CHARGE VARIANT LINKERS

BACKGROUND

Antibody-drug conjugates (ADCs) combine the tumor targeting specificity of monoclonal antibodies with the potent cell-killing activity of cytotoxic warheads. There has been a surge of interest in designing new ADC formats due in part to the recent clinical success of ADCs, which includes the approvals of brentuximab vedotin (ADCETRIS®) in relapsed Hodgkin lymphoma and anaplastic large-cell lymphoma, and ado-trastuzumab mertansine (KADCYLA®) in HER2-positive metastatic breast cancer.

The absolute quantity of delivered drug is limited, in part, by the level of antigen expression, the internalization rate of the ADC, and the number of molecules of drug conjugated to the antibody (the drug-antibody ratio or "DAR"). These restrictions contribute to the observation that highly potent cytotoxic molecules are typically used for the construction of active ADCs, because payloads of more modest potency tend to show more limited activity. One route to increasing the amount of drug delivered to cells is to increase the DAR of the conjugate; however, this approach often leads to a reduced half-life and reduced *in vivo* efficacy. The fast clearance of many such higher-loaded ADCs is often attributed to poor biophysical properties, but specific identification of these properties is lacking. Recent developments in higher loaded conjugates, such as those with hydrophobic drugs leading to ADC aggregation, have depended on hydrophilic polymer-based systems having heterogenous structure and drug loading to avoid aggregation and related issues.

SUMMARY

Some examples provide an antibody-drug conjugate (ADC) compound of Formula (I):

$$\mathbf{Ab–\{(S^*\text{-}L^1)–[(M)_x\text{-}(L^2\text{-}D)_y]\}_p} \qquad \text{(I)}$$

wherein:

Ab is an antibody;

each S* is a sulfur atom from a cysteine residue of the antibody, an ϵ-nitrogen atom from a lysine residue of the antibody, or a triazole moiety, and

each R^a, R^b, and R^c is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, halogen, -OH, =O, $-NR^dR^e$, $-C(O)NR^dR^e$, $-C(O)(C_{1-6}$ alkyl), $-(C_{1-6}$ alkylene)$-NR^dR^e$, and $-C(O)O(C_{1-6}$ alkyl);

each R^d and R^e are independently hydrogen or C_{1-3} alkyl; or R^d and R^e together with the nitrogen atom to which both are attached form a 5-6 membered heterocyclyl;

L^2 is an optional second linker optionally substituted with a PEG Unit selected from PEG2 to PEG20;

each M is a multiplexer;

subscript x is 0, 1, 2, 3, or 4;

subscript y is 2^x;

each D is a Drug Unit;

wherein L^1 and each $(M)_x$-$(D)_y$ when L^2 is absent, or each $(M)_x$-$(L^2$-$D)_y$ when L^2 is present, have a net zero charge at physiological pH;

subscript p is an integer ranging from 2 to 10; and

the ratio of D to Ab is 8:1 to 64:1.

In one aspect, the present disclosure refers to an antibody-drug conjugate (ADC) compound of Formula (I):

$$\mathbf{Ab–\{(S^*\text{-}L^1)–[(M)_x\text{-}(L^2\text{-}D)_y]\}_p} \qquad (I)$$

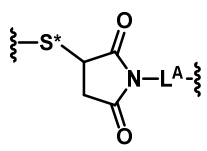
wherein:

Ab is an antibody;

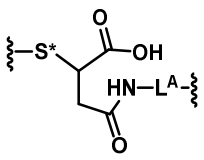
each S* is a sulfur atom from a cysteine residue of the antibody, an ϵ-nitrogen atom from a lysine residue of the antibody, or a triazole moiety, and

each L^1 is a first linker optionally substituted with a PEG Unit ranging from PEG2 to PEG72;

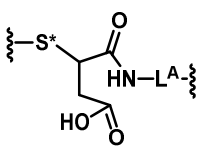
wherein S*-L^1 is selected from the group consisting of formulae A-K:



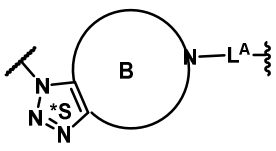
A



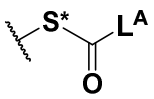
B

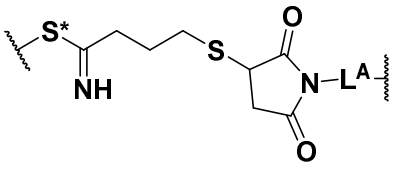


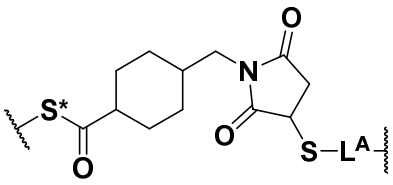
C



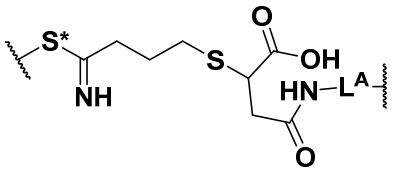
D

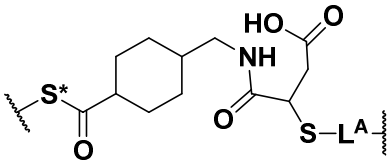




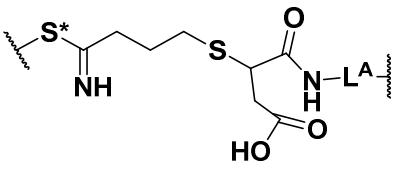


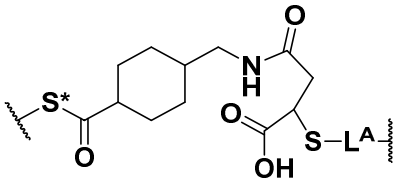
E F G





H I





J K

wherein:

each L^A is a C_{1-10} alkylene optionally substituted with 1-3 independently selected R^a, or a 2-24 membered heteroalkylene optionally substituted with 1-3 independently selected R^b;

each Ring B is an 8-12 membered heterocyclyl optionally substituted with 1-3 independently selected R^c, and further optionally fused to 1-2 rings each independently selected from the group consisting of C_{6-10} aryl and 5-6 membered heteroaryl;

each R^a, R^b, and R^c is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, halogen, -OH, =O, $-NR^dR^e$, $-C(O)NR^dR^e$, $-C(O)(C_{1-6}$ alkyl), $-(C_{1-6}$ alkylene)$-NR^dR^e$, and $-C(O)O(C_{1-6}$ alkyl);

each R^d and R^e are independently hydrogen or C_{1-3} alkyl; or R^d and R^e together with the nitrogen atom to which both are attached form a 5-6 membered heterocyclyl;

L^2 is an optional second linker optionally substituted with a PEG Unit selected from PEG2 to PEG20;

each M is a multiplexer;

subscript x is 0, 1, 2, 3, or 4;

subscript y is 2^x;

each D is a Drug Unit;

wherein L^1 and each $(M)_x$-$(D)_y$ when L^2 is absent, or each $(M)_x$-$(L^2$-$D)_y$ when L^2 is present, have a net zero charge at physiological pH;

subscript p is an integer ranging from 2 to 10; and

the ratio of D to Ab is 8:1 to 64:1.

Some examples provide a composition comprising an ADC as describe herein, or a pharmaceutically acceptable salt thereof. In one aspect, the present disclosure refers to a composition comprising the ADC as disclosed herein, or a pharmaceutically acceptable salt thereof.

Some examples provide a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount an ADC as describe herein, or a pharmaceutically acceptable salt thereof, or a composition comprising an ADC as describe herein, or a pharmaceutically acceptable salt thereof, as described herein. In one aspect, the present disclosure refers to use of the ADC as disclosed herein, or a pharmaceutically acceptable salt thereof, or the composition as disclosed herein in the manufacture of a medicament for treating cancer in a subject in need thereof.

Some examples provide a method of treating an autoimmune disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount an ADC as describe herein, or a pharmaceutically acceptable salt thereof, or a composition comprising an ADC as describe herein, or a pharmaceutically acceptable salt thereof, as described herein. In one aspect, the present disclosure refers to use of the ADC as disclosed herein, or a pharmaceutically acceptable salt thereof, or the composition as disclosed herein in the manufacture of a medicament for treating an autoimmune disorder in a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 provides the HIC chromatogram (at 280 nm) of hAC10ec and its conjugates with MC1 or MC3 (DAR = 10, 20, or 38.5).

FIG. 2 schematically depicts sequential reactions of MC2 and *N*-ethyl maleimide onto cysteine residues of an antibody. An antibody (cAC10) having a L0=23152 was reacted with MC2

WHAT IS CLAIMED IS:

1. An antibody-drug conjugate (ADC) compound of Formula (I):

$Ab–\{(S^*\text{-}L^1)–[(M)_x\text{-}(L^2\text{-}D)_y]\}_p$ (I)

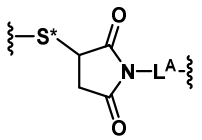
wherein:

Ab is an antibody;

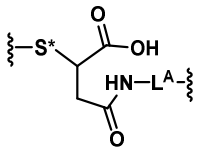
each S* is a sulfur atom from a cysteine residue of the antibody, an ϵ-nitrogen atom from a lysine residue of the antibody, or a triazole moiety, and

each L^1 is a first linker optionally substituted with a PEG Unit ranging from PEG2 to PEG72;

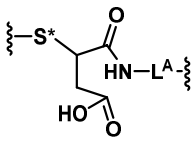
wherein S*-L^1 is selected from the group consisting of formulae A-K:



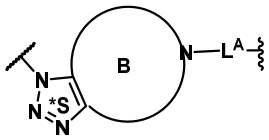
A



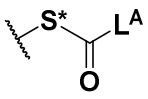
B



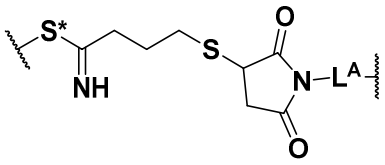
C



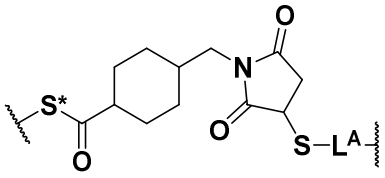
D



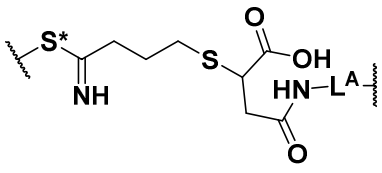
E



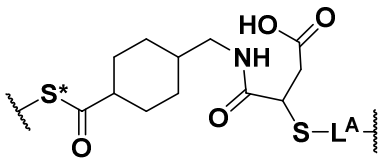
F



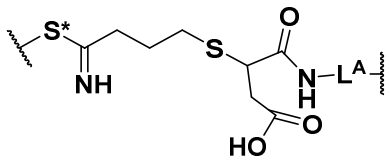
G



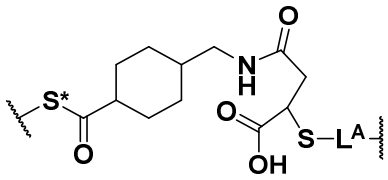
H



I



J



K

wherein:

each L^A is a C_{1-10} alkylene optionally substituted with 1-3 independently selected R^a, or a 2-24 membered heteroalkylene optionally substituted with 1-3 independently selected R^b;

each Ring B is an 8-12 membered heterocyclyl optionally substituted with 1-3 independently selected R^c, and further optionally fused to 1-2 rings each independently selected from the group consisting of C_{6-10} aryl and 5-6 membered heteroaryl;

each R^a, R^b, and R^c is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, halogen, -OH, =O, $-NR^dR^e$, $-C(O)NR^dR^e$, $-C(O)(C_{1-6}$ alkyl), $-(C_{1-6}$ alkylene$)-NR^dR^e$, and $-C(O)O(C_{1-6}$ alkyl);

each R^d and R^e are independently hydrogen or C_{1-3} alkyl; or R^d and R^e together with the nitrogen atom to which both are attached form a 5-6 membered heterocyclyl;

L^2 is an optional second linker optionally substituted with a PEG Unit selected from PEG2 to PEG20;

each M is a multiplexer;

subscript x is 0, 1, 2, 3, or 4;

subscript y is 2^x;

each D is a Drug Unit;

wherein L^1 and each $(M)_x$-$(D)_y$ when L^2 is absent, or each $(M)_x$-$(L^2$-$D)_y$ when L^2 is present, have a net zero charge at physiological pH;

subscript p is an integer ranging from 2 to 10; and

the ratio of D to Ab is 8:1 to 64:1.

2. The ADC compound of claim 1, wherein each S* is a sulfur atom from a cysteine residue of the antibody.

3. The ADC compound of claim 1 or 2, wherein the cysteine residues are native cysteine residues.

4. The ADC compound of claim 1 or 2, wherein the cysteine residues are from reduced interchain disulfide bonds, or are from engineered cysteine residues, or a combination thereof.

5. The ADC compound of claim 1 or 2, wherein the cysteine residues are engineered cysteine residues.

6. The ADC compound of claim 1 or 2, wherein one or more S* is a sulfur atom from an engineered cysteine residue(s); and each remaining S* is a sulfur atom from a native cysteine residue.

7. The ADC compound of claim 1, wherein each S* is an ϵ-nitrogen atom from a lysine residue of the antibody.

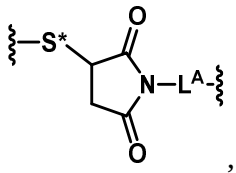
8. The ADC compound of claim 1 or 7, wherein the lysine residues are native lysine residues.

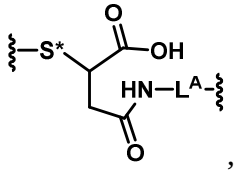
9. The ADC compound of claim 1 or 7, wherein the lysine residues are engineered lysine residues.

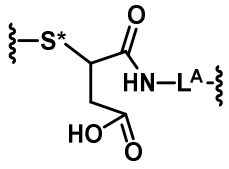
10. The ADC compound of claim 1 or 7, wherein one or more S* is an ϵ-nitrogen atom from an engineered lysine residue(s) of the antibody; and each remaining S* is an ϵ-nitrogen atom from a native lysine residue of the antibody.

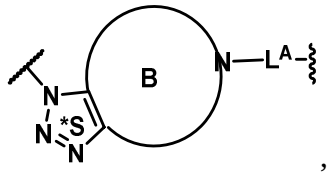
11. The ADC compound of claim 1, wherein each S* of formula D is a triazole moiety.

12. The ADC compound of any one of claims 1-11, wherein L^A is substituted with a PEG Unit ranging from PEG2 to PEG36.

13. The ADC compound of any one of claims 1-6, wherein S*-L^1 is: , wherein L^A is a C_{1-10} alkylene or a 2-10-membered heteroalkylene optionally substituted with 1 R^a or 1 R^b, respectively, and optionally substituted with a PEG Unit ranging from PEG8 to PEG24 or PEG12 to PEG32.

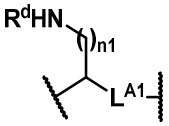
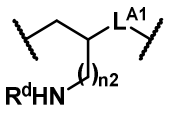
14. The ADC compound of any one of clams 1-6, wherein S*-L^1 is: , wherein L^A is a C_{2-10} alkylene or 2-10-membered heteroalkylene either of which is unsubstituted or substituted with 1 R^a, wherein R^a is -NR^dR^e.

15. The ADC compound of any one of claims 1-6, wherein S*-L^1 is:  wherein L^A is a C_{2-10} alkylene or 2-10-membered heteroalkylene; each optionally substituted with 1 R^a or 1 R^b, respectively.

16. The ADC compound of claim 1 or 11, wherein S*-L^1 is: , wherein L_A is C_{1-10} alkylene or a 2-10 membered heteroalkylene; each optionally substituted with 1-2 R^a or 1-2 R^b, respectively, provided

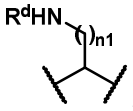
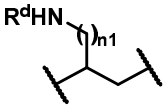
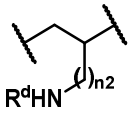
that one R^b is =O and the carbon atom of the 2-10 membered heteroalkylene so substituted is covalently attached to the nitrogen atom of Ring B;

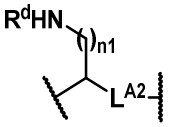
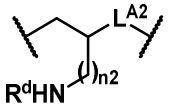
wherein Ring B is unsubstituted or substituted with 1-2 R^c, and is optionally fused to 1-2 rings each independently selected from the group consisting of C_{6-10} aryl and 5-6 membered heteroaryl.

17. The ADC compound of any one of claims 1-16, wherein L^A is  or  ; wherein L^{A1} is a bond or a C_{1-4} alkylene optionally substituted with 1 R^a; subscript n1 is 1-4; and subscript n2 is 0-4.

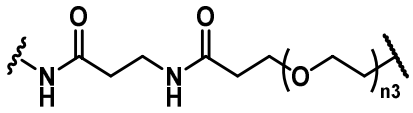
18. The ADC compound of any one of claims 1-17, wherein R^a and R^b are -(C_{1-6} alkylene)-NR^dR^e.

19. The ADC compound of any one of claims 1-18, wherein R^d and R^e are each hydrogen or are each methyl.

20. The ADC compound of claim 19, wherein L^A is , , or  ; wherein subscript n1 is 1 or 2; and subscript n2 is 0, 1, or 2.

21. The ADC compound of any one of claims 1-20, wherein L^A is  or  ; wherein L^{A2} is a C_{2-10} alkylene; subscript n1 is 1 or 2; subscript n2 is 0 or 1; and L^{A2} is further optionally substituted with a PEG Unit ranging from PEG12 to PEG32.

22. The ADC compound of any one of claims 1-21, wherein L^A is further optionally substituted with a PEG Unit ranging from PEG8 to PEG32.

23. The ADC compound of any one of claims 1-16 and 22, wherein L^A is  , wherein subscript n3 is 1-5.

24. The ADC compound of any one of claims 1, 7, and 16-23, wherein Ring B is an unsubstituted, unfused 8-12 membered heterocyclyl ring.

25. The ADC compound of any one of claims 1, 7, and 16-23, wherein Ring B is an unsubstituted 8-12 membered heterocyclyl fused to a C_{6-10} aryl or 5-6 membered heteroaryl ring.

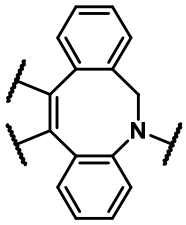
26. The ADC compound of any one of claims 1, 7, and 16-23, wherein Ring B is an unsubstituted 8-12 membered heterocyclyl fused to two C_{6-10} aryl rings or two 5-6 membered heteroaryl ring rings.

27. The ADC compound of any one of claims 1, 7, and 16-23, wherein Ring B is an unfused 8-12 membered heterocyclyl substituted with 1 R^c.

28. The ADC compound of any one of claims 1, 7, and 16-23, wherein Ring B is an 8-12 membered heterocyclyl substituted with 1 R^c, and fused to a C_{6-10} aryl or 5-6 membered heteroaryl ring.

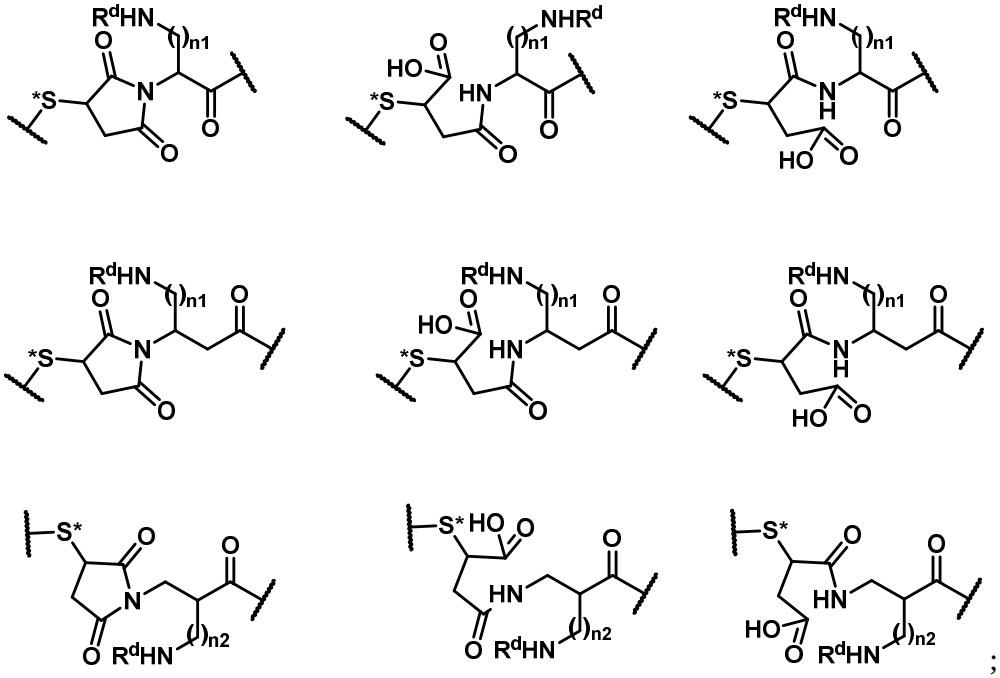
29. The ADC compound of any one of claims 1, 7, and 16-23, wherein Ring B is an unsubstituted 8-12 membered heterocyclyl and fused to two C_{6-10} aryl rings or two 5-6 membered heteroaryl ring rings.

30. The ADC compound of any one of claims 1, 7, and 16-23, wherein Ring B is:



.

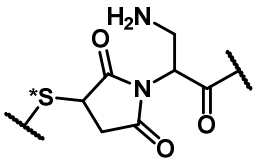
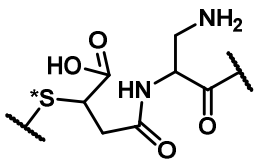
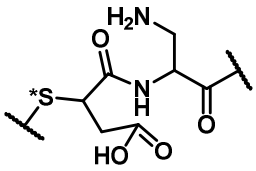
31. The ADC compound of any one of claim 1-6, wherein S*-L^1 is selected from the group consisting of:



;

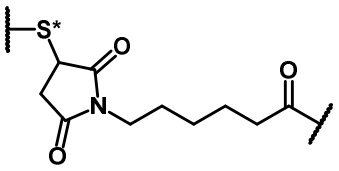
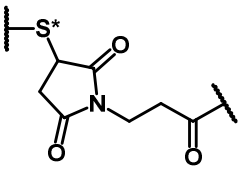
wherein subscript n1 is 1 or 2; and subscript n2 is 0, 1, or 2; and S* is a sulfur atom from a cysteine residue of the antibody.

32. The ADC compound of claim 31, wherein *S-L is selected from the group consisting of:

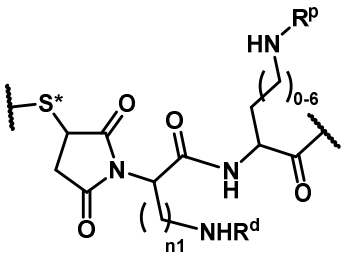
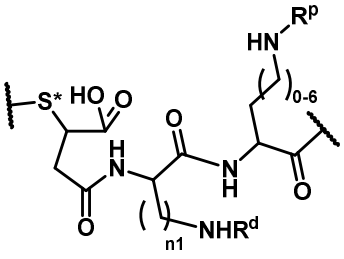
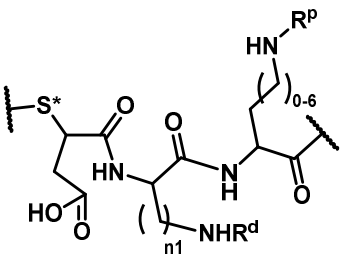



;

wherein S* is a sulfur atom from a cysteine residue of the antibody.

33. The ADC compound of any one of claims 1-6, wherein S*-L:

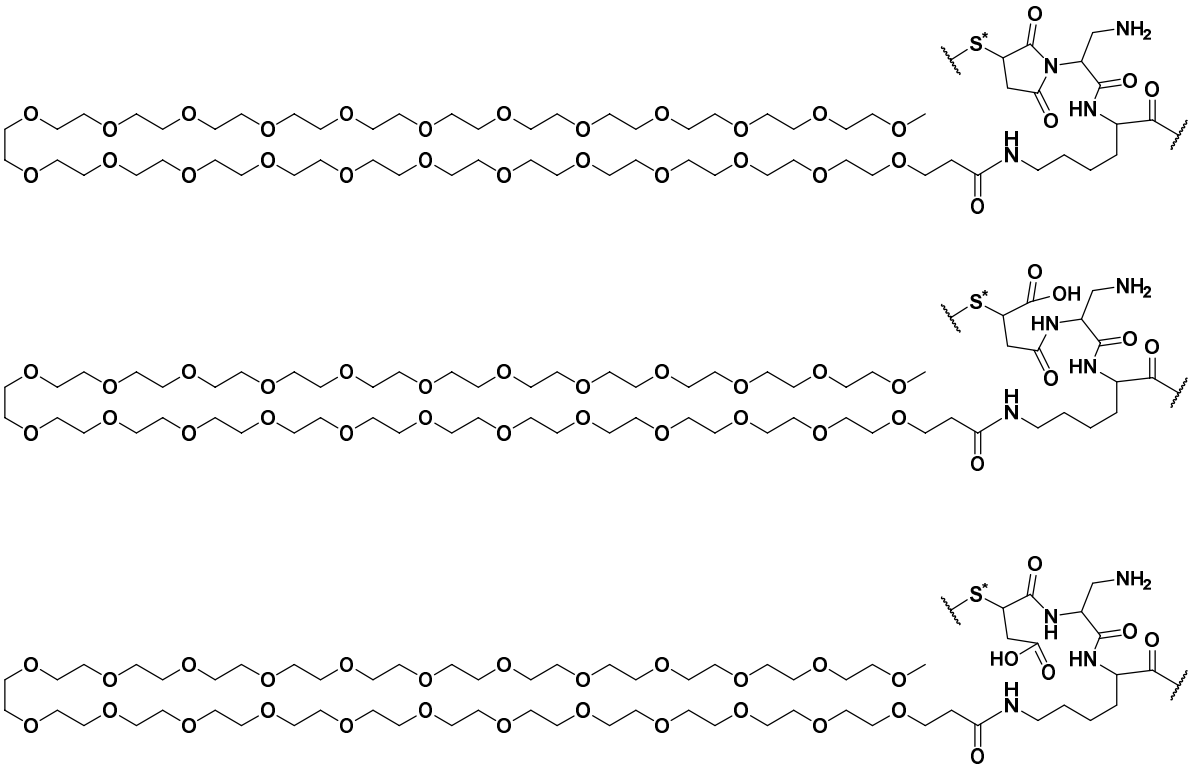

or

; wherein S* is a sulfur atom from a cysteine residue of the antibody.

34. The ADC compound of any one of claims 1-6, wherein *S-L^1 is selected from the group consisting of:

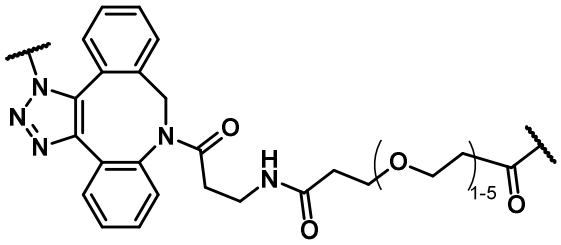




wherein R^p is a PEG Unit ranging from PEG8-PEG24, wherein the PEG Unit comprises a -(C_{1-3} alkylene)C(=O)- group, the carbonyl carbon atom of which provides covalent attachment of R^P to the nitrogen atom; and S* is a sulfur atom from a cysteine residue of the antibody.

35. The ADC compound of claim 34, wherein *S-L^1 is selected from the group consisting of:



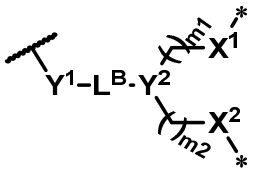
36. The ADC compound of claim 1 or 7, wherein *S-L^1 is:



.

37. The ADC compound of any one of claims 1-36, wherein subscript x is 1.

38. The ADC compound of claim 1 or 37, wherein M is:



wherein the wavy line represents the covalent attachment of M to L^1;

each * represents the covalent attachment of M to $–L^2$-D;

Y^1 is selected from the group consisting of: a bond, -S-, -O-, and –NH-;

Y^2 is selected from the group consisting of: CH and N;

L^B is absent or a C_{1-6} alkylene that is optionally interrupted with a group selected from the group consisting of: -O-, -NH-, -N(C_{1-3} alkyl)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, and -O(C=O)-;

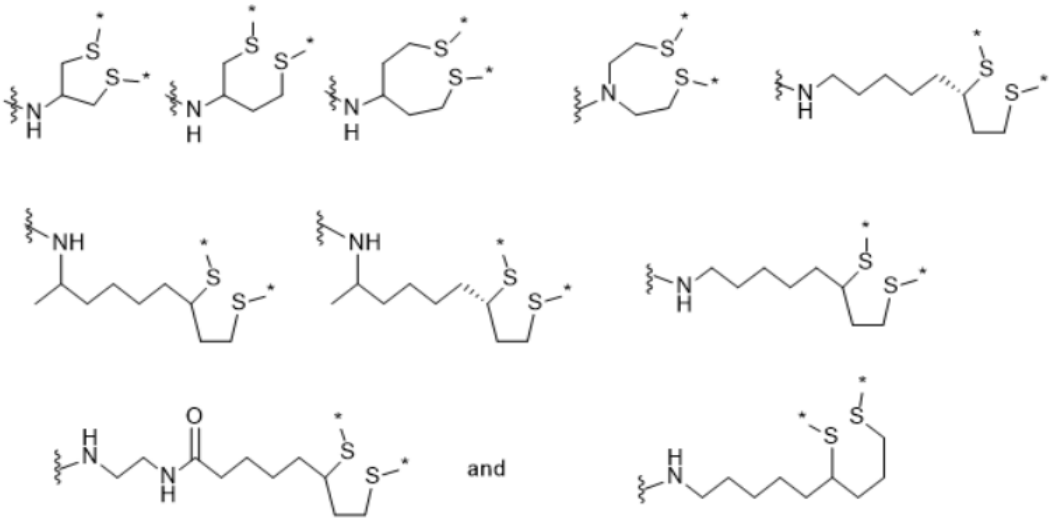
X^1 and X^2 are each independently –S-, -O-, or –NH-; and

subscripts m1 and m2 are each independently 1-4.

39. The ADC compound of any one of claims 1 or 37-38, wherein Y^1 is –NH-; L^B is present; Y^2 is CH; and X^1 and X^2 are each –S-.

40. The ADC compound of any one of claims 1 or 37-38, wherein Y^1 is a bond; L^B is absent; Y^2 is N; and X^1 and X^2 are each –S-.

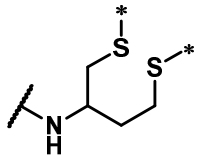
41. The ADC compound of any one of claims 1 or 37-38, wherein M is selected from the group consisting of:



;

wherein the wavy line represents the covalent attachment of M to L^1; and

wherein each * represents the covalent attachment of M to -(L^2-D).

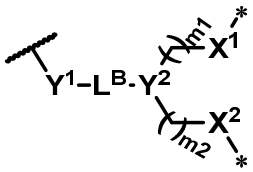
42. The ADC compound of any one of claims 1-36, wherein M is  .

43. The ADC compound of any one of claims 1-36, wherein subscript x is 2-4; and $(M)_x$ is $–M^1-(M^2)_{x-1}$, wherein M^1 and each M^2 are independently selected multiplexers.

44. The ADC compound of claim 43, wherein subscript x is 2; and $(M)_x$ is $–M^1-M^2$.

45. The ADC compound of claim 43, wherein subscript x is 3; and $(M)_x$ is $–M^1-(M^2)_2$.

46. The ADC compound of any one of claims 3-45, wherein M^1 is:



wherein the wavy line represents the covalent attachment of M to L^1;

each * represents the covalent attachment of M^1 to M^2;

Y^1 is selected from the group consisting of: a bond, -S-, -O-, and –NH-;

Y^2 is selected from the group consisting of: CH and N;

L^B is absent or a C_{1-6} alkylene that is optionally interrupted with a group selected from the group consisting of: -O-, -NH-, -N(C_{1-3} alkyl)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, and -O(C=O)-;

X^1 and X^2 are each independently –S-, -O-, or –NH-; and

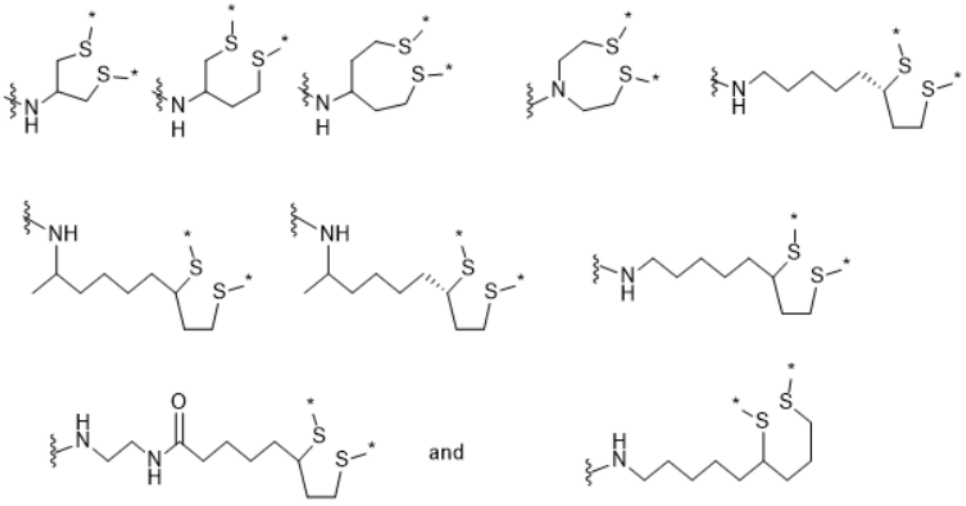
subscripts m1 and m2 are each independently 1-4.

47. The ADC compound of claim 46, wherein Y^1 is –NH-; L^B is present; Y^2 is CH; and X^1 and X^2 are each –S-.

48. The ADC compound of claim 46, wherein Y^1 is a bond; L^B is absent; Y^2 is N; and X^1 and X^2 are each –S-.

49. The ADC compound of claim 46, wherein Y^1 is a bond; L^B is absent; Y^2 is N; and X^1 and X^2 are each –NH.

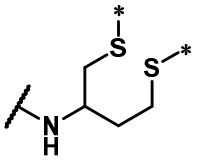
50. The ADC compound of claim 46, wherein M^1 is selected from the group consisting of:

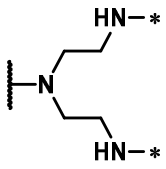


;

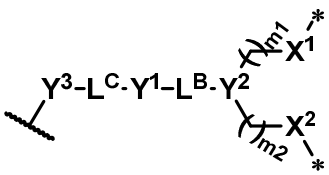
wherein the wavy line represents the covalent attachment of M to L^1; and

wherein each * represents the covalent attachment of M to -(L^2-D).

51. The ADC compound of claim 46, wherein M^1 is  .

52. The ADC compound claim 46, wherein M^1 is  .

53. The ADC compound of any one of claims 43-52, wherein each M^2 is independently:



wherein the wavy line represents the covalent attachment of M^2 to M^1 or to another M^2;

each * represents the covalent attachment of M^2 to L^2-D or another M^2;

Y^1 is a bond, -S-, -O-, or –NH-;

Y^2 is CH or N;

Y^3 is an optional group that provides covalent attachment of M^1 to the L^C (when present) or to Y^1 (when L^C is absent) of M^2;

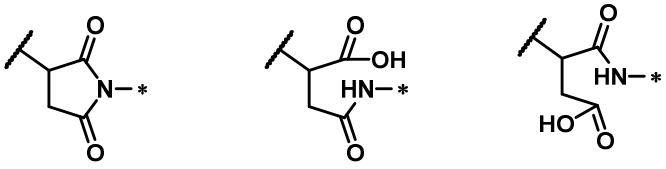
L^B is absent or a C_{1-6} alkylene that is optionally interrupted with a group selected from the group consisting of: -O-, -NH-, -N(C_{1-3} alkyl)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, and -O(C=O)-;

X^1 and X^2 are each independently –S-, -O-, or –NH-;

L^C is a C_{1-10} alkylene optionally substituted with 1-3 substituents each independently selected from -(C_{1-6} alkylene)-NR^dR^e, NRdRe, and oxo; and

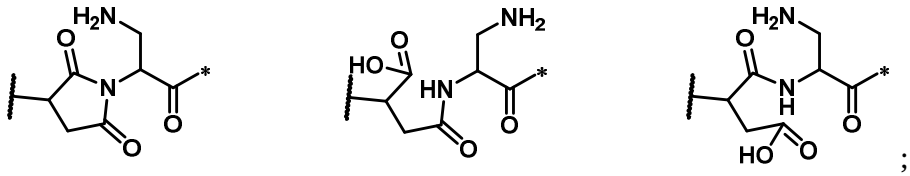
subscripts m1 and m2 are each independently 1-4.

54. The ADC compound of claim 53, wherein Y^3 is -C(=O)-.

55. The ADC compound of claim 53, wherein Y^3 is selected from the group consisting of:  ;

wherein * represents the covalent attachment to L^C; and the wavy line represents the covalent attachment to M^1 or another M^2.

56. The ADC compound of claim 53, wherein Y^3-L^C is selected from the group consisting of:

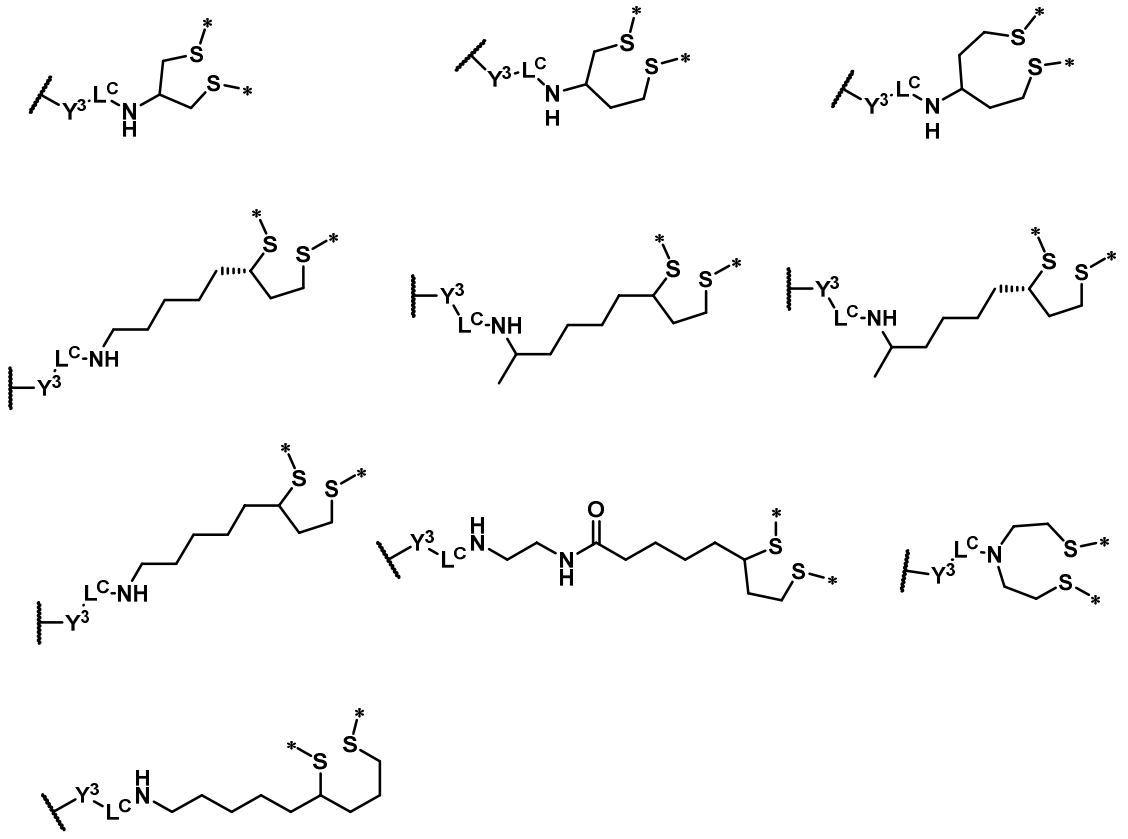
 ;

wherein * represents covalent attachment to Y^1; and the wavy line represents the covalent attachment to M^1 or another M^2.

57. The ADC compound of any one of claims 53-56, wherein Y^1 is –NH-; L^B is present; Y^2 is CH; and X^1 and X^2 are each –S-.

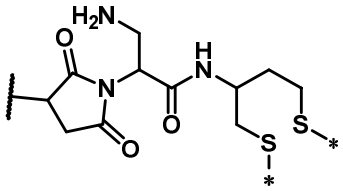
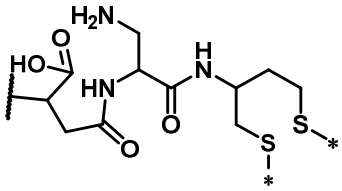
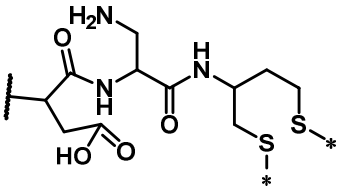
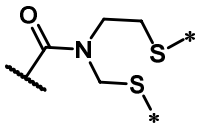
58. The ADC compound of any one of claims 53-56, wherein Y^1 is a bond; L^B is absent; Y^2 is N; and X^1 and X^2 are each –NH.

59. The ADC compound of any one of claims 43-52, wherein M^2 is selected from the group consisting of:



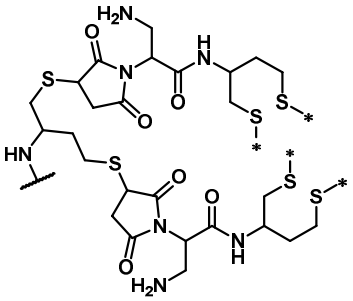
; wherein each * represents the covalent attachment to L^2-D or another M^2; and the wavy bond presents the covalent attachment to M^1 or another M^2.

60. The ADC compound of any one of claims 43-52, wherein M^2 is selected from the group consisting of:

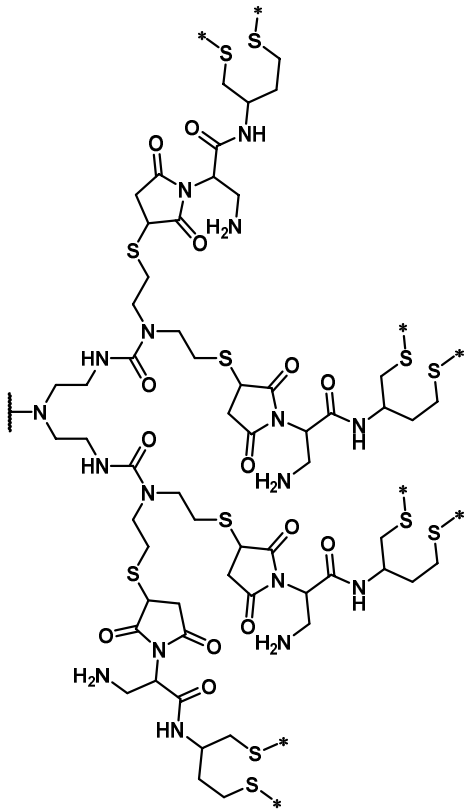
wherein each * represents the covalent attachment to L^2-D or another M^2; and the wavy bond presents the covalent attachment to M^1 or another M^2.

61. The ADC compound of any one of claims 43-52, wherein subscript x is 2; and $(M)_x$ is:



wherein each * represents the covalent attachment to L^2-D; the wavy line represents the covalent attachment to L^1; and each succinimide ring is in hydrolyzed form.

62. The ADC compound of any one of claims 1-36, wherein subscript x is 3; and $(M)_x$ is:



wherein each * represents the covalent attachment to L^2-D; and each succinimide ring is in hydrolyzed form.

63. The ADC compound of any one of claims 1-36, wherein subscript x is 0.

64. The ADC compound of any one of claims 1-63, wherein L^2 is substituted with a PEG Unit ranging from PEG2 to PEG36.

65. The ADC compound of any one of claims 1-63, wherein L^2 is not substituted with a PEG Unit.

66. The ADC compound of any one of claims 1-63, wherein L^2 has the formula $–(Q)_q$-$(A)_a$-$(W)_w$-$(Y)_y$, wherein:

A is a C_{2-20} alkylene optionally substituted with 1-3 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R^{b1};

each R^{a1} is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, halogen, -OH, =O, $-NR^{d1}R^{e1}$, $-(C_{1-6}$ alkylene$)-NR^{d1}R^{e1}$, $-C(=O)NR^{d1}R^{e1}$, $-C(=O)(C_{1-6}$ alkyl), and $-C(=O)O(C_{1-6}$ alkyl);

each R^{b1} is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, halogen, -OH, $-NR^{d1}R^{e1}$, $-(C_{1-6}$ alkylene$)-NR^{d1}R^{e1}$, $-C(=O)NR^{d1}R^{e1}$, $-C(=O)(C_{1-6}$ alkyl), and $-C(=O)O(C_{1-6}$ alkyl);

each R^{d1} and R^{e1} are independently hydrogen or C_{1-3} alkyl;

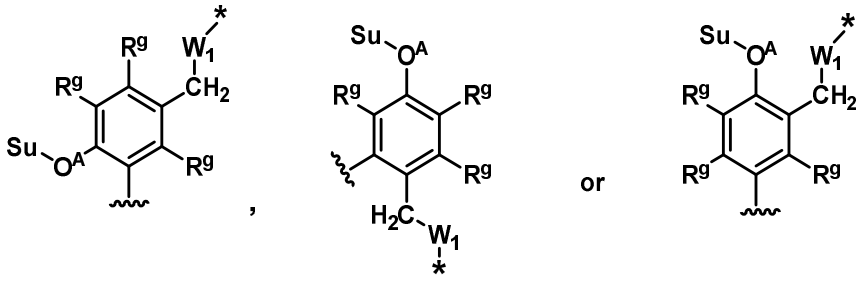
Q is a succinimide or hydrolyzed succinimide;

subscript q is 0 or 1;

subscript a is 0 or 1;

subscript w is 0 or 1;

wherein when subscript w is 1 then W is from 1-12 amino acids or has the structure:



wherein Su is a Sugar moiety;

$-O^{A}-$ represents the oxygen atom of a glycosidic bond;

each R^{g} is independently hydrogen, halogen, -CN, or $-NO_2$;

W^1 is selected from the group consisting of: a bond, -O-, -NH-, $-N(C_{1-6}$ alkyl$)-$, $-[N(C_{1-6}$ alkyl$)_2]^+-$, and -OC(=O)-;

the wavy line represents the covalent attachment to A, Q, or L^1; and

the * represents the covalent attachment to Y or D;

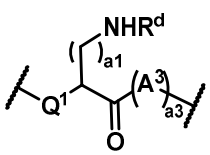
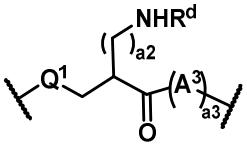
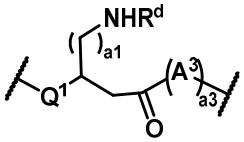
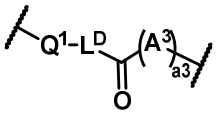
y is 0 or 1; and

Y is a self-immolative or non-self-immolative moiety; and y is 0 or 1.

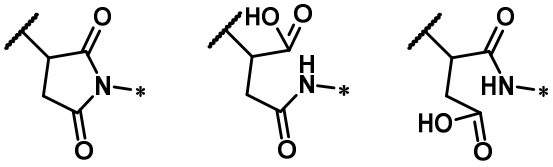
67. The ADC compound of any one of claims 1-66, wherein each L^2-D is uncharged.

68. The ADC compound of any one of claims 1-66, wherein each L^2-D has a net zero charge.

69. The ADC compound of any one of claims 66-68, wherein Q-A is selected from the group consisting of:

wherein Q^1 is selected from the group consisting of:



, wherein the wavy line adjacent to Q^1 represents covalent attachment to $(M)_x$;

subscript a1 is 1-4;

subscript a2 is 0-3;

subscript a3 is 0 or 1;

L^D is a C_{1-6} alkylene;

A^3 is -NH-(C_{1-10} alkylene)-C(=O)- or -NH-(2-20 membered heteroalkylene)-C(=O)-, wherein the C_{1-6} alkylene is optionally substituted with 1-3 independently selected R^a, and the 2-20 membered heteroalkylene is optionally substituted with 1-3 independently selected R^b; and

wherein A^3 is further optionally substituted with a PEG Unit selected from PEG8 to PEG24.

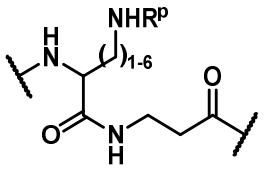
70. The ADC compound of claim 69, wherein subscript a3 is 1.

71. The ADC compound of any one of claims 68-70, wherein A^3 is -NH-(C_{1-10} alkylene)-C(=O)-.

72. The ADC compound of any one of claims 68-70, wherein A^3 is –NH-(CH_2CH_2)-C(=O)-.

73. The ADC compound of any one of claims 68-70, wherein A^3 is -NH-(2-20 membered heteroalkylene)-C(=O)-, wherein the 2-20 membered heteroalkylene is optionally substituted with 1-3 independently selected R^b; and

wherein A^3 is further optionally substituted with a PEG Unit selected from PEG8 to PEG24.

74. The ADC compound of claim 69, wherein A^3 is , wherein R^p is selected from PEG2 to PEG24.

75. The ADC compound of claim 74, wherein R^p is PEG12.

76. The ADC compound of claim 74, wherein the PEG Unit R^p comprises a -(C_{1-6} alkylene)C(=O)- group, the carbonyl carbon atom of which provides covalent attachment of R^P to the nitrogen atom.

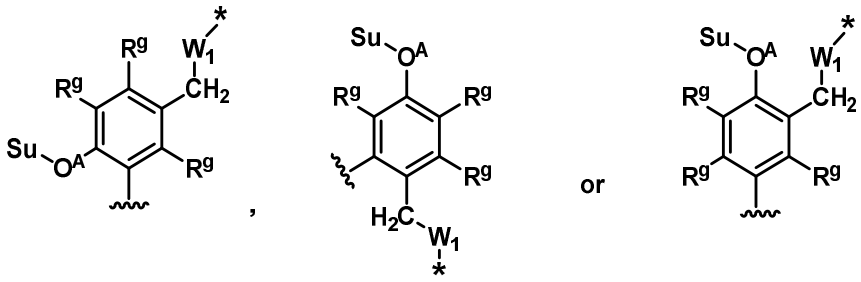
77. The ADC compound of any one of claims 66-76, wherein W is from 2 to 12 amino acids independently selected from natural and unnatural amino acids.

78. The ADC compound of claim 77, wherein W is a dipeptide.

79. The ADC compound of any one of claims 66-78, wherein the bond between W, and D or Y, is enzymatically cleavable by a tumor-associated protease.

80. The ADC compound of claim 79, wherein the tumor-associate protease is a cathepsin.

81. The ADC compound of any one of claims 66-76, wherein W has the structure of:



wherein Su is a Sugar moiety;

$-O^A-$ represents the oxygen atom of a glycosidic bond;

each R^g is independently hydrogen, halogen, -CN, or $-NO_2$;

W^1 is selected from the group consisting of: a bond, -O-, -C(=O)-, $-S(O)_{0-2}-$, -NH-, $-N(C_{1-6}$ alkyl)-, $–[N(C_{1-6}$ alkyl$)_2]^+-$, -OC(=O)-, -NHC(=O)-, -C(=O)O-, and -C(=O)NH-;

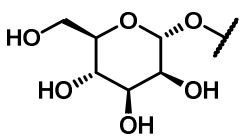
the wavy line represents the covalent attachment to A, Q, or L^1; and

the * represents the covalent attachment to Y or D.

82. The ADC compound of any one of claims 66-75 and 81, wherein O^A-Su is charge neutral at physiological pH.

83. The ADC compound of any one of claims 66-75 and 81-82, wherein Su of O^A-Su is mannose.

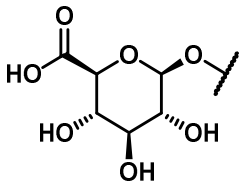
84. The ADC compound of any one of claims 66-75 and 81, wherein O^A-Su is



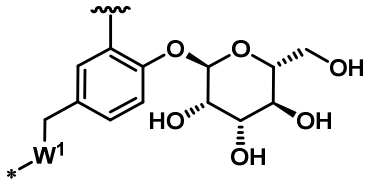
.

85. The ADC compound of any one of claims 66-75 and 81, wherein Su of O^A-Su comprises a carboxylate moiety.

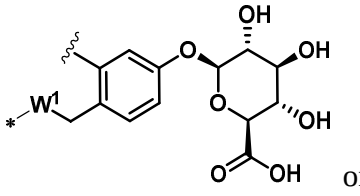
86. The ADC compound of any one of claims 66-75, 81, and 85, wherein Su of O^A-Su is glucuronic acid.

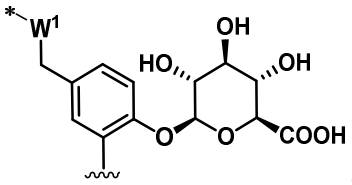
87. The ADC compound of claim 77, wherein O^A-Su is 

.

88. The ADC compound of any one of claims 66-75 and 81, wherein W is 

.

89. The ADC compound of any one of claims 66-75 and 81, wherein W is 

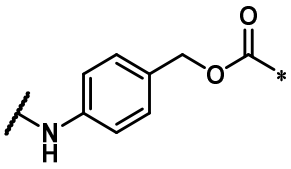
or 

.

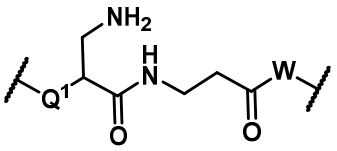
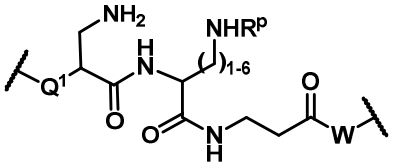
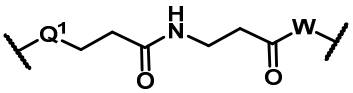
90. The ADC compound of any one of claims 66-89, wherein W^1 is a bond.

91. The ADC compound of any one of claims 66-89, wherein W^1 is -O(C=O)-.

92. The ADC compound of any one of claims 66-91, wherein subscript y is 0.

93. The ADC compound of claims 66-91, wherein subscript y is 1; and Y is , wherein the wavy line represents covalent attachment to W or A; and

the * represents covalent attachment to D.

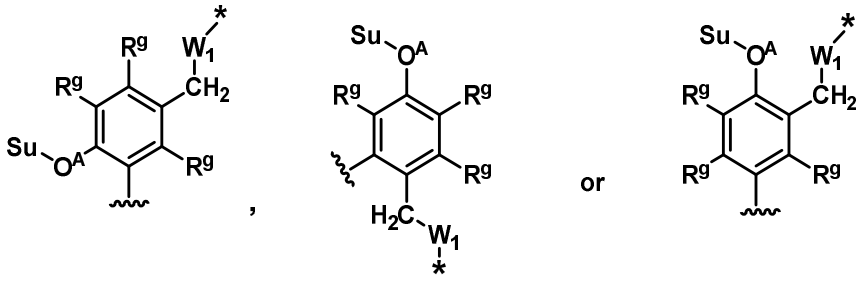
94. The ADC compound of any one of claims 66-68, wherein Q-A is , , or ,

wherein R^p is PEG8 to PEG24,

95. The ADC compound of claim 94, wherein R^p is PEG12.

96. The ADC compound of claim 94 or 95, wherein the PEG Unit R^p comprises a -(C_{1-6} alkylene)C(=O)- group, the carbonyl carbon atom of which provides covalent attachment of R^P to the nitrogen atom.

97. The ADC compound of any one of claims 66-76, 81, and 92-96, wherein W has the structure of:



wherein Su is a Sugar moiety;

$-O^A-$ represents the oxygen atom of a glycosidic bond;

each R^g is independently hydrogen, halogen, -CN, or $-NO_2$;

W^1 is selected from the group consisting of: a bond, -O-, -C(=O)-, $-S(O)_{0-2}-$, -NH-, $-N(C_{1-6}$ alkyl)-, and $–[N(C_{1-6}$ alkyl$)_2]^+-$;

the wavy line represents the covalent attachment to A, Q, or L^1; and

the * represents the covalent attachment to Y or D.

98. The ADC compound of any one of claims 66, 81, and 96, wherein each R^g is hydrogen or one R^g is halogen, -CN, or $-NO_2$ and each remaining R^g is hydrogen.

99. The ADC compound of claim 97, wherein W^1 is -OC(=O)-; and O^A-Su is charged neutral.

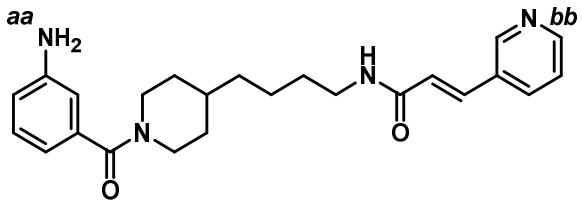
100. The ADC compound of claim 97, wherein W^1 is a bond; D is conjugated to W through a nitrogen atom which forms an ammonium cation at physiological pH; and O^A-Su comprises a carboxylate.

101. The ADC compound of any one of claims 1-100 wherein D is a hydrophilic Drug Unit.

102. The ADC compound of any one of claims 1-101, wherein D is from a cytotoxic agent.

103. The ADC compound of any one of claims 1-100 wherein D is from gemcitabine, MMAE, or MMAF.

104. The ADC compound of any one of claims 1-100 wherein D is a from a NAMPT inhibitor.

105. The ADC compound of any one of claims 1-100 and 104, wherein D has the following formula: 

, wherein D is covalently attached to L^2 at the aa or bb position.

106. The ADC compound of any one of claims 1-105, wherein each L^2-D has zero net charge at physiological pH.

107. The ADC compound of any one of claims 1-106, wherein each L^2-D has no charged species at physiological pH.

108. The ADC compound of any one of claims 1-105, wherein each L^2-D is zwitterionic at physiological pH.

109. The ADC compound of claims 1-106 and 108, wherein each L^2-D comprises a carboxylate and an ammonium.

110. The ADC compound of claim 109, wherein the ammonium is a quaternary ammonium.

111. The ADC compound of claim 110, wherein the quaternary ammonium is pyridinium.

112. The ADC compound of any one of claims 1-106, wherein L^2 is anionic; and D is cationic.

113. The ADC compound of any one of claims 1-106 and 108-109, wherein L^2 comprises a carboxylate; and D comprises an ammonium.

114. The ADC compound of any one of claims 1-113, wherein the ratio of D to Ab is 8:1.

115. The ADC compound of any one of claims 1-113, wherein the ratio of D to Ab is 16:1 to 64:1

116. The ADC compound of any one of claims 1-113, wherein the ratio of D to Ab is 16:1 to 32:1.

117. The ADC compound of any one of claims 1-113, wherein the ratio of D to Ab is 16:1.

118. The ADC of any one of claims 1-113, wherein the ratio of D to Ab is 8:1; subscript y of $(L^2\text{-}D)_y$ is 4; and subscript p is 2.

119. The ADC of any one of claims 1-113, wherein the ratio of D to Ab is 8:1; y of $(L^2\text{-}D)_y$ is 2; and subscript p is 4.

120. The ADC of any one of claims 1-113, wherein the ratio of D to Ab is 16:1; y of $(L^2\text{-}D)_y$ is 8; and subscript p is 2.

121. The ADC of any one of claims 1-113, wherein the ratio of D to Ab is 16:1; y of $(L^2\text{-}D)_y$ is 4; and subscript p is 4.

122. The ADC of any one of claims 1-113, wherein the ratio of D to Ab is 16:1; y of $(L^2\text{-}D)_y$ is 2; and subscript p is 8.

123. The ADC of any one of claims 1-122, wherein the total number of charges for each instance of $(M)_x\text{-}(L^2\text{-}D)_y$ is an even number at physiological pH.

124. The ADC of any one of claims 1-123, wherein the total number of charges for each instance of $(M)_x\text{-}(L^2\text{-}D)_y \geq 2(x + 2y)$ at physiological pH.

125. The ADC of any one of claims 1-124, wherein the total number of charges for each instance of $(M)_x\text{-}(L^2\text{-}D)_y$ is $2(x + 2y)$ at physiological pH.

126. A composition comprising the ADC of any one of claims 1-125, or a pharmaceutically acceptable salt thereof.

127. Use of the ADC of any one of claims 1-125, or a pharmaceutically acceptable salt thereof, or the composition of claim 126 in the manufacture of a medicament for treating cancer in a subject in need thereof.

128. Use of the ADC of any one of claims 1-125, or a pharmaceutically acceptable salt thereof, or the composition of claim 126 in the manufacture of a medicament for treating an autoimmune disorder in a subject in need thereof.