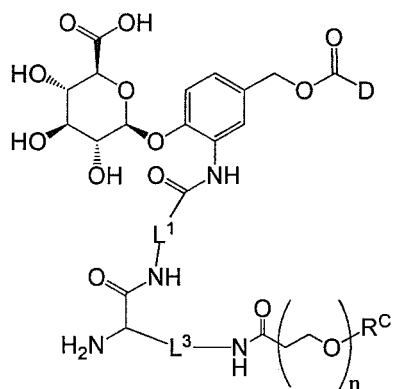


in yield. Therefore, there is a need for improved methods for preparing such Drug Linker compounds with reduced amounts of contaminating impurities, so as to improve purity and yields.

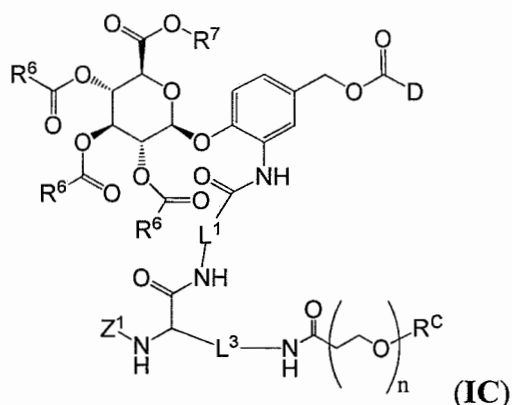
SUMMARY

[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**:



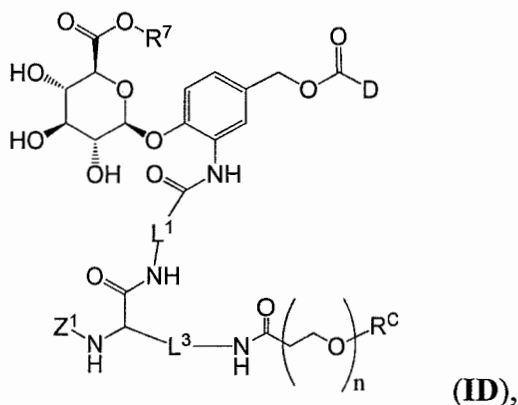
[0011] (IE),

[0012] or a salt thereof, wherein D is an auristatin Drug Unit; each of L¹ and L² is independently selected from the group consisting of optionally substituted C₁-C₂₀ alkylene, optionally substituted C₄-C₂₀ heteroalkylene, optionally substituted C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ heterocyclo; R⁷ is optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene so-OR⁷ 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:



[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**:



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;

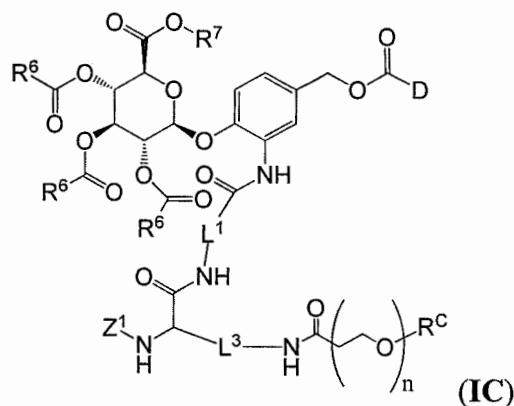
Z^1 is a first suitable amino protecting group;

R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

the method comprising the step of:

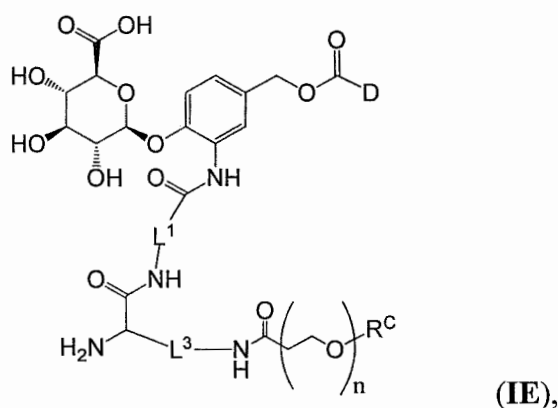
(c) contacting a Drug Linker intermediate compound of Formula **IC** with either a Grignard reagent or an alkoxy magnesium halide in a suitable alcohol-containing solvent, wherein the Formula **IC** Drug Linker intermediate compound has the structure of:



wherein each of R⁶ is independently optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene so that R⁶C(=O)- provides for an ester functional group that is a suitable hydroxyl protecting group; and 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 **IC** compound.

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



or a salt thereof,

wherein D is an auristatin Drug Unit,

each of L¹ and L² is independently selected from the group consisting of optionally substituted C₁-C₂₀ alkylene, optionally substituted C₄-C₂₀ heteroalkylene, optionally

substituted C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ heterocyclo;

R⁷ is optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene so—OR⁷ provides an ester functional group that is a suitable carboxylic acid protecting group;

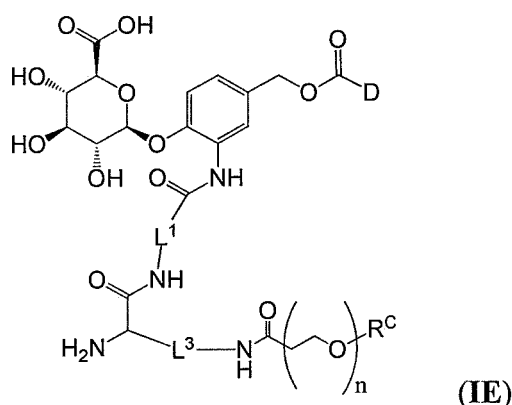
R^C is a PEG Capping Unit; and

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 Z¹ 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**:



or a salt thereof,

wherein D is an auristatin Drug Unit,

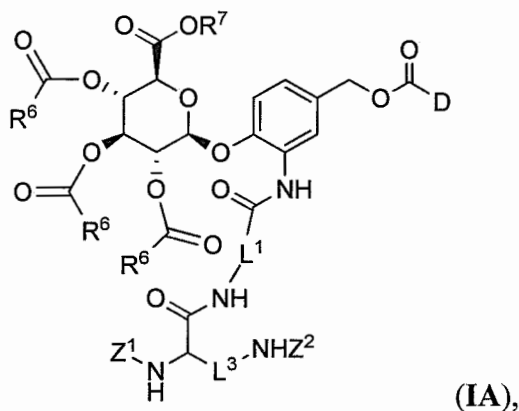
each of L¹ and L³ is independently selected from the group consisting of optionally substituted C₁-C₂₀ alkylene, optionally substituted C₄-C₂₀ heteroalkylene, optionally substituted C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ 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 :



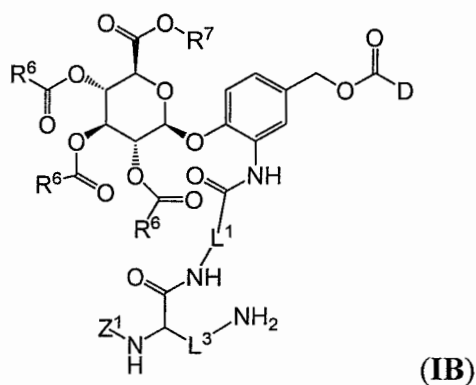
or a salt thereof, wherein

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

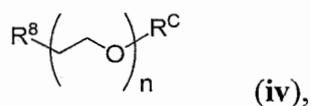
the remaining variable groups as previously defined,

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



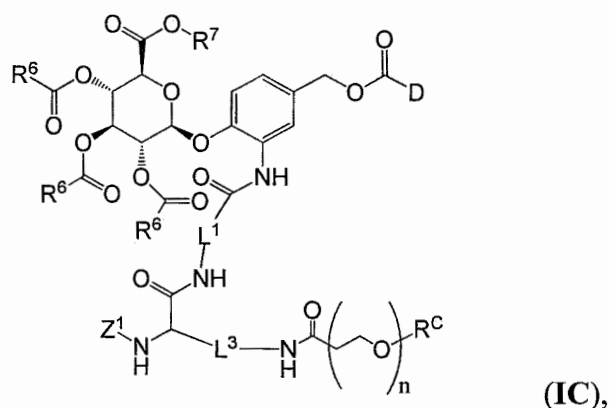
or a salt thereof, wherein the variable groups are as previously defined;

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



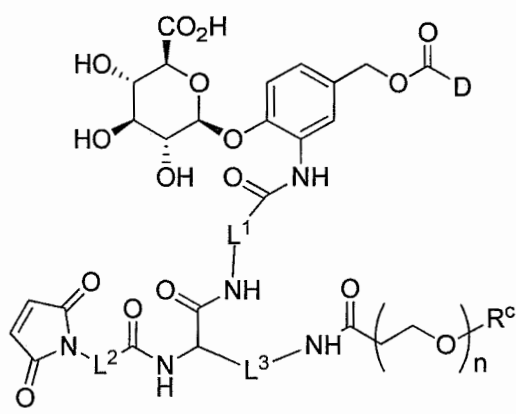
wherein R^8 is an activated ester group; and the remaining variable groups are as previously defined, or

(b') contacting the Formula **IB** Drug Linker intermediate compound in a suitable solvent with a Formula **iv** compound in which R^8 is $-\text{COOH}$ 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:



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**:

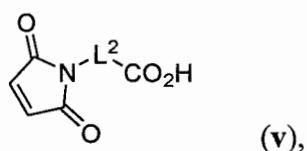


or a salt thereof,

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;

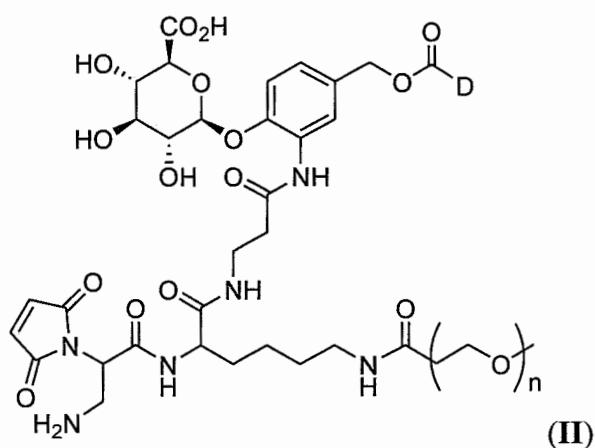
R^C is a PEG Capping Unit; and
 subscript n ranges from 2 to 24,
 the method comprising steps (a)-(d) disclosed herein, followed by the step of:
 (e) contacting the Formula **IE** Drug Linker intermediate compound in a suitable
 solvent with a compound of Formula **v**:



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**:



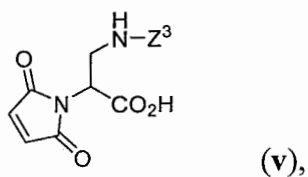
or a salt thereof,

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:



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 **IIIE**, Formula **IIIF**:



wherein

each of R⁶ and R⁷ is independently optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene so that R⁶C(=O)- provides for an ester functional group that is a suitable hydroxyl protecting group and – OR⁷ provides an ester functional group that is a suitable carboxylic acid protecting group;

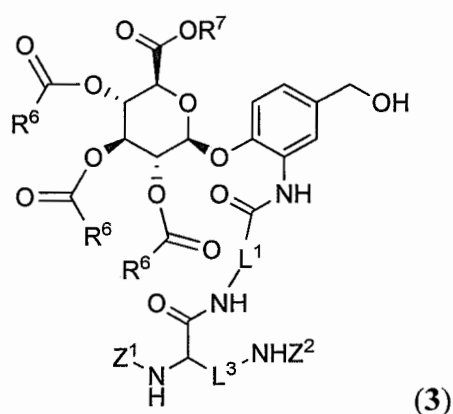
each of Z^1 , Z^2 and Z^3 is independently a first, second and third suitable amino protecting group, respectively

in particular Z^3 is an acid-labile amino protecting group, more particularly $-C(=O)O-t-Bu$,

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:



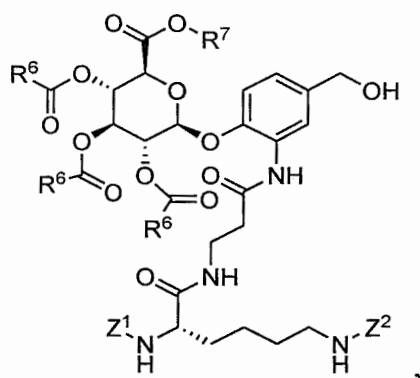
or a salt thereof, wherein

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, in particular 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,

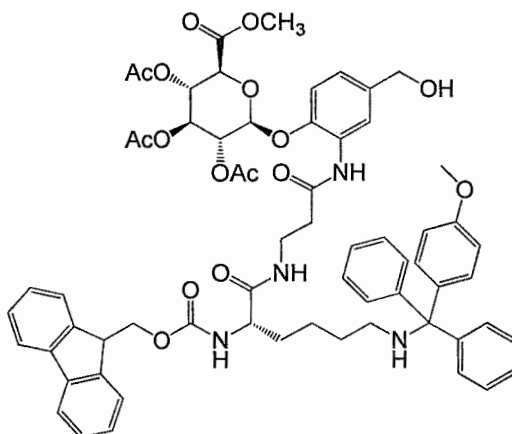
in particular, each R^6 is C_1-C_4 alkyl or optionally substituted phenyl and/or R^7 is methyl or ethyl, more particularly R^6 and R^7 are each methyl, or

Formula **3** has the structure of:

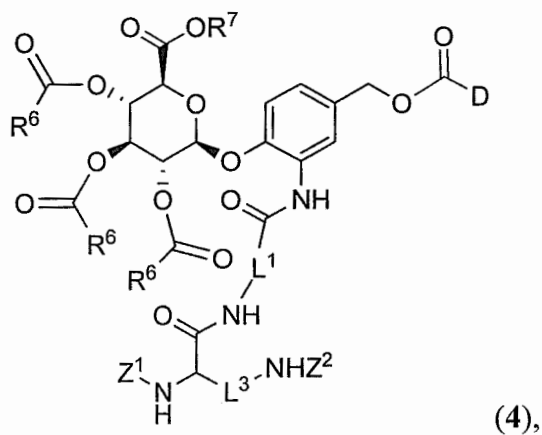


wherein Z^1 and Z^2 independently are a first and second suitable amino protecting group,

in particular, Z^1 and/or Z^2 is fluorenylmethyloxy carbonyl (Fmoc) and/or 4-methoxy trityl (MMTr), more particularly, 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:



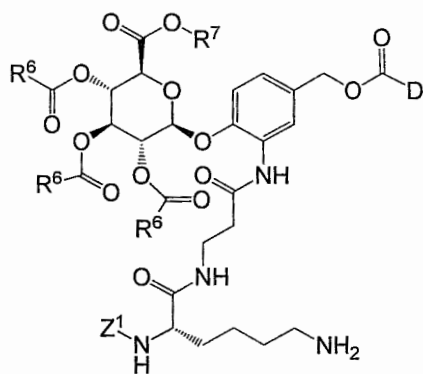
or a salt thereof, wherein

D is an auristatin Drug Unit;

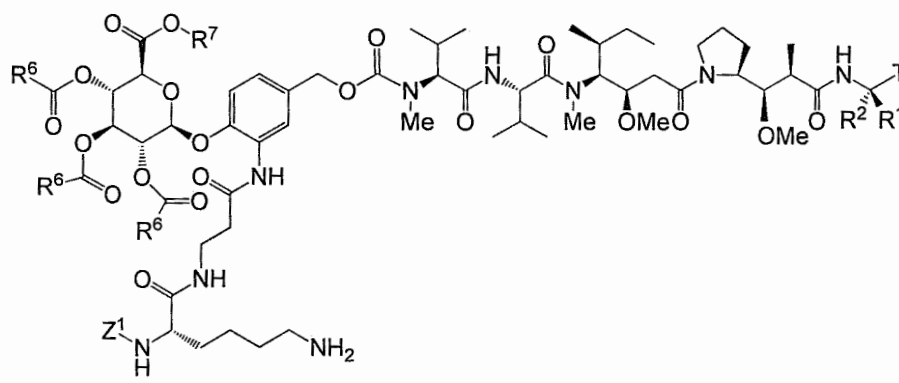
each of R⁶ and R⁷ is independently optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene so that R⁶C(=O)- provides for an ester functional group that is a suitable hydroxyl protecting group and – OR⁷ provides an ester functional group that is a suitable carboxylic acid protecting group; and

The chemical structure shows a central sugar ring (likely a pyranose) with several substituents. At the top, there is a group R^7 attached via an ester linkage. To the left, there are two R^6 groups attached via ester linkages. To the right, there is a group D attached via an ester linkage. The sugar ring is also connected to a side chain that includes an amide group (NH) and a chain ending in Z^1 and Z^2 groups.

R¹ is H or C₁-C₄ alkyl;



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



wherein

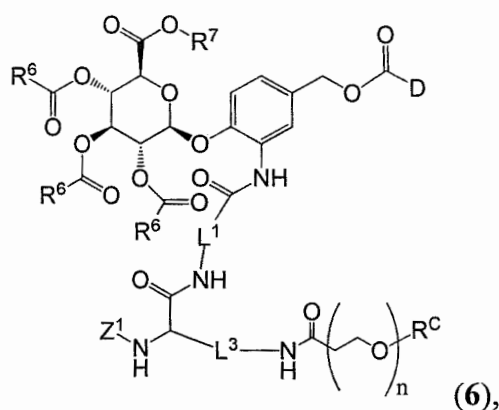
R^1 is H or C_1 - C_4 alkyl;

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:



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;

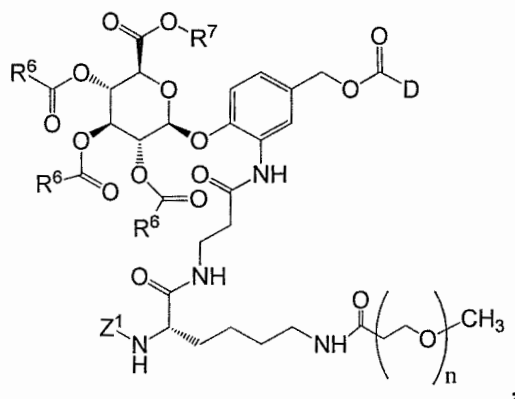
each of R^6 and R^7 is independently optionally substituted C_1 - C_8 alkyl, optionally substituted C_6 - C_{10} arylene or optionally substituted C_5 - C_{10} heteroarylene so that $R^6C(=O)-$ provides for an ester functional group that is a suitable hydroxyl protecting group and $-OR^7$ provides an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

Z^1 is a first suitable amino protecting group;

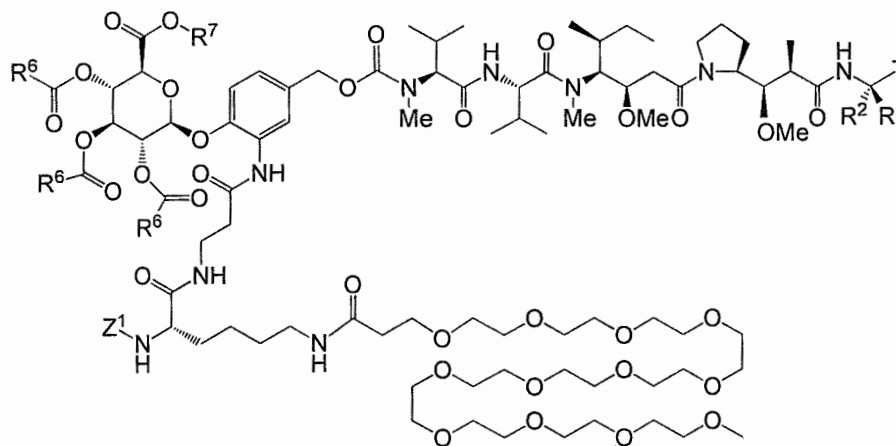
R^C is a PEG Capping Unit; and

subscript n ranges from 1 to 24,

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



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



wherein

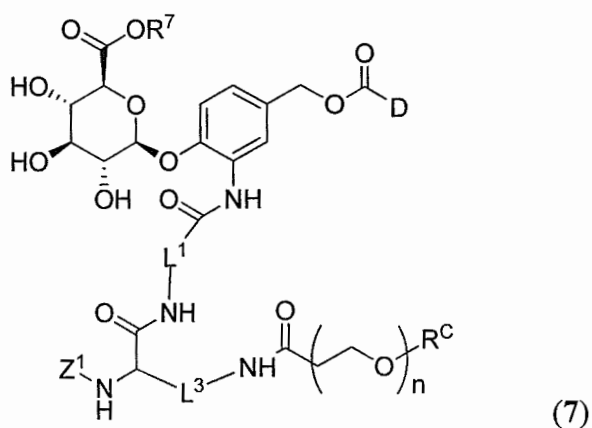
R^1 is H or C_1 - C_4 alkyl;

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 comprising a Drug Linker intermediate of Formula 7 having the structure of:



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;

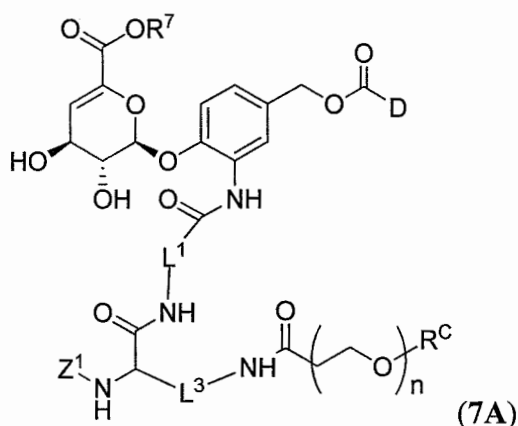
R^7 is optionally substituted C_1 - C_8 alkyl, optionally substituted C_6 - C_{10} arylene or optionally substituted C_5 - C_{10} heteroarylene so $-OR^7$ provides an ester functional group that is a suitable carboxylic acid protecting group, in particular R^7 is methyl;

Z^1 is a first suitable amino protecting group;

R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

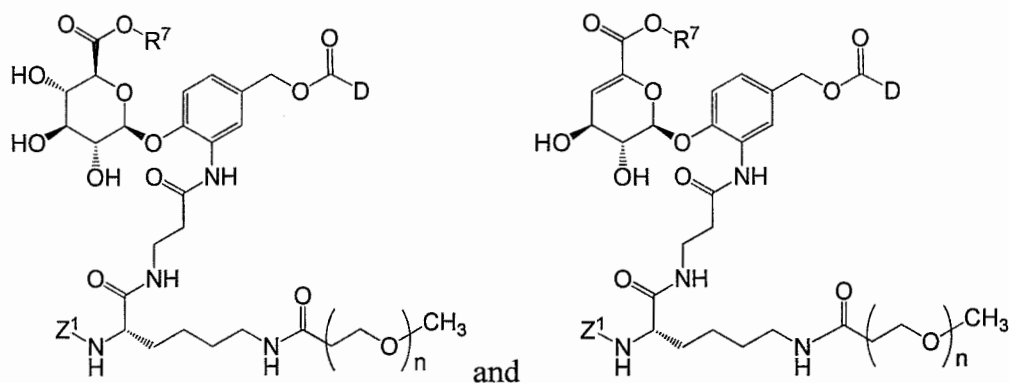
the composition further comprising no more than about 10 wt.%, in particular no more than about 5 wt.%, of a Drug Linker intermediate compound of Formula 7A having the structure of:



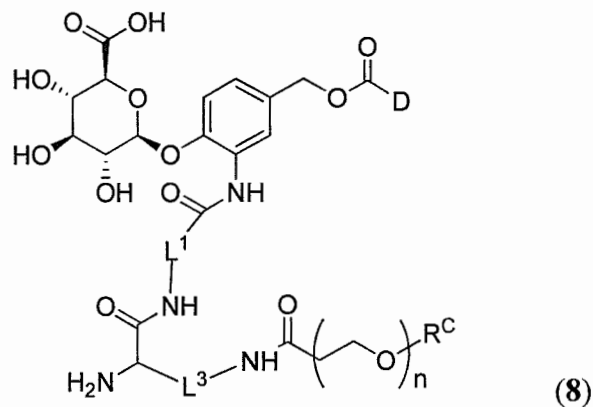
or a salt thereof,

wherein the variable groups are as previously defined,

in particular, Z^1 is Fmoc and/or the Formula 7 and Formula 7A Drug linker intermediate compounds, optionally in salt form, have the structures of:



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



or a salt thereof,

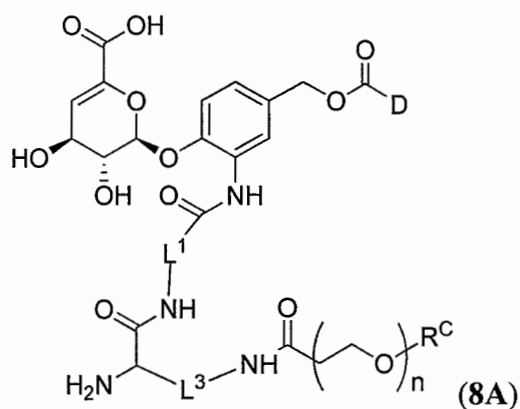
wherein D is an auristatin Drug Unit,

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,

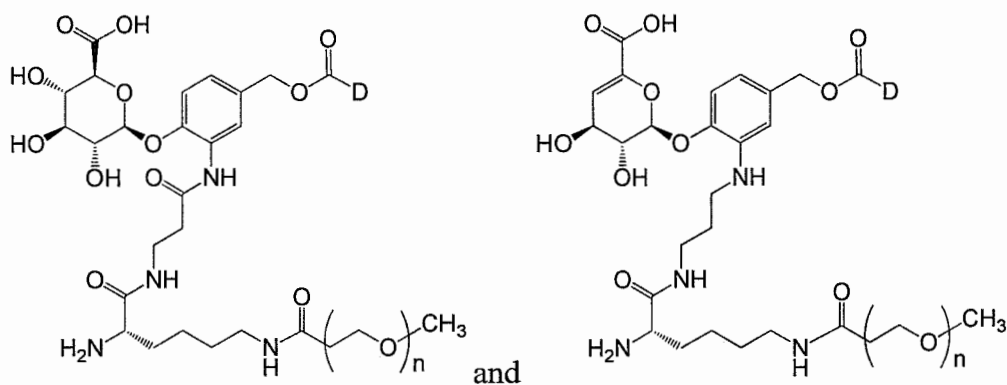
the composition further comprising no more than about 10 wt.%, in particular no more than about 5 wt.%, more particularly, no more than between about 3 wt.% and 4 wt.%, of a Drug Linker intermediate compound of Formula **8A** having the structure of:



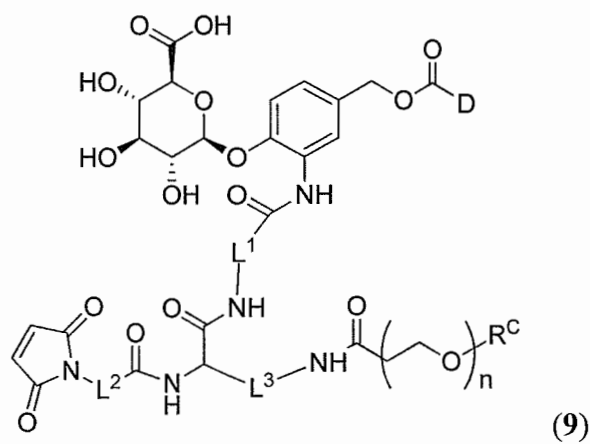
or a salt thereof,

wherein the variable groups are as previously defined,

in particular, the Formula 8 and Formula 8A Drug Linker intermediate compounds, optionally in salt form have the structures of:



[00131] In another aspect, there is provided a composition comprising a Drug Linker intermediate or Drug Linker compound of Formula 9 having the structure of:



or a salt thereof,

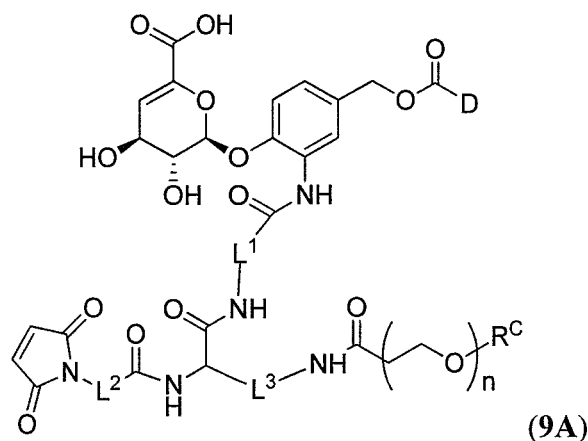
wherein D is an auristatin Drug Unit,

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,

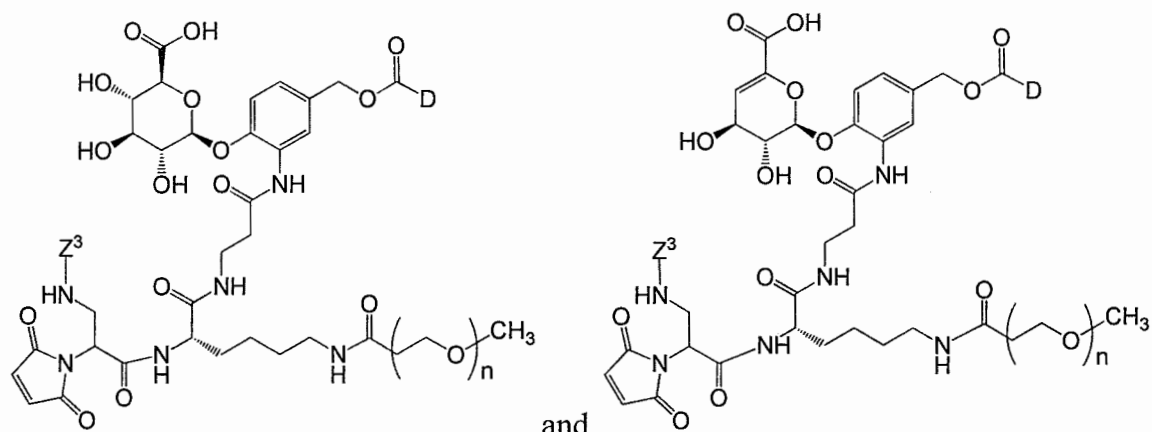
the composition further comprising no more than about 10 wt.%, in particular no more than 5 wt.% of a Drug Linker intermediate or Drug Linker compound of Formula **9A** having the structure of:



or a salt thereof,

wherein the variable groups are as previously defined,

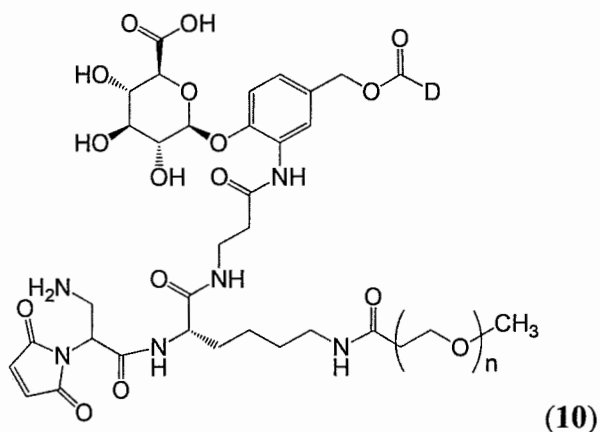
in particular, the Formula **9** and Formula **9A** Drug Linker intermediate or Drug Linker compounds, optionally in salt form, have the structures of:



wherein

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

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

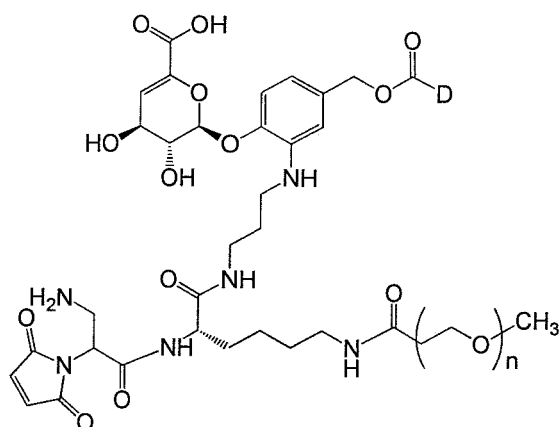


or a salt thereof, wherein

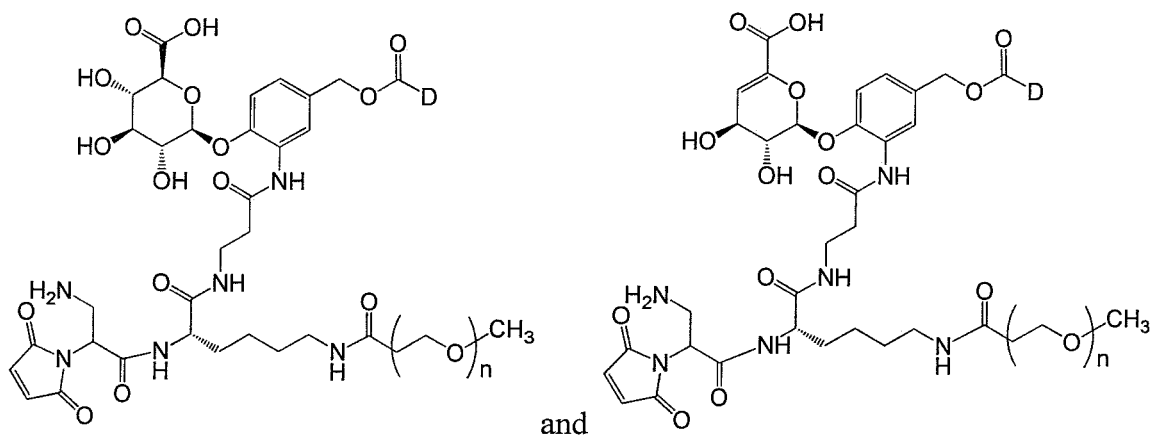
D is an auristatin Drug Unit; and

subscript n ranges from 2 to 24,

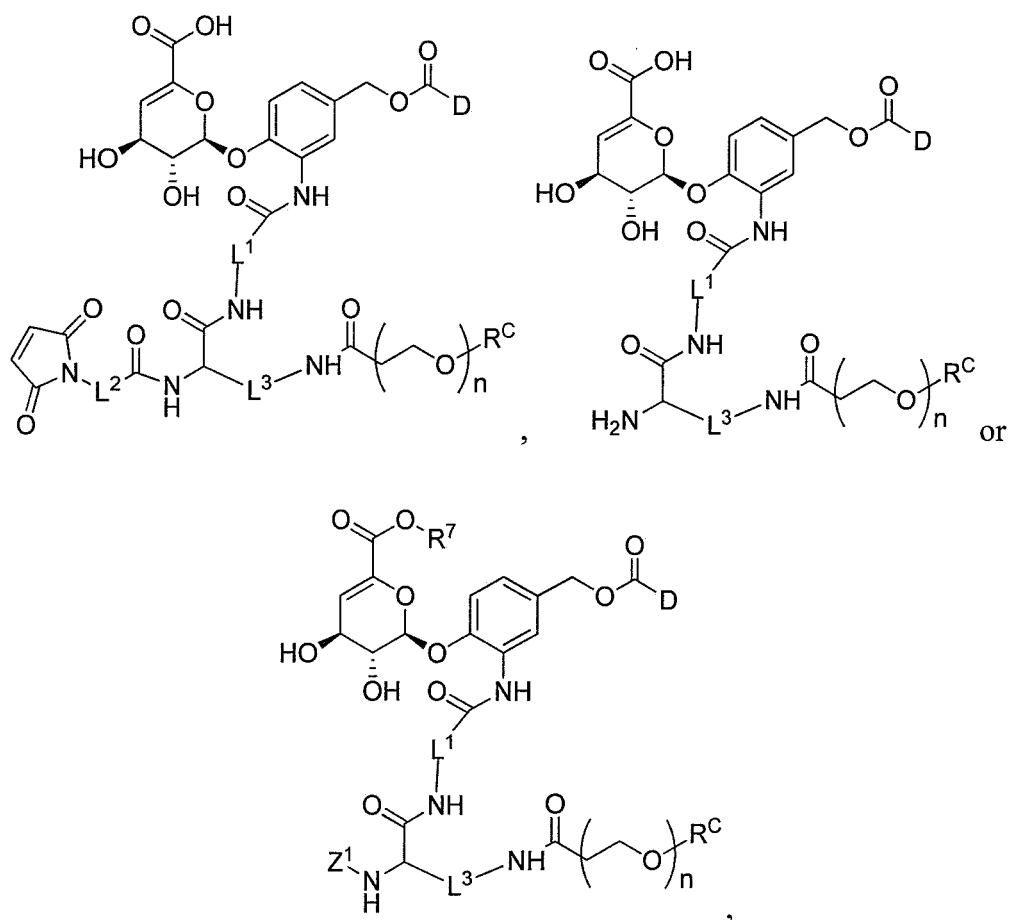
the composition further comprising no more than about 10 wt.%, in particular no more than about 5 wt.%, of a Drug Linker compound of Formula **10A** having the structure of:



or a salt thereof,
 wherein the variable groups are as previously defined,
 in particular, the Formula **10** and Formula **10A** Drug Linker compounds, optionally in salt form, have the structures of:



[0013n] In another aspect, there is provided a Drug Linker intermediate or Drug Linker compound, wherein the Drug Linker intermediate or Drug Linker compound, optionally in salt form, has the structure of:



wherein

D is an auristatin Drug Unit;

L¹, L² and L³, independently are selected from the group consisting of optionally substituted C₁-C₂₀ alkylene, optionally substituted C₄-C₂₀ heteroalkylene, optionally substituted C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ heterocyclo, in particular L¹, L² and L³ are independently C₁-C₄ alkyl and L² is independently optionally substituted C₁-C₄ alkyl;

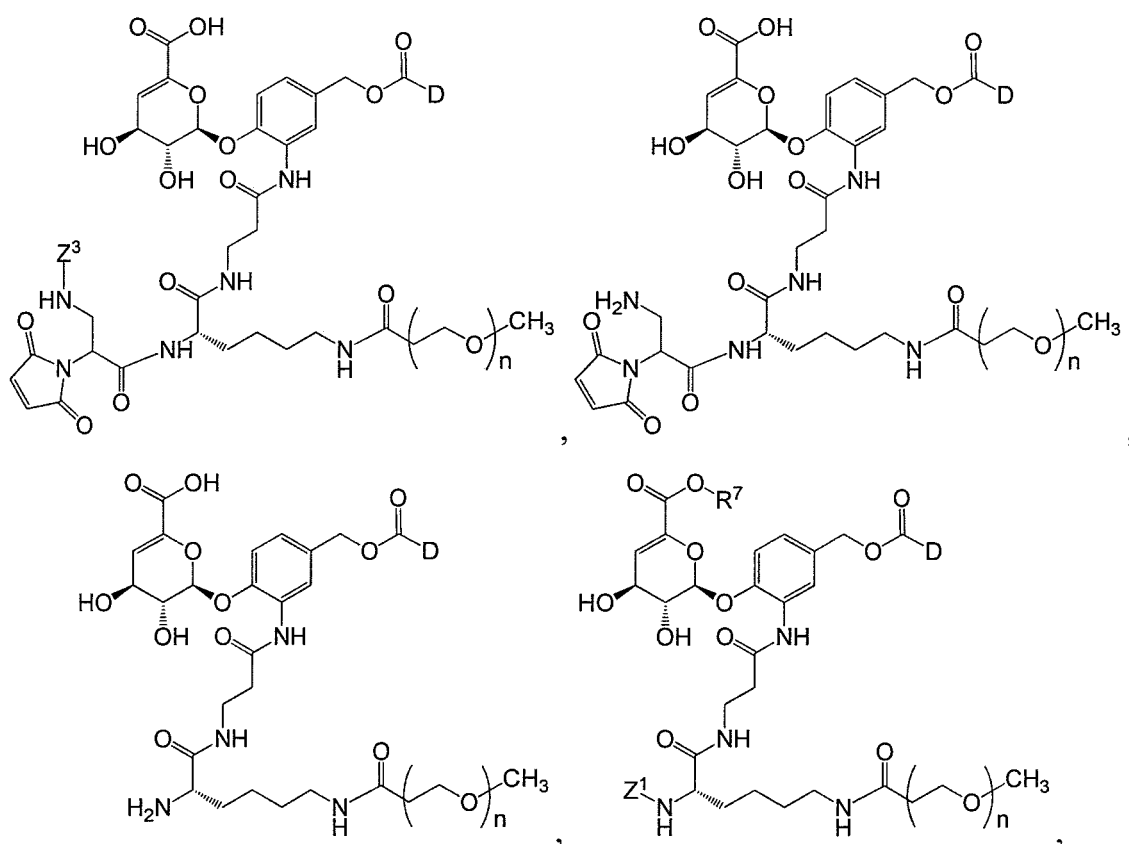
Z¹ is a first suitable amino protecting group;

R⁷ is optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene;

R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

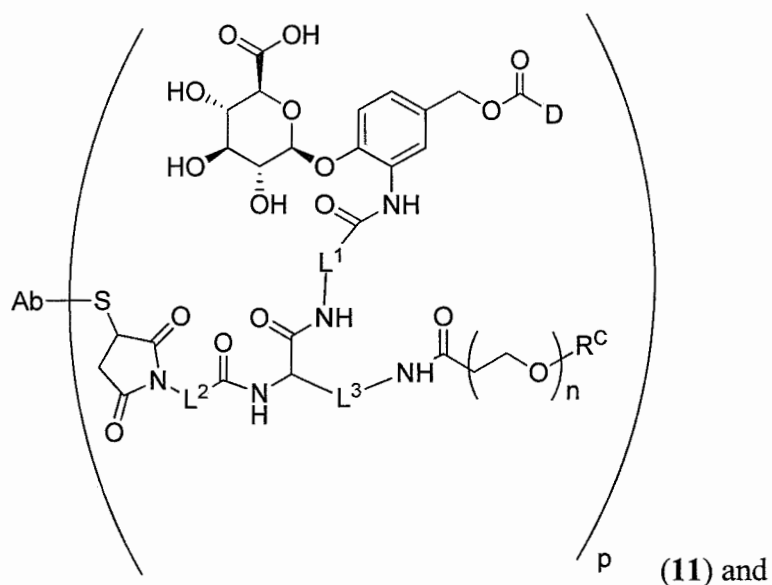
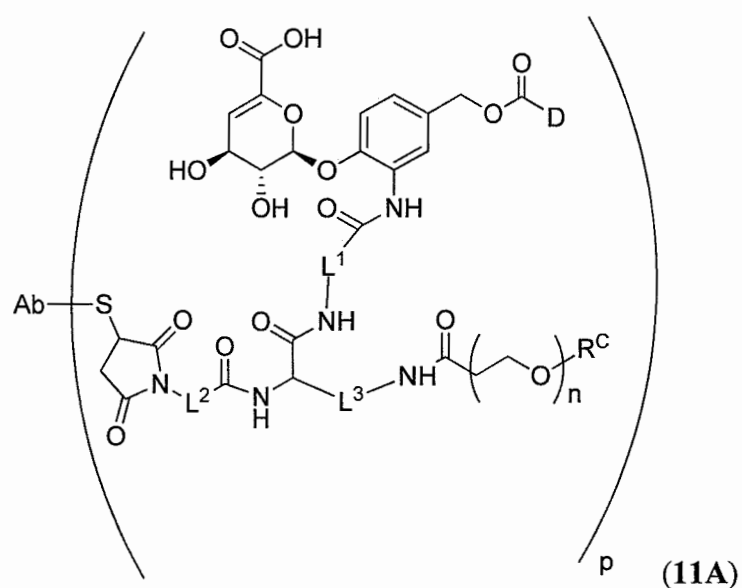
in particular, subscript n is 8 or 12 and/or the Drug Linker intermediate or Drug Linker compound has the structure selected from the group consisting of:



and salts thereof, wherein

Z^3 is an acid-labile amino protecting group, particularly a carbamate having the structure of $-C(=O)O-R^8$, wherein R^8 is C_1 - C_4 alkyl or optionally substituted phenyl; and R_7 is a C_1 - C_4 alkyl, particularly methyl or ethyl.

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



or pharmaceutically acceptable salts thereof, wherein

Ab is an antibody;

S is a sulfur atom from the antibody;

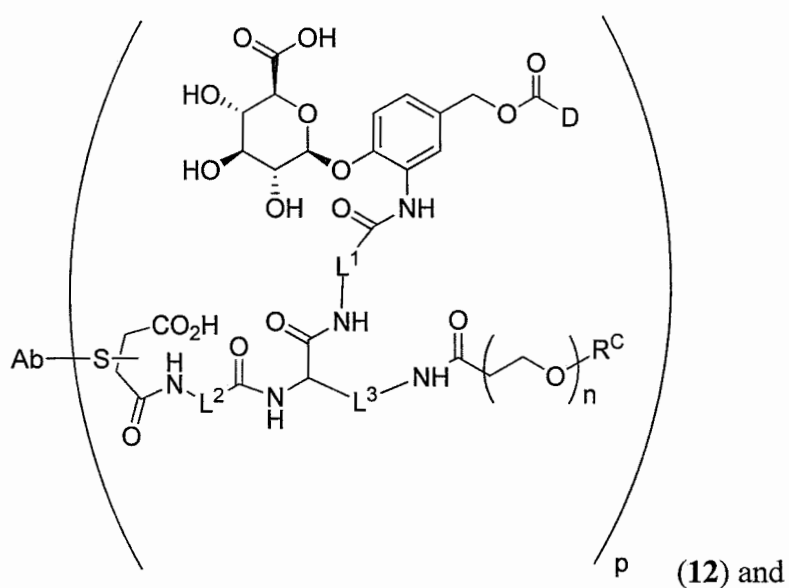
D is an auristatin Drug Unit;

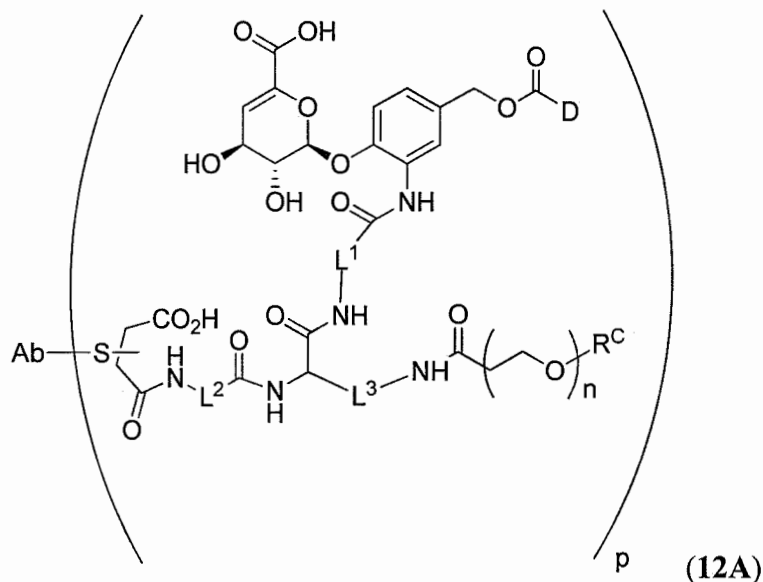
L^1 , L^2 and L^3 , independently are selected from the group consisting of optionally substituted C_1 - C_{20} alkylene, optionally substituted C_4 - C_{20} heteroalkylene, optionally substituted C_3 - C_8 carbocyclo, optionally substituted C_6 - C_{10} arylene, optionally substituted C_5 - C_{10} heteroarylene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

R^C is a PEG Capping Unit;

subscript n ranges from 2 to 24; and
subscript p ranges from about 1 to about 16,
wherein the composition contains no more than 10 wt.%, in particular no more than 5 wt.%, of Formula **11A** Antibody Drug Conjugate.

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



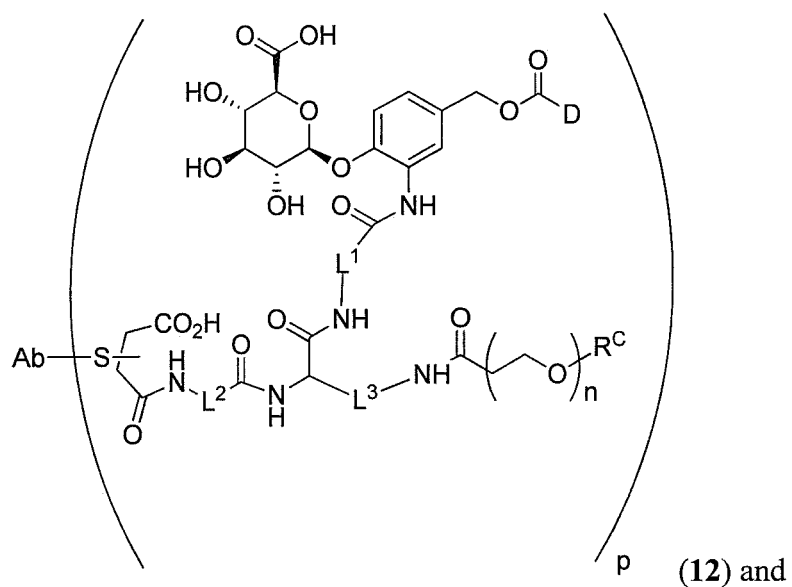
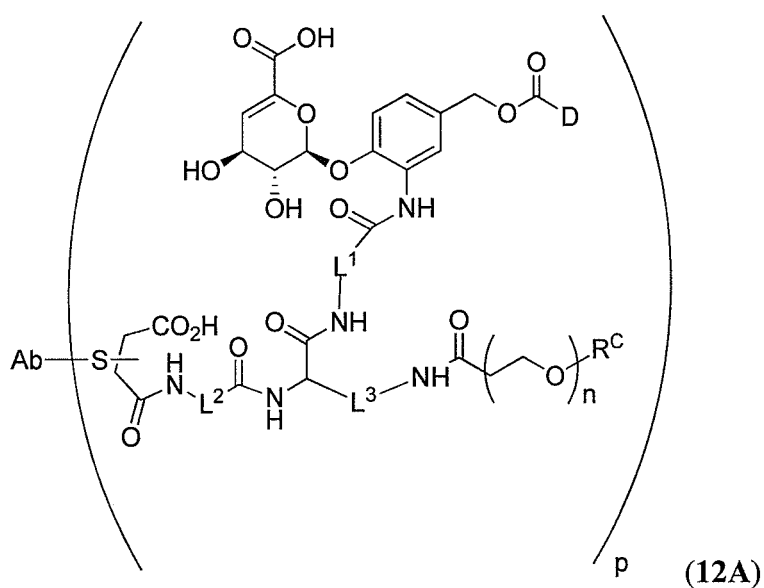


[0016]

[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:



wherein

Ab is an antibody;

S is a sulfur atom from the antibody;

the Ab-S- moiety 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 C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ heterocyclo;

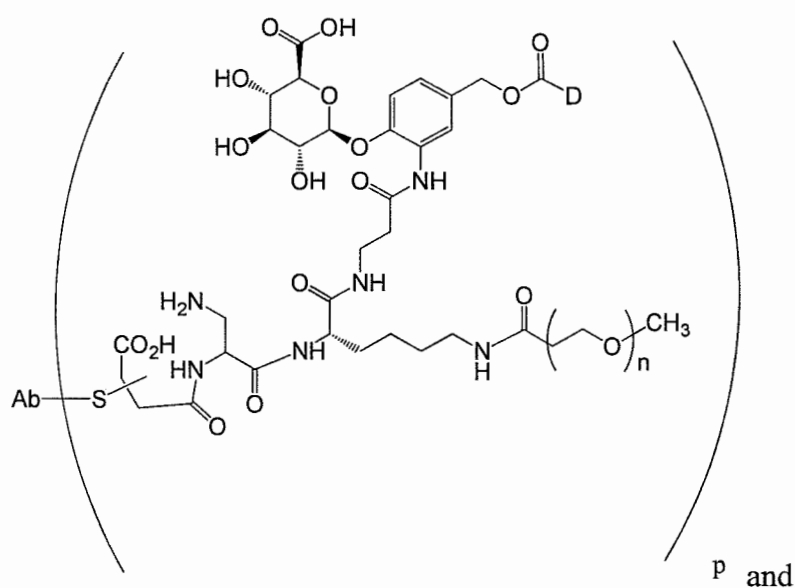
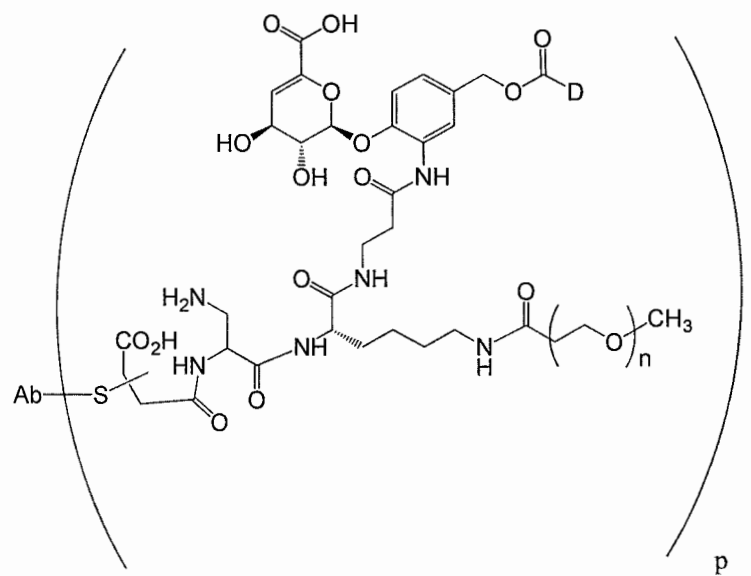
R^C is a PEG Capping Unit;

subscript n ranges from 2 to 24; and

subscript p ranges from about 1 to about 16,

wherein the composition contains no more than 10 wt.% Formula **12A** Antibody Drug Conjugate,

in particular, the Formula **12** and Formula **12A** Antibody drug Conjugates, optionally in pharmaceutically acceptable salt form, have the structures of:



[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, particularly a leukemia or 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 moiety 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 Grignard reagent with the alcohol-

an abnormal cell, more particularly one that is capable of internalization upon binding by an Antibody Drug Conjugate compound of the composition.

50. Use of a composition of any one of claims **44-49**, in the manufacture of a medicament for the treatment of a haematological malignancy in a subject, particularly a leukemia or lymphoma, more particularly a B-cell malignancy.