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

In one aspect, there is provided an antibody-drug conjugate represented by Formula (I)

Ab—(L—D)$_p$,

Ab is an antibody;

L is a peptidomimetic linker represented by the following formula

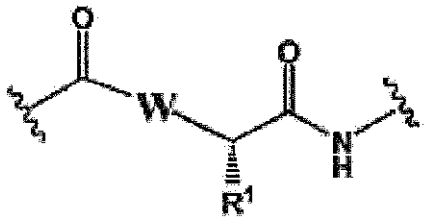
—Str—(PM)—Sp—

wherein

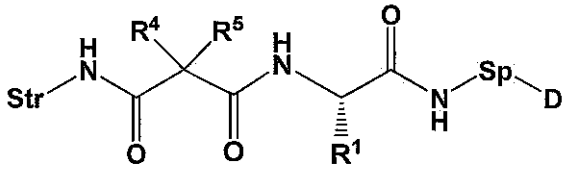
Str is a stretcher unit covalently attached to Ab;

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

PM is a non-peptide chemical moiety represented by the following formula:



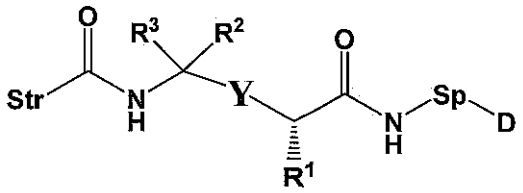
W is –NH-heterocycloalkyl- or heterocycloalkyl;
each R^1 is independently C_1-C_{10}alkyl, C_1-C_{10}alkenyl, (C_1-C_{10}alkyl)NHC(NH)NH_2 or (C_1-C_{10}alkyl)NHC(O)NH_2;
p is an integer from 1 to 8; and
D is a drug moiety.
Disclosed is a non-peptide compound of Formula (I)(B)(LD1):



(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.

Disclosed is 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_6alkenyl, C_1-C_6alkenyl or - C_1-C_6alkenyl-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 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 breast cancer, pancreatic cancer, colorectal cancer, ovarian cancer, non-small cell lung cancer or gastric cancer in a patient.

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

BRIEF DESCRIPTION OF THE FIGURES

Claims

1. An antibody-drug conjugate represented by Formula (I)

$$Ab—(L—D)_p,$$

Ab is an antibody;

L is a peptidomimetic linker represented by the following formula

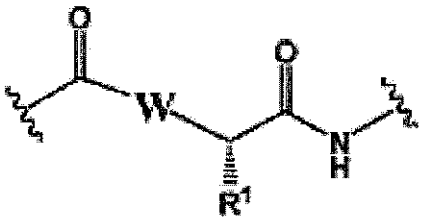
—Str—(PM)—Sp—

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 represented by the following formula:



W is –NH-heterocycloalkyl- or heterocycloalkyl;

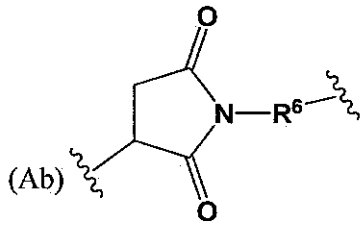
each R^1 is independently C_1-C_{10}alkyl, C_1-C_{10}alkenyl, (C_1-C_{10}alkyl)NHC(NH)NH_2 or (C_1-C_{10}alkyl)NHC(O)NH_2;

p is an integer from 1 to 8; and

D is a drug moiety.

2. An antibody-drug conjugate of claim 1, wherein

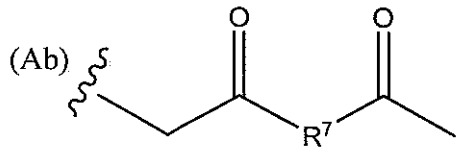
Str is a chemical moiety represented by the following formula:



wherein R^6 is selected from the group consisting of C_1-C_{10}alkylene, C_1-C_{10}alkenyl, C_3-C_8cycloalkyl, (C_1-C_8alkylene)O-, and C_1-C_{10}alkylene–C(O)N(R^a)–C_2-C_6alkylene, where each alkylene may be substituted by one to five substituents selected from the group consisting of halo, trifluoromethyl, difluoromethyl, amino, alkylamino, cyano, sulfonyl, sulfonamide, sulfoxide, hydroxy, alkoxy, ester, carboxylic acid, alkylthio, C_3-C_8cycloalkyl, C_4-C_7heterocycloalkyl, heteroarylalkyl, aryl arylalkyl, heteroarylalkyl and heteroaryl each R^a is independently H or C_1-C_6alkyl;

Sp is -C_1-C_6alkylene-C(O)NH- or —Ar—R^b—, wherein Ar is aryl or heteroaryl, R^b is (C_1-C_{10}alkylene)O-.

3. The antibody-drug conjugate of claim 1, wherein Str has the formula:

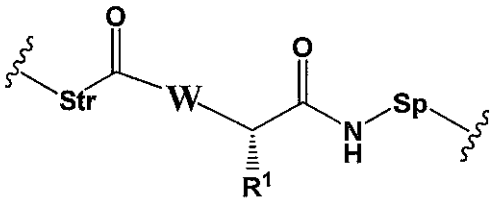


wherein R^7 is selected from C_1-C_{10}alkylene, C_1-C_{10}alkenyl, (C_1-C_{10}alkylene)O-, N(R^c)–(C_2-C_6 alkylene)–N(R^c) and N(R^c)–(C_2-C_6alkylene); where each R^c is independently H or C_1-C_6 alkyl; Sp is -C_1-C_6alkylene-C(O)NH- or —Ar—R^b—, wherein Ar is aryl or heteroaryl, R^b is (C_1-C_{10}alkylene)O-.

4. The antibody-drug conjugate of claim 1,

wherein Ab is an antibody;

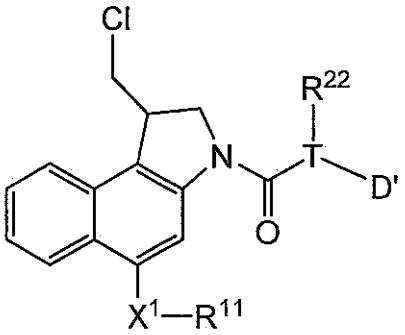
L is non-peptide chemical moiety represented by the following formula



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

5. The antibody-drug conjugate of claim 1-4, wherein

D is the dimer drug moiety having the formula:



wherein

R^{11} is selected from H, $P(O)_3H_2$, $C(O)NR^{aa}R^{bb}$, or a bond to L;

R^{22} is selected from H, $P(O)_3H_2$, $C(O)NR^{aa}R^{bb}$, or a bond to L;

R^{aa} and R^{bb} are independently selected from H and C_1–C_6alkyl optionally substituted with one or more F,

or R^{aa} and R^{bb} form a five or six membered heterocycloalkyl group;

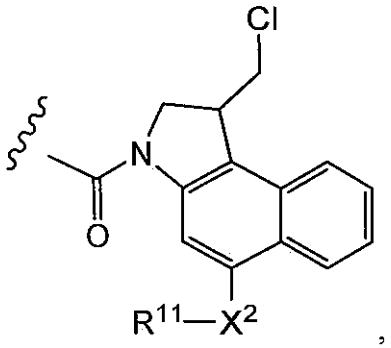
T is a tether group selected from C_3–C_{12}alkylene, Y^1, (C_1–C_6alkylene)– Y^1–(C_1–C_6 alkylene), (C_1–C_6alkylene)– Y^1–(C_1–C_6alkylene)– Y^1–(C_1–C_6alkylene), (C_2–C_6alkenylene)– Y^1–(C_2–C_6alkenylene), and (C_2–C_6alkynylene)– Y^1–(C_2–C_6alkynylene);

where Y^1 is independently selected from O, S, NR^{11}, aryl, and heteroaryl;

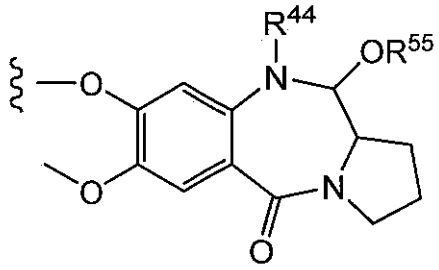
where alkylene, alkenylene, aryl, and heteroaryl are independently and optionally substituted with F, OH, O(C_1–C_6alkyl), NH_2, $NHCH_3$, $N(CH_3)_2$, $NHC(O)(C_1$-C_6alkylene$)_m$, $OP(O)_3H_2$, and C_1–C_6alkyl, where alkyl is optionally substituted with one or more F, m is 0 or 1;

or alkylene, alkenylene, aryl, and heteroaryl are independently and optionally substituted with a bond to L, wherein the bond to L may connect through one of the optional substituents;

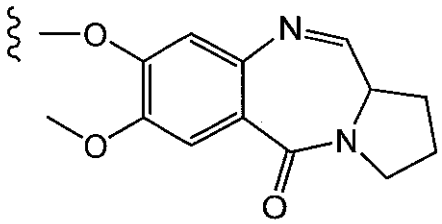
D' is a drug moiety selected from:



,



, and



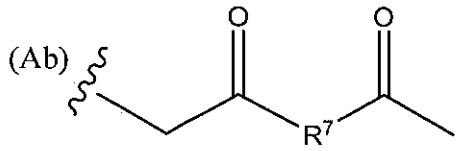
where the wavy line indicates the site of attachment to T;

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.

6. The compound of claim 5, wherein Str has the formula:



wherein R^7 is selected from C_1-C_{10}alkylene, C_1-C_{10}alkylene–O, N(R^c)–(C_2-C_6 alkylene)–N(R^c) and N(R^c)–(C_2-C_6alkylene); where each R^c is independently H or C_1-C_6 alkyl; Sp is -C_1-C_6alkylene-C(O)NH- or —Ar—R^b—, wherein Ar is aryl or heteroaryl, R^b is (C_1-C_{10} alkylene)O-.

7. The antibody-drug conjugate according to any one of claims 1-5, wherein p is 2.

8. The antibody conjugate of any one of claims 1-5, wherein the antibody binds to one or more of polypeptides selected from the group consisting of:

CLL1;
BMPR1B;
E16;
STEAP1;
0772P;
MPF;
NaPi2b;
Sema 5b;
PSCA hlg;
ETBR;
MSG783;
STEAP2;
TrpM4;
CRIPTO;
CD21;
CD79b;
FcRH2;
HER2;
NCA;
MDP;
IL20Rα;
Brevican;
EphB2R;
ASLG659;

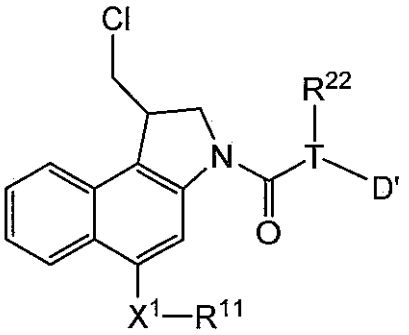
PSCA;
GEDA;
BAFF-R;
CD22;
CD79a;
CXCR5;
HLA-DOB;
P2X5 ;
CD72;
LY64;
FcRH1;
IRTA2;
TENB2;
PMEL17;
TMEFF1;
GDNF-Ra1;
Ly6E;
TMEM46;
Ly6G6D;
LGR5;
RET;
LY6K;
GPR19;
GPR54;
ASPHD1;
Tyrosinase;
TMEM118;
GPR172A;
MUC16 and
CD33.

9. A compound according to any of claims 1-8, wherein D is an anti-tumor agent or an antibiotic moiety.

10. The compound of any one of claims 1-9, wherein D is selected from the group consisting of: methotrexate, adriamicin, vincristine, vinblastine, etoposide, doxorubicin, melphalan, mitomycin C, chlorambucil and daunorubicin.

11. The compound of claim 6,

wherein D is the dimer drug moiety having the formula:



wherein

R^{11} is selected from H, $P(O)_3H_2$, $C(O)NR^{aa}R^{bb}$, or a bond to L;

R^{22} is selected from H, $P(O)_3H_2$, $C(O)NR^{aa}R^{bb}$, or a bond to L;

R^{aa} and R^{bb} are independently selected from H and C_1–C_6alkyl optionally substituted with one or more F,

or R^{aa} and R^{bb} form a five or six membered heterocycloalkyl group;

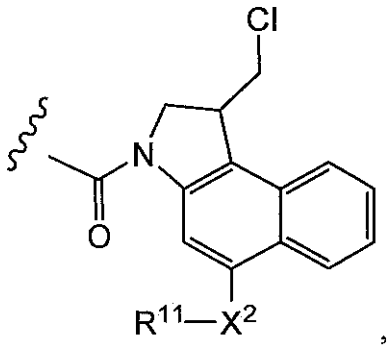
T is a tether group selected from C_3–C_{12}alkylene, Y^1, (C_1–C_6alkylene)– Y^1–(C_1–C_6 alkylene), (C_1–C_6alkylene)– Y^1–(C_1–C_6alkylene)– Y^1–(C_1–C_6alkylene), (C_2–C_6alkenylene)–Y^1–(C_2–C_6alkenylene), and (C_2–C_6alkynylene)– Y^1–(C_2–C_6alkynylene);

where Y^1 is independently selected from O, S, NR^{11}, aryl, and heteroaryl;

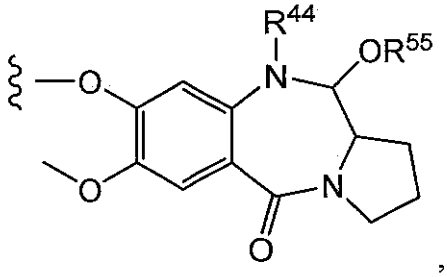
where alkylene, alkenylene, aryl, and heteroaryl are independently and optionally substituted with F, OH, O(C_1–C_6alkyl), NH_2, $NHCH_3$, $N(CH_3)_2$, $NHC(O)(C_1$-C_6alkylene$)_m$, $OP(O)_3H_2$, and C_1–C_6alkyl, where alkyl is optionally substituted with one or more F, m is 0 or 1;

or alkylene, alkenylene, aryl, and heteroaryl are independently and optionally substituted with a bond to L, wherein the bond to L may connect through one of the optional substituents;

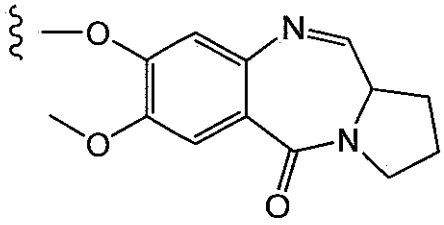
D' is a drug moiety selected from:



,



, 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.

12. An antibody conjugate compound of which is prepared by covalently attaching an antibody with one to eight compounds of claim 6.

13. Use of an Antibody-drug conjugate of claim 1 in the manufacture of a medicament for treating breast cancer, pancreatic cancer, colorectal cancer, ovarian cancer, non-small cell lung cancer or gastric cancer in a patient.

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

15. The antibody-drug conjugate of any one of claims 1-5, wherein the antibody binds to CD33.

16. The antibody-drug conjugate of claim 15, wherein the anti-CD33 antibody comprise an HVR-L1 comprising the amino acid sequence of SEQ ID NO:11, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:12, an HVR-L3 comprising the amino acid sequence of SEQ ID NO:13, an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 14, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:15, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 16.

17. The antibody-drug conjugate of claim 15, wherein said anti-CD33 antibody comprises a VL domain comprising the amino acid sequence of SEQ ID NO:17 and a VH domain comprising the amino acid sequence of SEQ ID NO:18.

18. The antibody-drug conjugate of any one of claims 1-5, wherein the antibody binds to NaPi2b.

19. The antibody-drug conjugate of claim 18, wherein the NaPi2b antibody comprise an HVR-L1 comprising the amino acid sequence of SEQ ID NO:1, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:2, an HVR-L3 comprising the amino acid sequence of SEQ ID NO:3, an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 4, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:5, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 6.

20. The antibody-drug conjugate of claim 18, wherein said NaPi2b antibody comprises a VL domain comprising the amino acid sequence of SEQ ID NO:7 and a VH domain comprising the amino acid sequence of SEQ ID NO:8.

21. The antibody-drug conjugate of claim 18, wherein said NaPi2b antibody comprises an amino acid sequence of SEQ ID NO:9 and an amino acid sequence of SEQ ID NO: 10.

22. The antibody-drug conjugate of any one of claims 1-5, wherein the antibody binds to CD-22.

23. The antibody-drug conjugate of claim 22, wherein the CD-22 antibody comprise an HVR-L1 comprising the amino acid sequence of SEQ ID NO:41, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:42, an HVR-L3 comprising the amino acid sequence of SEQ ID NO:43, an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 44, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:45, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 46.

24. The antibody-drug conjugate of claim 22, wherein said CD-22 antibody comprises a VL domain comprising the amino acid sequence of SEQ ID NO:47 and a VH domain comprising the amino acid sequence of SEQ ID NO:48.

25. The antibody-drug conjugate of claim 22, wherein said CD-22 antibody comprises an amino acid sequence of SEQ ID NO:49 and an amino acid sequence of SEQ ID NO: 50.

26. The antibody-drug conjugate of claim 22, wherein said CD-22 antibody comprises an amino acid sequence that has at least 95% sequence identity with amino acid sequence of SEQ ID NO:49 and that comprises an amino acid sequence that has at least 95%sequence identity with an amino acid sequence of SEQ ID NO: 50.