Cit), that can be hydrolyzed by lysosomal enzymes (such as Cathepsin B) have been used to connect the drug with the antibody (US6214345). They have been particularly useful, due in part to their relative stability in systemic circulation and the ability to efficiently release the drug in tumor. ADCs containing the Val-Cit linker have been shown to be relatively stable in vivo (t1/2 for drug release ~7 days (Doronina et al (2008), Bioconjugate Chem., 19, 1960-1963). However, the chemical space represented by natural peptides is limited; therefore, it is desirable to have a variety of non-peptide linkers which act like peptides and can be effectively cleaved by lysosomal proteases. The greater diversity of non-peptide structures may yield novel, beneficial properties that are not afforded by the peptide linkers. Provided herein are different types of non-peptide linkers for ADC that can be cleaved by lysosomal enzymes.

SUMMARY ~~OF THE INVENTION~~

~~This invention relates to~~In one aspect, there is provided an antibody-drug conjugates represented by Formula (I)

Ab—(L—D)$_p$,

Ab is an antibody;

L is a peptidomimetic linker represented by the following formula

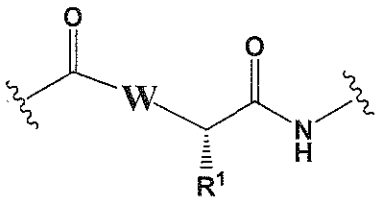
—Str—(PM)—Sp—

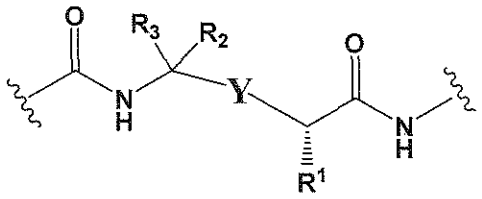
wherein

Str is a stretcher unit covalently attached to Ab;

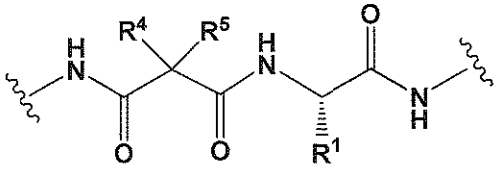
Sp is a bond or spacer unit covalently attached to a drug moiety;

PM is a non-peptide chemical moiety selected from the group consisting of:



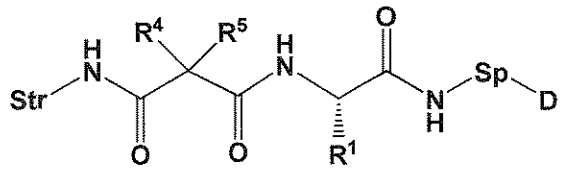


and



W is –NH-heterocycloalkyl- or heterocycloalkyl;
Y is heteroaryl, aryl, -C(O)C_1-C_6alkylene, C_1-C_6alkylene-NH_2, C_1-C_6alkylene-NH-CH_3, C_1-C_6alkylene-N-$(CH_3)_2$, C_1-C_6alkenyl or C_1-C_6alkylenyl;
each R^1 is independently C_1-C_{10}alkyl, C_1-C_{10}alkenyl, (C_1-C_{10}alkyl)NHC(NH)NH_2 or (C_1-C_{10}alkyl)NHC(O)NH_2;
R^3 and R^2 are each independently H, C_1-C_{10}alkyl, C_1-C_{10}alkenyl, arylalkyl or heteroarylalkyl, or R^3 and R^2 together may form a C_3-C_7cycloalkyl;
R^4 and R^5 are each independently C_1-C_{10}alkyl, C_1-C_{10}alkenyl, arylalkyl, heteroarylalkyl, (C_1-C_{10}alkyl)OCH_2-, or R^4 and R^5 together may form a C_3-C_7cycloalkyl ring;
p is an integer from 1 to 8;
D is a drug moiety.

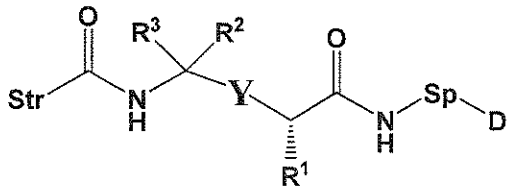
In one aspect, there is provided a non-peptide compound of Formula (I)(B)(LD1):



(I)(B)(LD1)

wherein
Str is a stretcher unit which can be covalently attached to an antibody;
Sp is a bond or a spacer unit covalently attached to a drug moiety;
R^1 is C_1-C_{10}alkyl, (C_1-C_{10}alkyl)NHC(NH)NH_2 or (C_1-C_{10}alkyl)NHC(O)NH_2;
R^4 and R^5 are each independently C_1-C_{10}alkyl, arylalkyl, heteroarylalkyl, (C_1-C_{10}alkyl)OCH_2-, or R^4 and R^5 may form a C_3-C_7cycloalkyl ring;
D is a drug moiety.

In one aspect, there is provided a compound of Formula:



(I)(A)(LD1)

wherein

Str is a stretcher unit which can be covalently attached to an antibody;

Sp is an optional spacer unit covalently attached to a drug moiety;

Y is heteroaryl, aryl, -C(O)C_1-C_8alkenyl, C_1-C_8alkenyl or - C_1-C_8alkenyl-NH-;

R^1 is C_1-C_{10}alkyl, (C_1-C_{10}alkyl)NHC(NH)NH_2 or (C_1-C_{10}alkyl)NHC(O)NH_2;

R^3 and R^2 are each independently H, C_1-C_{10}alkyl, arylalkyl or heteroarylalkyl, or R^3 and R^2 together may form a C_3-C_7cycloalkyl;

D is a drug moiety.

In one aspect, there is provided an antibody conjugate compound of which is prepared by covalently attaching an antibody with one to eight compounds as described herein.

This ~~invention~~ disclosure also relates to pharmaceutical compositions of antibody-drug conjugates of Formula (I).

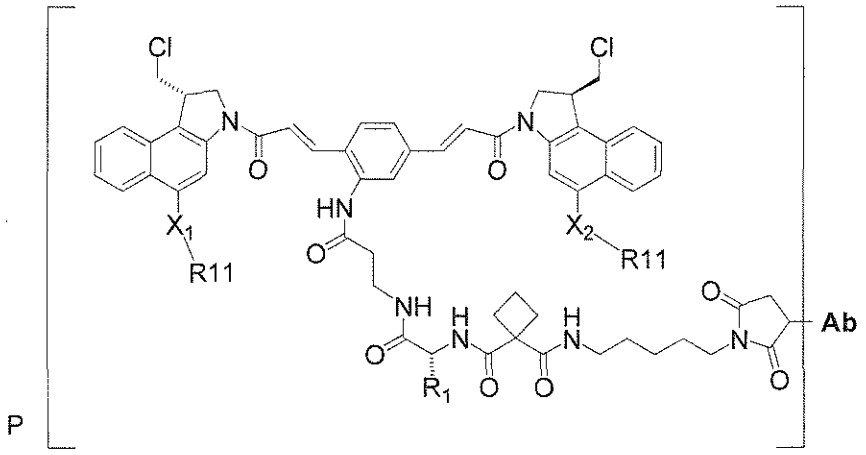
In one aspect, there is provided a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable carrier thereof.

In one aspect, there is provided use of an Antibody-drug conjugate as described herein in the manufacture of a medicament for treating a disease in a human in need thereof.

This ~~invention~~ disclosure also relates to a method of treating cancer, use of antibody-drug conjugates of Formula (I) in therapy, and use of compounds of Formula (I) in manufacturing a medicament for treating cancer.

This ~~invention~~ disclosure also relates to method of preparing antibody-drug conjugates of Formula (I).

BRIEF DESCRIPTION OF THE FIGURES



(I)(B9)

wherein,

Ab is an antibody that binds to a target seleted from Her2, CLL1, CD33, CD22 and NaPi2b;

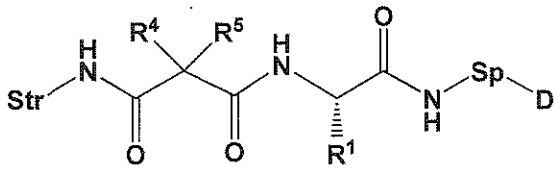
P is 1-4;

R^1 is C_1-C_6alkyl-NH_2, (C_1-C_6alkyl)NHC(NH)NH_2 or (C_1-C_6alkyl)NHC(O)NH_2;

X^1 and X^2 are each independently absent or O;

Each R^{11} is independently C(O)N-piperazine(CH_3) or $P(O)_3H_2$.

23. A non-peptide compound of Formula (I)(B)(LD1):



(I)(~~D~~B)(LD1)

wherein

Str is a stretcher unit which can be covalently attached to an antibody;

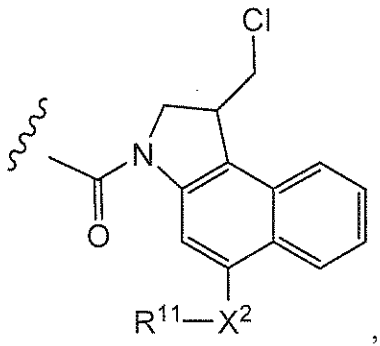
Sp is a bond or a spacer unit covalently attached to a drug moiety;

R^1 is C_1-C_{10}alkyl, (C_1-C_{10}alkyl)NHC(NH)NH_2 or (C_1-C_{10}alkyl)NHC(O)NH_2;

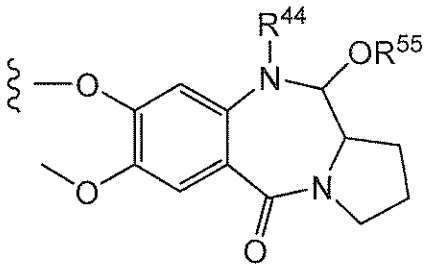
R^4 and R^5 are each independently C_1-C_{10}alkyl, arylalkyl, heteroarylalkyl, (C_1-C_{10}alkyl)OCH_2-, or R^4 and R^5 may form a C_3-C_7cycloalkyl ring;

D is a drug moiety.

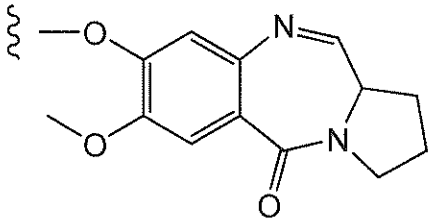
24. The compound of claim 23 represented by the following formula



,



, and



where the wavy line indicates the site of attachment to T;

X^1 and X^2 are independently selected from O and NR^{33}, where R^{33} is selected from H, C(O), and C_1–C_6alkyl optionally substituted with one or more F, or X^1 and X^2 are each independently absent;

R^{44} is H, CO_2R, C(O), or a bond to L, where R is C_1–C_6alkyl or benzyl; and

R^{55} is H or C_1–C_6alkyl.

39. An antibody conjugate compound of which is prepared by covalently attaching an antibody with one to eight compounds of claims 23-33.

40. ~~A method of treating a disease in a human in need thereof, comprising administering to said human an effective amount~~Use of an Antibody-drug conjugate of claim 1 in the manufacture of a medicament for treating a disease in a human in need thereof.

41. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier thereof.

42. A compound of claim 30, wherein the antibody binds to one or more of polypeptides selected from the group consisting of:

CLL1;

STEAP1;