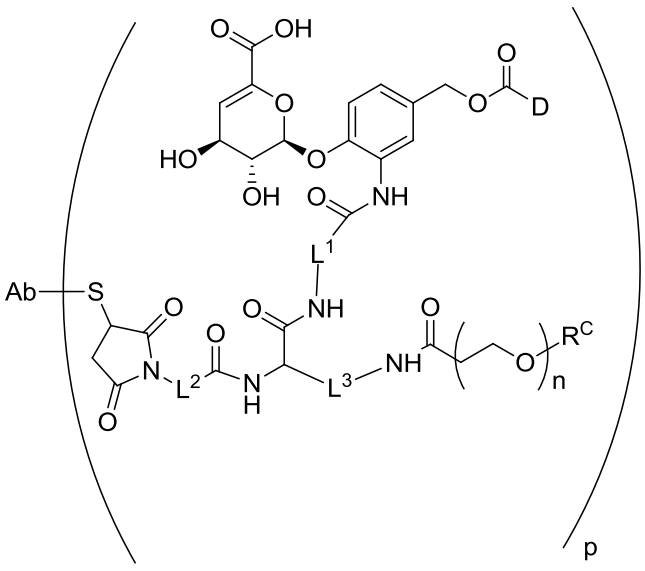
, ,

, ,

42. A composition comprising Antibody Drug Conjugates represented by Formula **11** and Formula **11A** having the structures of:



(**11**) and



(**11A**)

or pharmaceutically acceptable salts thereof, wherein in Formula 11 and Formula 11A:

Ab is an antibody;

S is a sulfur atom from the antibody;

D is an auristatin Drug Unit;

L^1, L^2 and L^3, independently are selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

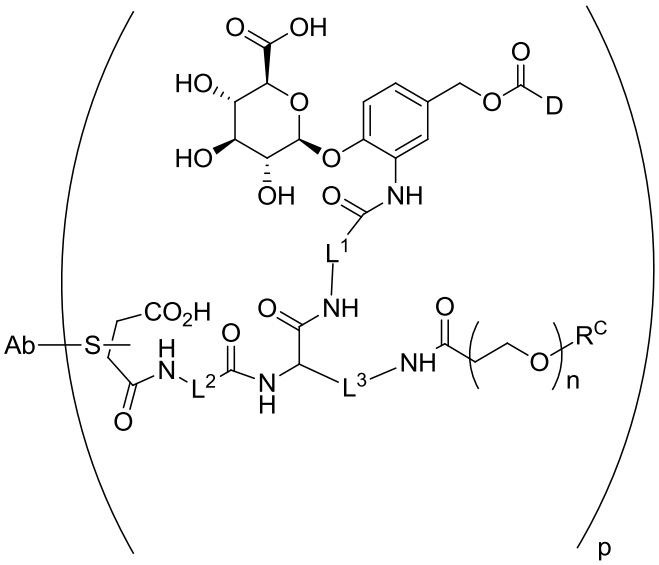
R^C is a PEG Capping Unit;

subscript n is from 2 to 24; and

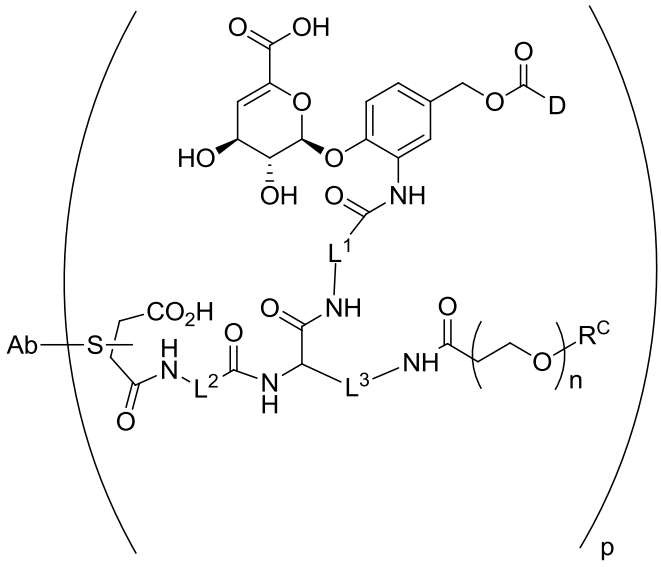
subscript p is from 1 to 16,

wherein the composition contains no more than 5 wt.%, of Formula **11A** Antibody Drug Conjugate.

43. A composition comprising Antibody Drug Conjugates represented by Formula **12** and Formula **12A**, optionally in pharmaceutically acceptable salt forms, having the structures of:



(**12**) and



(**12A**)

wherein in Formula 12 and Formula 12A:

Ab is an antibody;

S is a sulfur atom from the antibody;

the Ab-S- moeity is attached to the carbon atom α or β to the carboxylic acid functional group

D is an auristatin Drug Unit;

L^1, L^2 and L^3, independently are selected from the group consisting of optionally substituted C_1-C_{20} alkylene, optionally substituted C_4-C_{20} heteroalkylene, optionally substituted C_3-C_8 carbocyclo, optionally substituted C_6-C_{10} arylene, optionally substituted C_5-C_{10} heteroarylene and optionally substituted C_3-C_8 heterocyclo;

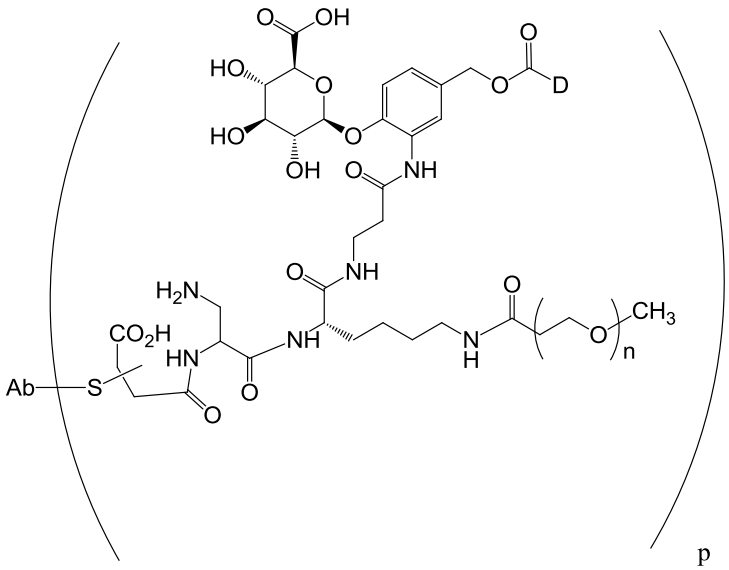
R^C is a PEG Capping Unit;

subscript n is from 2 to 24; and

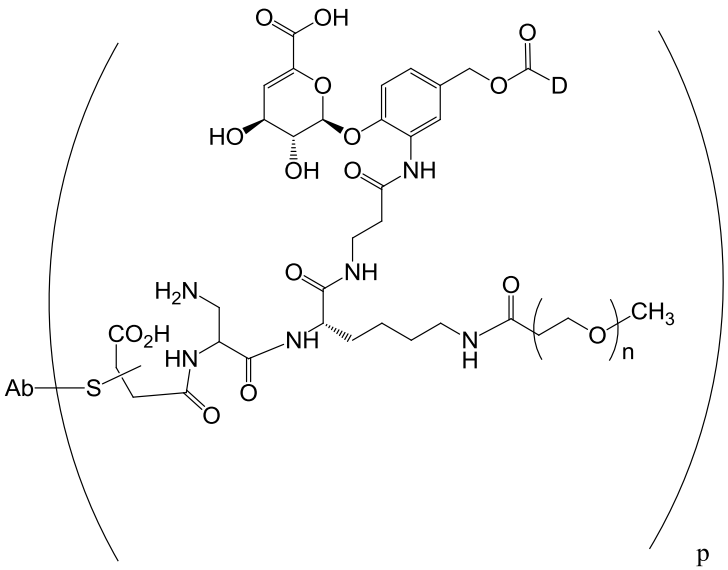
subscript p is from about 1 to about 16,

wherein the composition contains no more than 5 wt.% Formula **12A** Antibody Drug Conjugate, or

the Formula **12** and Formula **12A** Antibody Drug Conjugates, optionally in pharmaceutically acceptable salt forms, have the structures of:



p and



p

respectively, wherein Ab is an antibody;

S is a sulfur atom from the antibody;

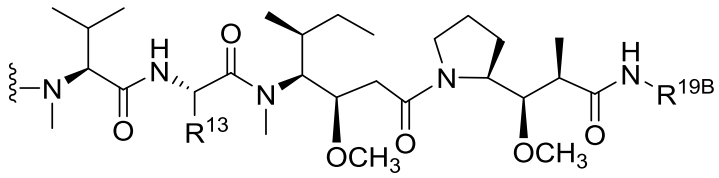
the Ab-S- moeity is attached to the carbon atom α or β to the carboxylic acid functional group; and

the remaining variable groups are as previously defined by the claim,

wherein the composition contains no more than 5 wt.% Formula **12A** Antibody Drug Conjugate.

44. The composition or compound of claim **42** or **43**, wherein the auristatin Drug Unit has the has any one of the structures of claim **9**, or wherein the auristatin Drug Unit

has the structure of Formula $\mathbf{D_{F/E\text{-}3}}$:



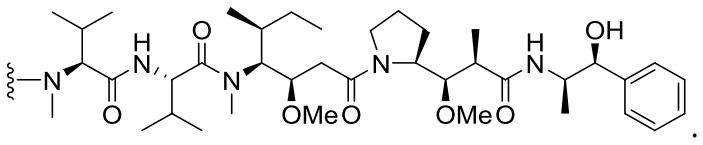
(**$D_{F/E\text{-}3}$**),

wherein

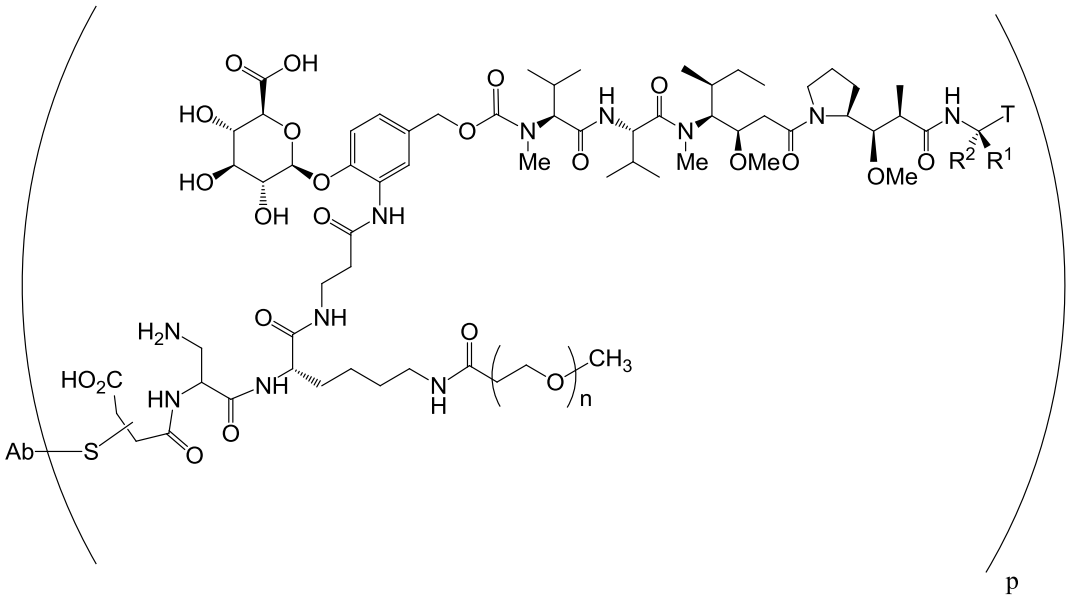
R^{13} is isopropyl or $–CH_2\text{-}CH(CH_3)_2$; and

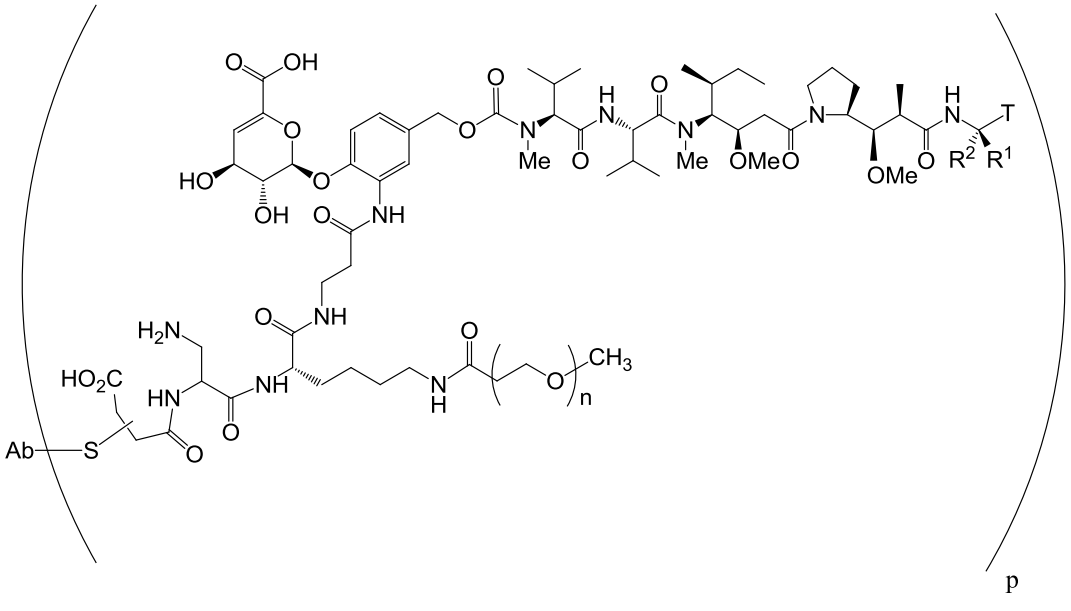
R^{19B} is $–CH(CH_3)\text{-}CH(OH)Ph$, $\text{-}CH(CO_2H)CH_2Ph$, $\text{-}CH(CH_2Ph)$-2-thiazole, $\text{-}CH(CH_2Ph)$-2-pyridyl, $\text{-}CH(CH_2\text{-}p\text{-}Cl\text{-}Ph)$, $\text{-}CH(CO_2Me)\text{-}CH_2Ph$, $\text{-}CH(CO_2Me)\text{-}CH_2CH_2SCH_3$, $CH(CH_2CH_2SCH_3)C(=O)$NH-3-quinolyl, or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

wherein the auristatin Drug Unit has the structure of:



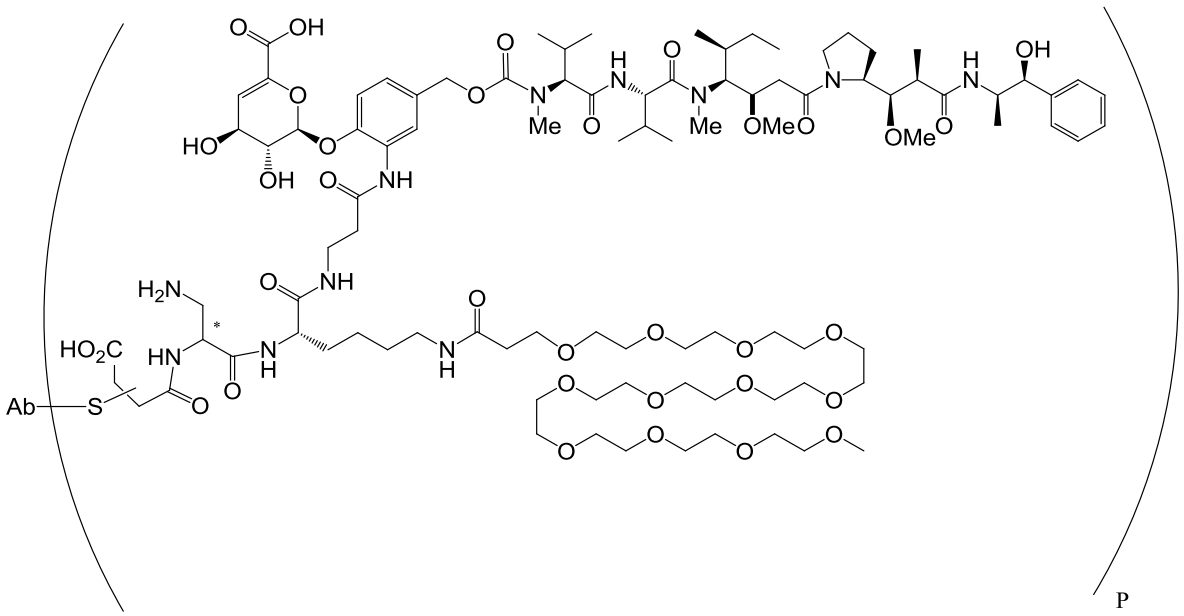
45. The composition of claim **43**, wherein the Formula **12** and Formula **12A** Antibody Drug Conjugates, optionally in pharmaceutically acceptable salt forms, have the structures of:

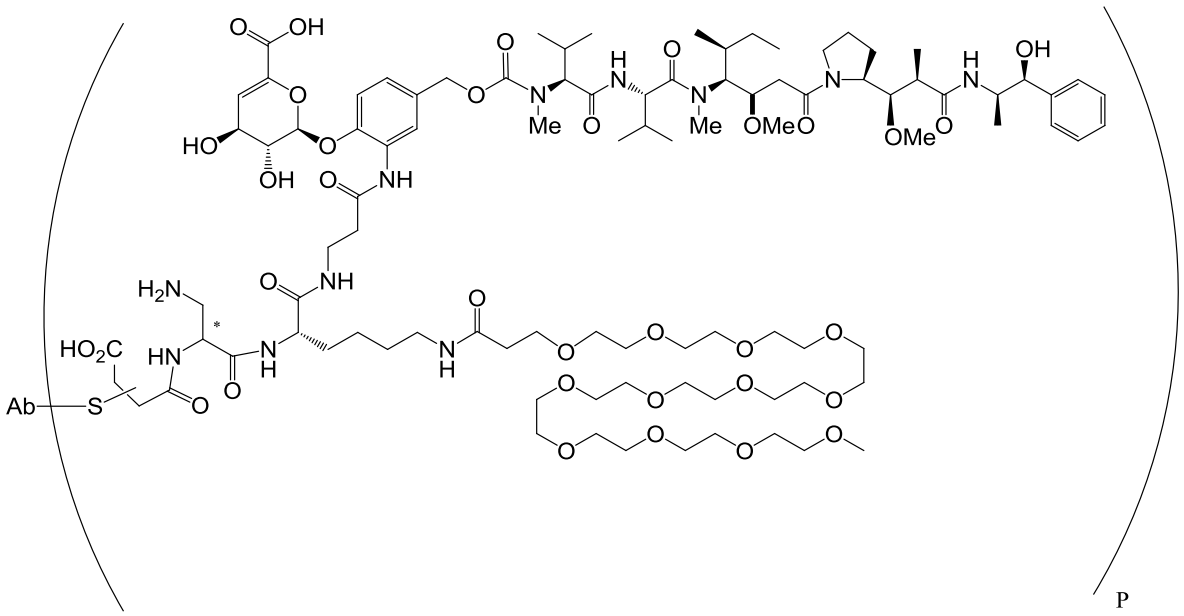




respectively, or

the Formula **12** and Formula **12A** Antibody Drug Conjugates, optionally in pharmaceutically acceptable salt forms, have the structures of:





respectively, wherein the indicated carbon atom (*) is predominately in the S configuration, and subscript p is 8.

46. The composition of any one of claims **42-45**, wherein the antibody is capable of selectively binding to a tumor associated antigen.

47. The composition of claim **46**, wherein the tumor associated antigen is comprised of an extracellular domain of a cell-surface protein or glycoprotein to which the antibody is capable of binding, or

wherein the tumor associated antigen is comprised of an extracellular domain of a cell-surface glycoprotein that is capable of internalization upon binding by an Antibody Drug Conjugate compound of the composition.

48. Use of a composition of any one of claims **42**-**47**, in the manufacture of a medicament for the treatment of a haematological malignancy in a subject, or for treatment of a leukemia or lymphoma, or for treatment of a B-cell malignancy.