IMMUNOSTIMULATORY COMPOUNDS AND CONJUGATES

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority from U.S. Provisional Application No. 63/145,367, filed February 3, 2021, which is hereby incorporated by reference in its entirety.

INCORPORATION BY REFERENCE

[0002] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BACKGROUND

[0003] Toll-like receptors (TLRs) play an important role in activitating the immune system against invading pathogens and against damaged cells that may lead to cancer. *See* Kaczanowska, et al., *J. Leukoc. Biol.* 2013; 93(6): 847-863. TLRs are a family of single-pass membrane bound proteins that, when activated, recuit adaptor proteins to propagate the antigen-induced signal transduction pathway. As immunostimulatory compounds, TLR agonists have been developed as vaccine adjuvants, to boost production of immune cells that target the desired viral or bacterial antigen in the vaccine. TLRs also recognize endogenous markers of tumorigenesis such as cell death and chronic inflammation and activate an innate immune response to these cells. *See,* e.g.*,* Ellerman, et al., *Clin. Cancer Res.* 2007; 13: 2836-2848; Hernandez, et al., *Oncogene* 2016; 35: 5931-5941; and Urban-Wojciuk, et al., *Front. Immunol.*, Vol. 10, pp. 2388-2398 (2019). However, due to their immunostimulatory properties, systemic use of TLR agonists may be restricted by dose-limiting toxicities resulting from systemic cytokine induction. *See* Adams, S., *Immunotherapy* 2009; 1(6): 949-964. Thus, there remains a need for targeted immunostimulatory compounds to localize the immune response to the desired cells while minimizing off-target effects.

SUMMARY

[0004] The present disclosure provides compounds and biomolecular complexes (e.g., antibody-drug conjugates) which elicit cell- and tissue-specific immune responses. As cancer immunosuppression is often localized within microenvironments proximal to the cancerous cells, such targeted molecules and complexes can activate immune responses at cancer sites while minimizing undesired responses in healthy tissues. To achieve this end, ~~in certain~~

~~embodiments,~~ the present disclosure provides antibody-drug conjugates (ADCs) configured to selectively activate immune responses in the presence of cancer cells. In addition to localizing to targeted cancer sites, ADCs of the present disclosure can be configured to release their payloads (e.g., TLR agonists) only within the presence of or upon uptake by the cancerous (or cancer-associated) cells, thereby limiting immune activation to cancer sites, and preventing off-target (e.g., broad systemic) immune activation.

[0005] The ADCs described herein, as well as pharmaceutically acceptable salts thereof, can be configured for uptake by a target cell or tissue. In ~~some embodiments~~the disclosure, an ADC is configured to endocytose upon binding to a membrane bound and/or surface displayed antigen. In such cases, the ADC may target intracellular receptors such as TLR7 or TLR8, which are often primarily localized within endosomes. Endocytosis can be aided by lipophilic groups appended to the ADC, such as PEGylated or neutral and nonpolar peptidic linkers.

[0006] In addition to targeting, release of an ADC drug unit can be controlled such that the release occurs at a designated site (e.g, within a cell targeted by the antibody). As a linker (L) cleavable group can be configured for cleavage within particular physiological conditions or by specific enzymes, release of the Drug Unit can be limited primarily to the target site. Accordingly, the biological effects of the Drug Unit (such as immunostimulatory effects) can be localized to a target site. Alternatively, the Drug Unit can be configured to remain attached to the antibody, or a portion of the antibody and/or linker and induce its biological effect while coupled to the antibody.

[0007] ~~In various embodiments,~~ ~~t~~The present disclosure provides antibody drug conjugates (ADC) having the structure:

$$\mathbf{Ab\text{-}(L\text{-}D)_p}$$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody as defined herein;

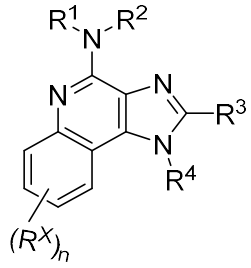
each L is a linker as defined herein;

wherein each D is conjugated to a linker as described herein;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ϵ-amino group of a lysine residue as described herein;

subscript p is as defined herein.

[0008] In ~~some aspects~~the disclosure, each D has the structure of Formula (A):

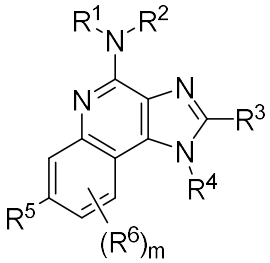


(A)

or a pharmaceutically acceptable salt thereof;

wherein each of R^1, R^2, R^3, R^4, R^X, and n are as defined herein.

[0009] In ~~other aspects~~the disclosure, each D has the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^6, and m are as defined here.

[0009a] In one aspect, the present disclosure provides an antibody drug conjugate (ADC) having the structure:

Ab-(L-D)$_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

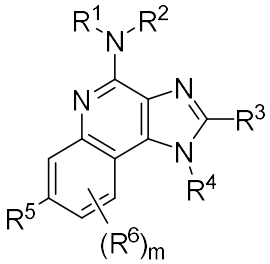
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ϵ-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $–NR^AR^B$;

R^2 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $–NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, $–NR^AR^B$, $–C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) the point of covalent attachment to L; (b) $-OR^C$; (c) $-S(=O)2R^C$; (d) $-C(=O)NR^DR^E$; (e) $-C(=O)OR^C$; (f) $-C(=O)SR^C$; (g) $-C(=S)R^C$; (h) $-PO_3R^C$; or (j) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$;

wherein when R^4 is (j), the C_1-C_6 alkyl, or a substituent thereof, may be further substituted with the point of covalent attachment to L;

R^5 is selected from the group consisting of $-C(=O)OR^F$, $-NO_2$, -CN, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, $-N(R^I)-S(O_2)R^K$, and SO_3R^K;

each R^6 is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $–NR^AR^B$; wherein no more than one R^6 is the point of covalent attachment to L;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is (a) the point of covalent attachment to L, (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^A and R^B is the point of covalent attachment to L;

R^C is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H are (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^D, R^E, R^G, and R^H is the point of covalent attachment to L;

R^F is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

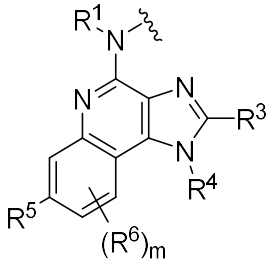
each R^I, R^J, and R^K is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein only one of R^I, R^J, and R^K is the point of covalent attachment to L;

wherein only one of R^1, R^2, R^3, R^4, R^5, R^6, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, and R^K is the point of covalent attachment to L;

R^1 and R^4 are each optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and

wherein each D has only one point of covalent attachment to L.

[0010] In ~~further embodiments~~the disclosure, each D has the structure of Formula (II):

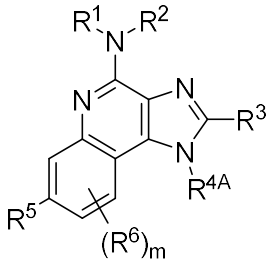


(II)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^3, R^4, R^5, R^6, and m are as defined herein.

[0011] In ~~other embodiments~~the disclosure, each D has the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^{4A}, R^5, R^6, and m are as defined herein.

[0011a] In another aspect, the present disclosure provides an antibody drug conjugate (ADC) having the structure:

$Ab-(L-D)_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

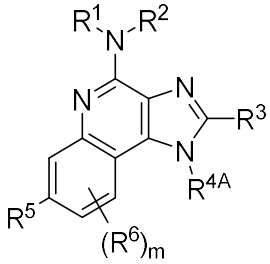
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ϵ-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl,

halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^{4A} is (a) the point of covalent attachment to L or (b) C_1-C_6 alkyl substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -$[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, -NR^DR^E, C_1-C_6 alkoxy, -$C(=O)NR^DR^E$, or -CO_2H;

wherein when R^{4A} is (b), the C_1-C_6 alkyl, or a substituent thereof, is further substituted with the point of covalent attachment to L;

R^5 is selected from the group consisting of -$C(=O)OR^F$, -NO_2, -CN, -CF_3 -$C(=O)NR^GR^H$, -$S(O_2)NR^GR^H$, -$N(R^I)$-$C(=O)R^J$, -$N(R^I)$-$S(O_2)R^K$, and -SO_3R^K;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and –NR^AR^B;

subscript m is 0, 1, 2, or 3;

each R^A and R^B independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

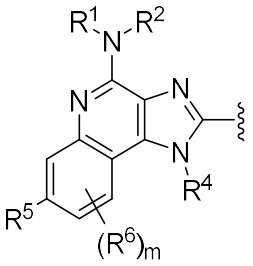
each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

R^1 is optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

[0012] In ~~some embodiments~~the disclosure, each D has the structure of Formula (IV):

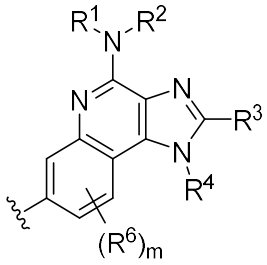


(IV)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^4, R^5, R^6, and m are as defined herein.

[0013] In ~~further embodiments~~the disclosure, each D has the structure of Formula (V):

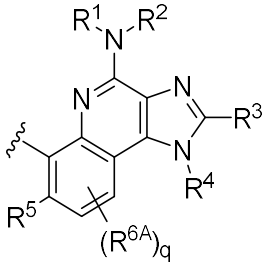


(V)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^6, and m are as defined herein.

[0014] In ~~some aspects~~the disclosure, each D has the structure of Formula (VI):

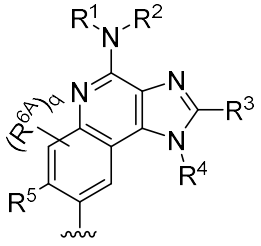


(VI)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^{6A}, and q are as defined herein.

[0015] In ~~certain embodiments~~the disclosure, each D has the structure of Formula (VII):

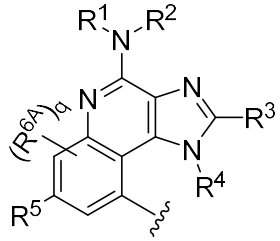


(VII)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^{6A}, and q are as defined herein.

[0016] In the disclosure~~some aspects~~, each D has the structure of Formula (VIII):

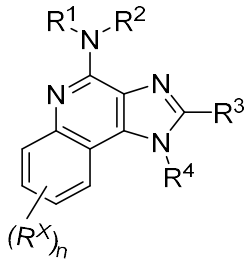


(VIII)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^{6A}, and q are as defined herein.

[0017] In the disclosure~~some embodiments~~, each D has the structure of Formula (A):

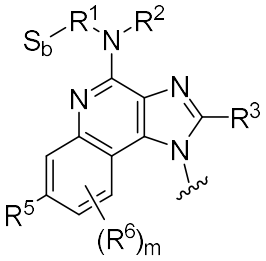


(A)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^X, and n are as defined herein.

[0018] In the disclosure~~some aspects~~, each D has the structure of Formula (XI):

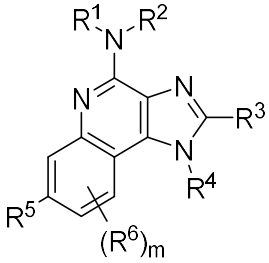


(XI)

or a pharmaceutically acceptable salt thereof;

wherein S_b, R^1, R^2, R^3, R^5, R^6, and m are as defined herein.

[0019] ~~In further aspects,~~ T~~t~~he present disclosure provides compounds of Formula (IX):

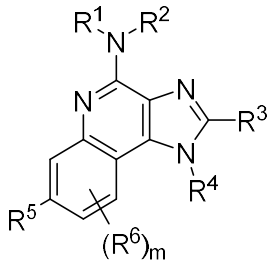


(IX)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^6, and m are as defined herein.

[0019a] In another aspect, the present disclosure provides a compound of Formula (IX):



(IX)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $–NR^AR^B$;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $–NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen, $–NR^AR^B$, $–C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the

group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) $-OR^C$; (b) $-S(=O)_2R^C$; (c) $-C(=O)NR^DR^E$; (d) $-C(=O)OR^C$; (e) $-C(=O)SR^C$; (f) $-C(=S)R^C$; (g) $-PO_3R^C$; or (h) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is $-C(=O)OR^F$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $–NR^AR^B$;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

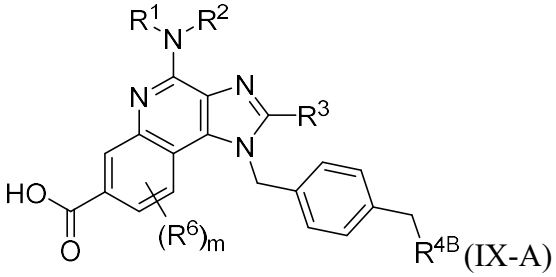
R^F is hydrogen;

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

and

each instance of R^1 and R^4 is optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide.

[0020] ~~In further aspects,~~ Tthe present disclosure provides compounds of Formula (IX-A):

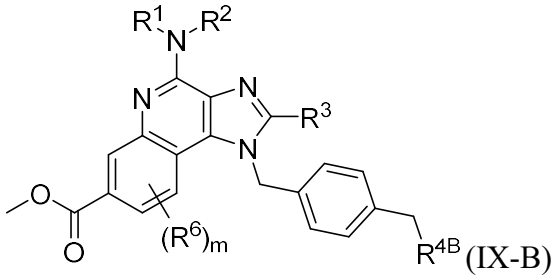


(IX-A)

or a pharmaceutically acceptable salt thereof,

wherein R^1, R^2, R^3, R^{4B}, R^6, and m are as defined herein.

[0021] ~~In other aspects,~~ The present disclosure provides compounds having the structure of Formula (IX-B):

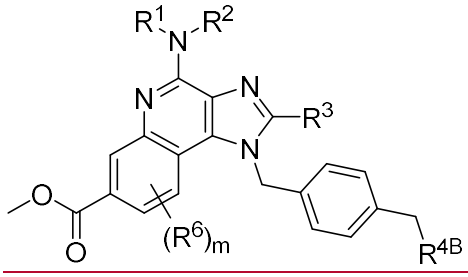


(IX-B)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^{4B}, R^6, and m are as defined herein.

[0021a] In another aspect, the present disclosure provides a compound of Formula (IX-B):



(IX-B)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^2 is selected from the group consisting of hydrogen and C_1-C_6 alkyl; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_1-C_6 alkoxy, and C_1-C_6 alkylthio;

R^{4B} is selected from the group consisting of $-NR^DR^E$ and $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$;

R^6 selected from the group consisting of halogen, hydroxyl, nitro, cyano, $C_1\text{-}C_6$ alkyl, $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkanoyl, $C_1\text{-}C_6$ alkanoyloxy, $C_1\text{-}C_6$ alkoxycarbonyl, $C_1\text{-}C_6$ haloalkyl, and $C_1\text{-}C_6$ haloalkoxy;

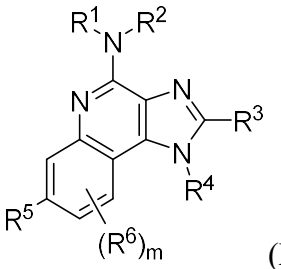
subscript m is 0 or 1; and

R^D and R^E are independently selected from the group consisting of $C_1\text{-}C_6$ alkyl, $C_2\text{-}C_6$ alkenyl, $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkyl($C_1\text{-}C_6$ alkyl)-, aryl, and aryl($C_1\text{-}C_6$ alkyl)-.

[0022] ~~In other aspects,~~ T~~t~~he present disclosure provides compounds having the formula L^1-D, or a pharmaceutically acceptable salt thereof, wherein:

L^1 is a linker intermediate as defined herein; and

D has the structure of Formula (X):



(X)

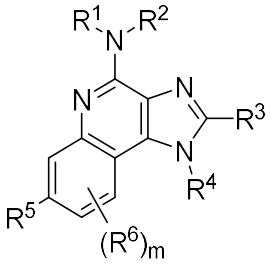
or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^6, and m are as defined herein.

[0023] ~~In further aspects, t~~T~~h~~he present disclosure provides compounds having the formula L^1-D, or a pharmaceutically acceptable salt thereof, wherein:

L^1 is a linker intermediate; and

D is a compound of Formula (X):



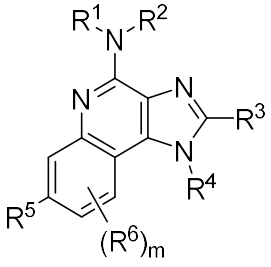
(X)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^6, and m are as defined herein.

[0023a] In another aspect, the present disclosure provides a compound having the formula L^1-D, or a pharmaceutically acceptable salt thereof, wherein:

L^1 is a linker intermediate; and
D has the structure of Formula (X):



(X)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $–NR^AR^B$;

R^2 is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently

selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) the point of covalent attachment to L^1; (b) $-OR^C$; (c) $-S(=O)2R^C$; (d) $-C(=O)NR^DR^E$; (e) $-C(=O)OR^C$; (f) $-C(=O)SR^C$; (g) $-C(=S)R^C$; (h) $-PO_3R^C$; or (j) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, -NR^DR^E, C_1-C_6 alkoxy, -$C(=O)NR^DR^E$, -SR^C, (C_1-C_6)alkoxycarbonyl, or -CO_2H;

R^5 is selected from the group consisting of -$C(=O)OR^F$, -NO_2, -CN, -CF_3 -$C(=O)NR^GR^H$, -$S(O_2)NR^GR^H$, -$N(R^I)$-$C(=O)R^J$, -$N(R^I)$-$S(O_2)R^K$, and SO_3R^K;

each R^6 is (a) the point of covalent attachment to L^1; or (b) independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and –NR^AR^B; wherein no more than one R^6 is the point of covalent attachment to L^1;

wherein when R^4 is (c), the C_1-C_6 alkyl, or a substituent thereof, may be further substituted with the point of covalent attachment to L^1;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is (a) the point of covalent attachment to L^1, (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^A and R^B is the point of covalent attachment to L^1;

R^C is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H are (a) the point of covalent attachment to L^1; or (b) independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^D, R^E, R^G, and R^H is the point of covalent attachment to L^1;

R^F is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

each R^I, R^J, and R^K is (a) the point of covalent attachment to L^1; or (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein only one of R^I, R^J, and R^K is the point of covalent attachment to L^1.

each instance of R^1 and R^4 is optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide;

wherein only one of R^1, R^2, R^3, R^4, R^5 R^A, R^6, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, and R^K is the point of covalent attachment to L^1; and

wherein Formula (X) has only one point of covalent attachment to L^1.

[0024] ~~Additional aspects of t~~The present disclosure provide methods of making and using the compounds of the present disclosure.

[0024a] In another aspect, the present disclosure provides a composition comprising a distribution of the ADCs as defined herein, or a pharmaceutically acceptable salt thereof.

[0024b] In another aspect, the present disclosure provides use of an antibody drug conjugate (ADC) as defined herein, a composition as defined herein, or a compound as defined herein in the manufacture of a medicament for the treatment of cancer.

[0024c] In another aspect, the present disclosure provides an antibody drug conjugate (ADC) as defined herein, a composition as defined herein, or a compound as defined herein for use in therapy.

BRIEF DESCRIPTION OF THE FIGURES

[0025] FIGURE 1 illustrates the responses of human PBMCs from a single donor to selected small molecule TLR7/8 agonists.

[0026] FIGURE 2 illustrates the average response of human PBMCs isolated from 3 donors to selected small molecule TLR7/8 agonists.

[0027] FIGURE 3 illustrates the responses of human PBMCs to selected TLR7/8 agonists having either a carboxylic acid (**S5b**, **S8b**, **S11b**) or methyl ester functional group (**S5a**, **S8a**, **S11a**).

[0028] FIGURE 4 illustrates the responses of human immune cells to various small molecule TLR7/8 agonists.

[0029] FIGURE 5 illustrates the responses of human immune cells to selected TLR7/8 agonists having either a carboxylic acid (**S18b**) or methyl ester functional group (**S18a**).

[0030] FIGURE 6 illustrates the responses of human immune cells to various TLR7/8 agonists conjugated to a targeting antibody.

[0031] FIGURE 7 illustrates the responses of human immune cells to selected TLR7/8 agonists having either a carboxylic acid (**S18b**) or methyl ester functional group (**S18a**) conjugated to a targeting antibody.

[0032] FIGURE 8 illustrates the responses of human immune cells to selected TLR7/8 agonists having either a carboxylic acid (**S14b, S18b, S76b**) or methyl ester functional group (**S14a, S18a, S76a**) conjugated to a targeting antibody.

[0033] FIGURE 9 illustrates the comparison of level of aggregation of various conjugated immunostimulatory ADCs.

WHAT IS CLAIMED IS:

1. An antibody-drug conjugate (ADC) having the structure:

$$Ab-(L-D)_p$$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

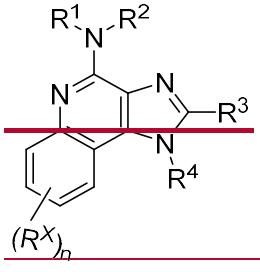
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (A):



(A)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^2 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with

~~1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$; or~~

~~R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;~~

~~R^3 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;~~

~~R^4 is (a) the point of covalent attachment to L; (b) $-OR^C$; (c) $-S(=O)_2R^C$; (d) $-C(=O)NR^DR^E$; (e) $-C(=O)OR^C$; (f) $-C(=O)SR^C$; (g) $-C(=S)R^C$; (h) $-PO_3R^C$; or (j) C_1-C_6 alkyl optionally substituted with:~~

~~(i) 1-3 independently selected halogen;~~

~~(ii) $-OR^C$;~~

~~(iii) $-SR^C$;~~

~~(iv) $-NH-S(O_2)R^C$;~~

~~(v) $-OC(=O)R^C$;~~

~~(vi) $-CO_2H$;~~

~~(vii) C_1-C_6 alkoxycarbonyl;~~

~~(viii) $-C(=O)NR^DR^E$;~~

~~(ix) $-NR^DR^E$;~~

~~(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;~~

~~(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;~~

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, -$C(=O)NR^DR^E$, or -CO_2H;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$;

wherein when R^4 is (j), the C_1-C_6 alkyl, or a substituent thereof, may be further substituted with the point of covalent attachment to L;

each R^X is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, $-N(R^I)-S(O_2)R^K$, halogen, hydroxyl, nitro, cyano, $-CF_3$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B; wherein no more than one R^X is the point of covalent attachment to L;

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

each R^A and R^B is (a) the point of covalent attachment to L, (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^A and R^B is the point of covalent attachment to L;

R^C is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H are (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl) , aryl, and aryl(C_1-C_6 alkyl) ; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^D, R^E, R^G, and R^H is the point of covalent attachment to L;

R^F is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8

~~cycloalkyl, aryl, aryl(C_1-C_6 alkyl), and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;~~

~~each R^I, R^J, and R^K is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein only one of R^I, R^J, and R^K is the point of covalent attachment to L;~~

~~wherein only one of R^1, R^2, R^3, R^4, R^X, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, and R^K is the point of covalent attachment to L;~~

~~R^1 and R^4 are each optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and~~

~~wherein each D has only one point of covalent attachment to L.~~

~~2.~~1. An antibody drug conjugate (ADC) having the structure:

Ab-(L-D)$_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

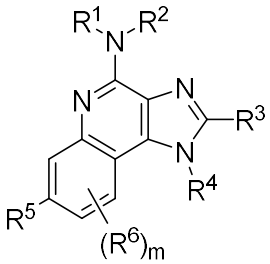
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ϵ-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $–NR^AR^B$;

R^2 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $–NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, $–NR^AR^B$, $–C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) the point of covalent attachment to L; (b) $-OR^C$; (c) $-S(=O)2R^C$; (d) $-C(=O)NR^DR^E$; (e) $-C(=O)OR^C$; (f) $-C(=O)SR^C$; (g) $-C(=S)R^C$; (h) $-PO_3R^C$; or (j) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$;

wherein when R^4 is (j), the C_1-C_6 alkyl, or a substituent thereof, may be further substituted with the point of covalent attachment to L;

R^5 is ~~(a) the point of covalent attachment to L; or (b)~~ selected from the group consisting of ~~hydrogen,~~ $-C(=O)OR^F$, $-NO_2$, -CN, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)$-$C(=O)R^J$, $-N(R^I)$-$S(O_2)R^K$, and SO_3R^K;

each R^6 is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $–NR^AR^B$; wherein no more than one R^6 is the point of covalent attachment to L;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is (a) the point of covalent attachment to L, (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^A and R^B is the point of covalent attachment to L;

R^C is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H are (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered

heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^D, R^E, R^G, and R^H is the point of covalent attachment to L;

R^F is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

each R^I, R^J, and R^K is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein only one of R^I, R^J, and R^K is the point of covalent attachment to L;

wherein only one of R^1, R^2, R^3, R^4, R^5, R^6, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, and R^K is the point of covalent attachment to L;

R^1 and R^4 are each optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and

wherein each D has only one point of covalent attachment to L.

~~3. An antibody drug conjugate (ADC) having the structure:~~

~~$Ab-(L-D)_p$~~

~~or a pharmaceutically acceptable salt thereof;~~

~~wherein:~~

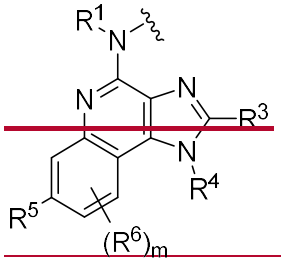
~~Ab is an antibody;~~

~~wherein each D is conjugated to a linker (L);~~

~~wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;~~

~~subscript p is an integer from 1 to 16;~~

~~each D has the structure of Formula (II):~~



~~(II)~~

~~or a pharmaceutically acceptable salt thereof;~~

~~wherein:~~

~~~~ represents covalent attachment to L;~~
~~~~

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) $-OR^C$ (b) $-S(=O)2R^C$; (c) $-C(=O)NR^DR^E$; (d) $-C(=O)OR^C$; (e) $-C(=O)SR^C$; (f) $-C(=S)R^C$; (g) $-PO_3R^C$; or (h) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-NO_2$, $-CN$, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)C(=O)R^J$, $-N(R^I)S(O_2)R^K$, and SO_3R^K;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^1 and R^4 are each optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

4. An antibody drug conjugate (ADC) having the structure:

$Ab\text{-}(L\text{-}D)_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

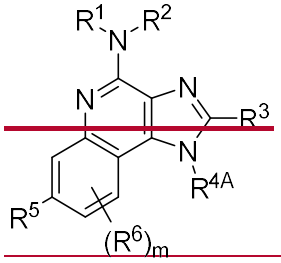
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^{4A} is (a) the point of covalent attachment to L or (b) C_1-C_6 alkyl substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

wherein when R^{4A} is (b), the C_1-C_6 alkyl, or a substituent thereof, is further substituted with the point of covalent attachment to L;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-NO_2$, $-CN$, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, $-N(R^I)-S(O_2)R^K$, and $-SO_3R^K$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B;

subscript m is 0, 1, 2, or 3;

each R^A and R^B independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

R^I is optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

5. An antibody drug conjugate (ADC) having the structure:

$Ab-(L-D)_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

wherein each D is conjugated to a linker (L);

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula $-M-(A)_a-(W)_w-(Y)_y-(X)_x-$, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, or a triazole;

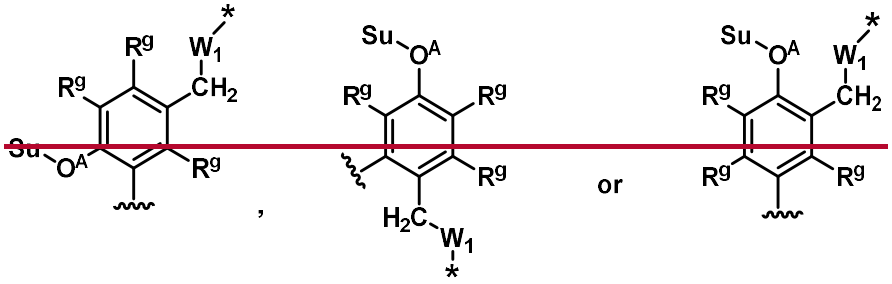
A is a C_{2-20} alkylene optionally substituted with 1-4 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1};

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;

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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, * C(=O)-O , or * O-C(=O) ;

~~~~ represents covalent attachment to A or M;

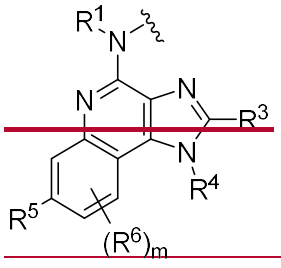
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (II):
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(II)

or a pharmaceutically acceptable salt thereof;

wherein:

---- represents covalent attachment to L;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^3 is selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) $-OR^C$, (b) $-S(=O)_2R^C$; (c) $-C(=O)NR^DR^E$; (d) $-C(=O)OR^C$; (e) $-C(=O)SR^C$; (f) $-C(=S)R^C$; (g) $-PO_3R^C$; or (h) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-NO_2$, -CN, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)C(=O)R^J$, $-N(R^I)S(O_2)R^K$, and $-SO_3R^K$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

R^1 and R^4 are each optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

6. An antibody drug conjugate (ADC) having the structure:

$Ab-(L-D)_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula $-M-(A)_a-(W)_w-(Y)_y-(X)_x-$, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, or a triazole;

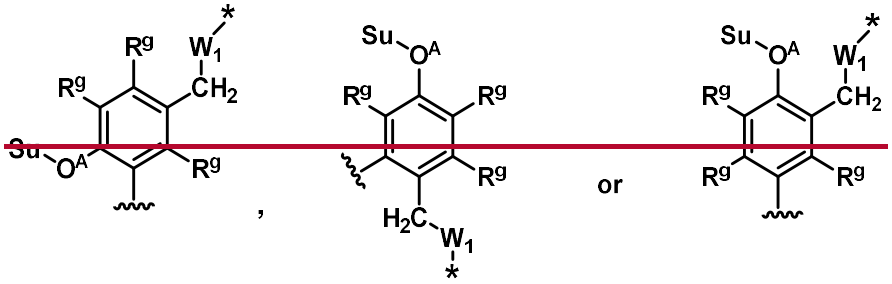
A is a C_{2-20} alkylene optionally substituted with 1-4 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1};

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;

1. 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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, * C(=O) O , or * O C(=O) ;

~~~~ represents covalent attachment to A or M;

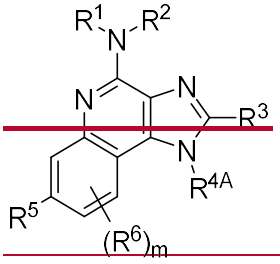
* represents covalent attachment to X, Y, or D;

Y is self immolative moiety, a non self immolative releasable moiety, or a non cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10
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membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^{4A} is (a) the point of covalent attachment to L or (b) C_1-C_6 alkyl substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

wherein when R^{4A} is (b) the C_1-C_6 alky, or a substituent thereof, is further substituted with the point of covalent attachment to L;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-NO_2$, $-CN$, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)C(=O)R^J$, $-N(R^I)S(O_2)R^K$, and $-SO_3R^K$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is i independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

R^I is optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

7. An antibody drug conjugate (ADC) having the structure:

$$\mathbf{Ab\text{-}(L\text{-}D)_p}$$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula -M-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$-, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, or a triazole;

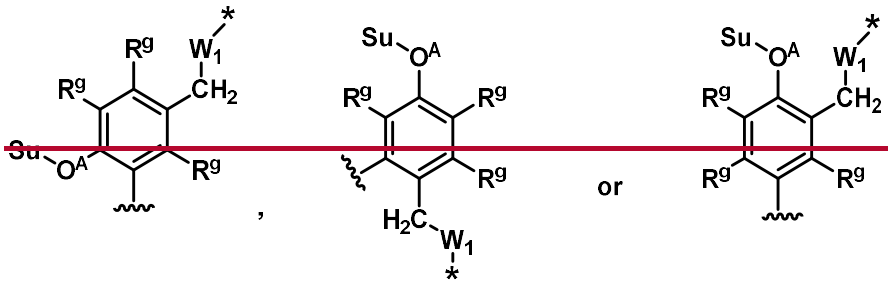
A is a C_{2-20} alkylene optionally substituted with 1-4 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1};

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;

2. 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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, -NHC(=O)(C_1-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, *-C(=O)-O-, or *-O-C(=O)-;

~~~~ represents covalent attachment to A or M;
~~~~

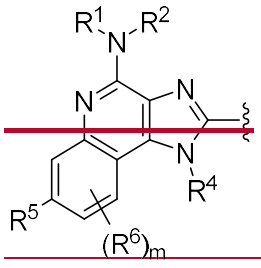
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

3. each D has the structure of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof;

wherein:

~~~~ represents covalent attachment to L;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^4 is (a) $-OR^C$; (b) $-S(=O)_2R^C$; (c) $-C(=O)NR^DR^E$; (d) $-C(=O)OR^C$; (e) $-C(=O)SR^C$; (f) $-C(=S)R^C$; (g) $-PO_3R^C$; or (h) C_1-C_6 alkyl optionally substituted with:
~~~~

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-NO_2$, -CN, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, $-N(R^I)-S(O_2)R^K$, and $-SO_3R^K$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which

they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl) , and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

R^1 and R^4 are each optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

8. An antibody drug conjugate (ADC) having the structure:

$$\mathbf{Ab\text{-}(L\text{-}D)_p}$$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula $-M-(A)_a-(W)_w-(Y)_y-(X)_x-$, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, or a triazole;

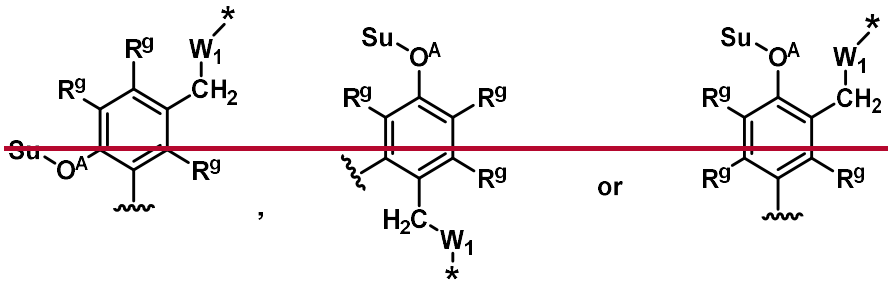
A is a $C_{2\text{-}20}$ alkylene optionally substituted with 1-4 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1};

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

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

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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, * C(=O) O , or * O-C(=O) ;

~~~~ represents covalent attachment to A or M;

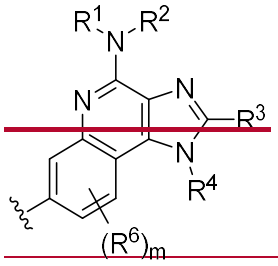
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (V):



(V)

or a pharmaceutically acceptable salt thereof;

wherein:

~~~~ represents covalent attachment to L;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl,

~~C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;~~

~~R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or~~

~~R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;~~

~~R^3 is selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;~~

~~R^4 is (a) $-OR^C$, (b) $-S(=O)_2R^C$; (c) $-C(=O)NR^DR^E$; (d) $-C(=O)OR^C$; (e) $-C(=O)SR^C$; (f) $-C(=S)R^C$; (g) $-PO_3R^C$; or (h) C_1-C_6 alkyl optionally substituted with:~~

- ~~(i) 1-3 independently selected halogen;~~
- ~~(ii) $-OR^C$;~~
- ~~(iii) $-SR^C$;~~
- ~~(iv) $-NH-S(O_2)R^C$;~~
- ~~(v) $-OC(=O)R^C$;~~
- ~~(vi) $-CO_2H$;~~
- ~~(vii) C_1-C_6 alkoxycarbonyl;~~
- ~~(viii) $-C(=O)NR^DR^E$;~~
- ~~(ix) $-NR^DR^E$;~~
- ~~(x) $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$;~~

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D and R^E is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; and

R^1 and R^4 are each optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide.

9. An antibody drug conjugate (ADC) having the structure:

$$\mathbf{Ab\text{-}(L\text{-}D)_p}$$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula -M-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$-, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, or a triazole;

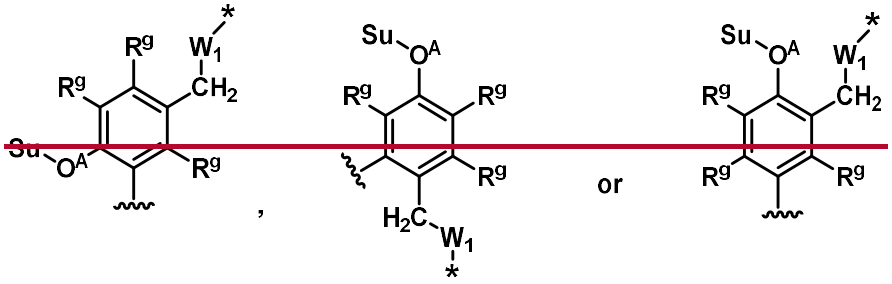
A is a C_{2-20} alkylene optionally substituted with 1-4 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1};

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;

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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, -NHC(=O)(C_1-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, *-C(=O)-O-, or *-O-C(=O)-;

~~~~ represents covalent attachment to A or M;

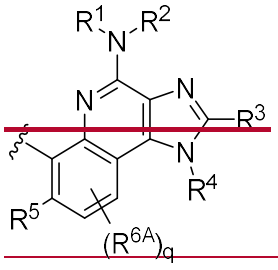
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;
~~~~

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof;

wherein:

~~~~ represents covalent attachment to L;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the
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group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) $-OR^C$, (b) $-S(=O)_2R^C$; (c) $-C(=O)NR^DR^E$; (d) $-C(=O)OR^C$; (e) $-C(=O)SR^C$; (f) $-C(=S)R^C$; (g) $-PO_3R^C$; or (h) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-NO_2$, $-CN$, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, $-N(R^I)-S(O_2)R^K$, and $-SO_3R^K$;

each R^{6A} is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript q is 0, 1, or 2;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

R^1 and R^4 are each optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

10. An antibody-drug conjugate (ADC) having the structure:

$$\mathbf{Ab\text{-}(L\text{-}D)_p}$$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula -M-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$-, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, or a triazole;

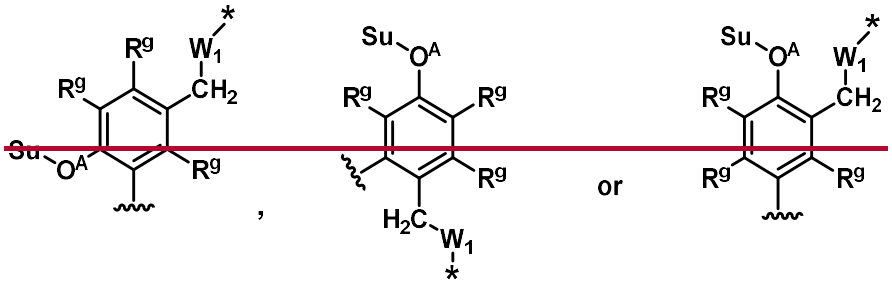
A is a C_{2-20} alkylene optionally substituted with 1-4 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1};

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, $-NR^{d1}R^{e1}$, $-(C_{1-6}\text{ alkylene})-NR^{d1}R^{e1}$, $-C(=O)NR^{d1}R^{e1}$, $-C(=O)(C_{1-6}\text{ alkyl})$, and $-C(=O)O(C_{1-6}\text{ alkyl})$;

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, $-NR^{d1}R^{e1}$, $-(C_{1-6}\text{ alkylene})-NR^{d1}R^{e1}$, $-C(=O)NR^{d1}R^{e1}$, $-C(=O)(C_{1-6}\text{ alkyl})$, and $-C(=O)O(C_{1-6}\text{ alkyl})$;

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

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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, * C(=O) O , or * O-C(=O) ;

~~~~ represents covalent attachment to A or M;

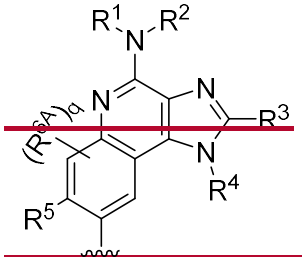
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (VII):



(VII)

or a pharmaceutically acceptable salt thereof;

wherein:

~~~~ represents covalent attachment to L;

~~R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C1-C6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C1-C6 sulfone, C1-C6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C1-C6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C1-C6 sulfone, C1-C6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;~~

~~R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or~~

~~R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;~~

~~R^3 is selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;~~

~~R^4 is (a) OR^C; (b) $S(=O)_2R^C$; (c) $C(=O)NR^DR^E$; (d) $C(=O)OR^C$; (e) $C(=O)SR^C$; (f) $C(=S)R^C$; (g) PO_3R^C; or (h) C_1-C_6 alkyl optionally substituted with:~~

~~(i) 1-3 independently selected halogen;~~

~~(ii) OR^C;~~

~~(iii) SR^C;~~

~~(iv) $NH\text{-}S(O_2)R^C$;~~

~~(v) $OC(=O)R^C$;~~

~~(vi) CO_2H;~~

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-NO_2$, -CN, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)\text{-}C(=O)R^J$, $-N(R^I)\text{-}S(O_2)R^K$, and $-SO_3R^K$;

each R^{6A} is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript q is 0, 1, or 2;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl; and

R^1 and R^4 are each optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

11. An antibody drug conjugate (ADC) having the structure:

$Ab-(L-D)_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula $-M-(A)_a-(W)_w-(Y)_y-(X)_x-$, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, or a triazole;

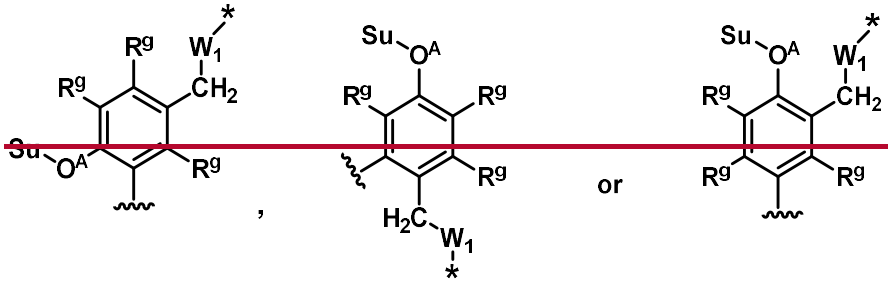
A is a C_{2-20} alkylene optionally substituted with 1-4 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1};

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;

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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), $-CN$, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, * C(=O)-O , or * O-C(=O) ;

~~~~ represents covalent attachment to A or M;

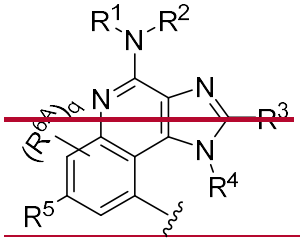
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (VIII):



(VIII)

or a pharmaceutically acceptable salt thereof;

wherein:

~~~~ represents covalent attachment to L;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

~~R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$; or~~

~~R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;~~

~~R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;~~

~~R^4 is (a) $-OR^C$, (b) $-S(=O)_2R^C$; (c) $-C(=O)NR^DR^E$; (d) $-C(=O)OR^C$; (e) $-C(=O)SR^C$; (f) $-C(=S)R^C$; (g) $-PO_3R^C$; or (h) C_1-C_6 alkyl optionally substituted with:~~

- ~~(i) 1-3 independently selected halogen;~~
- ~~(ii) $-OR^C$;~~
- ~~(iii) $-SR^C$;~~
- ~~(iv) $-NH-S(O_2)R^C$;~~
- ~~(v) $-OC(=O)R^C$;~~
- ~~(vi) $-CO_2H$;~~
- ~~(vii) C_1-C_6 alkoxycarbonyl;~~
- ~~(viii) $-C(=O)NR^DR^E$;~~
- ~~(ix) $-NR^DR^E$;~~
- ~~(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;~~
- ~~(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;~~
- ~~(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;~~

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-NO_2$, $-CN$, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)C(=O)R^J$, $-N(R^I)S(O_2)R^K$, and $-SO_3R^K$;

each R^{6A} is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript q is 0, 1, or 2;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

R^1 and R^4 are each optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

12. An antibody drug conjugate (ADC) having the structure:

$$\mathbf{Ab\text{-}(L\text{-}D)_p}$$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

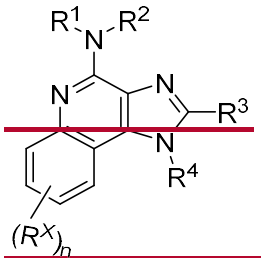
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (A):



(A)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^2 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered

heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) the point of covalent attachment to L; (b) $-OR^C$; or (c) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$;

wherein when R^4 is (c), the C_1-C_6 alkyl, or a substituent thereof, may be further substituted with the point of covalent attachment to L;

each R^X is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)$-$C(=O)R^J$, $-N(R^I)$-$S(O_2)R^K$, halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6

haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B; wherein no more than one R^X is the point of covalent attachment to L;

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

each R^A and R^B is (a) the point of covalent attachment to L, (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^A and R^B is the point of covalent attachment to L;

R^C is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H are (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^D, R^E, R^G, and R^H is the point of covalent attachment to L;

R^F is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

each R^I, R^J, and R^K is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein only one of R^I, R^J, and R^K is the point of covalent attachment to L;

wherein only one of R^1, R^2, R^3, R^4, R^X, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, and R^K is the point of covalent attachment to L; and

wherein each D has only one point of covalent attachment to L.

13. An antibody-drug conjugate (ADC) having the structure:

$$\mathbf{Ab\text{-}(L\text{-}D)_p}$$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

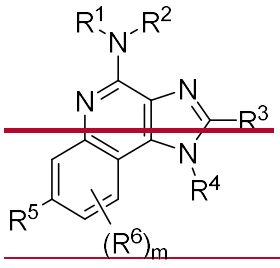
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^2 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3

~~substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;~~

~~R^4 is (a) the point of covalent attachment to L; (b) $-OR^C$; or (c) C_1-C_6 alkyl optionally substituted with:~~

~~(i) 1-3 independently selected halogen;~~

~~(ii) $-OR^C$;~~

~~(iii) $-SR^C$;~~

~~(iv) $-NH-S(O_2)R^C$;~~

~~(v) $-OC(=O)R^C$;~~

~~(vi) $-CO_2H$;~~

~~(vii) C_1-C_6 alkoxycarbonyl;~~

~~(viii) $-C(=O)NR^DR^E$;~~

~~(ix) $-NR^DR^E$;~~

~~(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;~~

~~(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;~~

~~(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;~~

~~(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or~~

~~(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$;~~

~~wherein when R^4 is (c), the C_1-C_6 alkyl, or a substituent thereof, may be further substituted with the point of covalent attachment to L;~~

~~R^5 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, and $-N(R^I)-S(O_2)R^K$;~~

~~each R^6 is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$; wherein no more than one R^6 is the point of covalent attachment to L;~~

subscript m is 0, 1, 2, or 3;

each R^A and R^B is (a) the point of covalent attachment to L, (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^A and R^B is the point of covalent attachment to L;

R^C is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H are (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl) , aryl, and aryl(C_1-C_6 alkyl) ; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^D, R^E, R^G, and R^H is the point of covalent attachment to L;

R^F is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl) , and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

each R^I, R^J, and R^K is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein only one of R^I, R^J, and R^K is the point of covalent attachment to L;

wherein only one of R^1, R^2, R^3, R^4, R^5, R^6, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, and R^K is the point of covalent attachment to L; and

wherein each D has only one point of covalent attachment to L.

14. An antibody drug conjugate (ADC) having the structure:

$$\mathbf{Ab\text{-}(L\text{-}D)_p}$$

or a pharmaceutically acceptable salt thereof;

wherein:

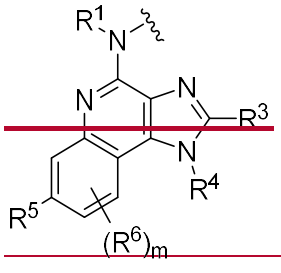
Ab is an antibody;

wherein each D is conjugated to a linker (L);

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof;

wherein:

~~~~ represents covalent attachment to L;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^3 is selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) $-OR^C$ or (b) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;
~~~~

(ix) $-NR^DR^E$;

(x) $-[N(C_1-C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1-C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1-C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, and $-N(R^I)-S(O_2)R^K$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

15. An antibody-drug conjugate (ADC) having the structure:

Ab-(L-D)$_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

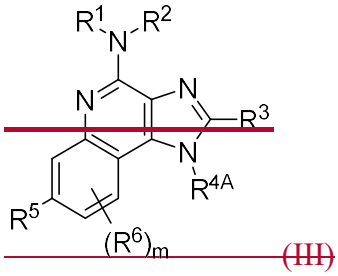
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^{4A} is (a) the point of covalent attachment to L or (b) C_1-C_6 alkyl substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

wherein when R^{4A} is (b), the C_1-C_6 alkyl, or a substituent thereof, is further substituted with the point of covalent attachment to L;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, and $-N(R^I)-S(O_2)R^K$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B;

subscript m is 0, 1, 2, or 3;

each R^A and R^B independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

16. An antibody drug conjugate (ADC) having the structure:

$Ab-(L-D)_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

wherein each D is conjugated to a linker (L);

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula $-M-(A)_a-(W)_w-(Y)_y-(X)_x-$, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, or a triazole;

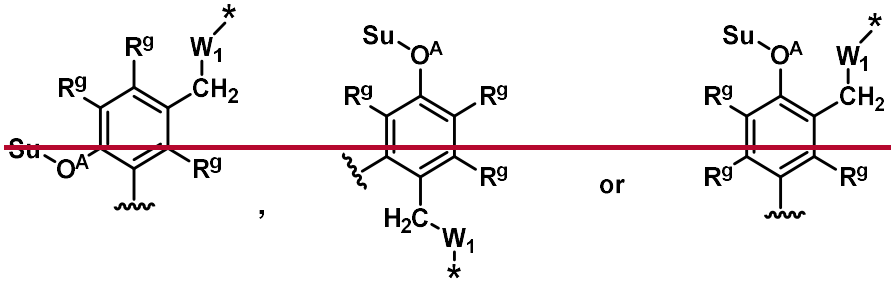
A is a C_{2-20} alkylene optionally substituted with 1-3 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R^{b1};

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;

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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, * C(=O) O , or * O C(=O) ;

~~~~ represents covalent attachment to A or M;

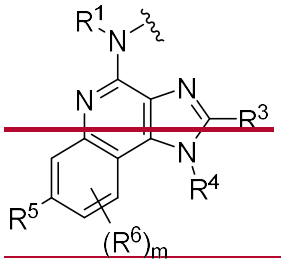
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (II):



(II)
~~~~

or a pharmaceutically acceptable salt thereof;

wherein:

~~~~ represents covalent attachment to L;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) $-OR^C$ or (b) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;
~~~~

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)$-$C(=O)R^J$, and $-N(R^I)$-$S(O_2)R^K$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

17. An antibody drug conjugate (ADC) having the structure:

Ab-(L-D)$_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula -M-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$-, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, or a triazole;

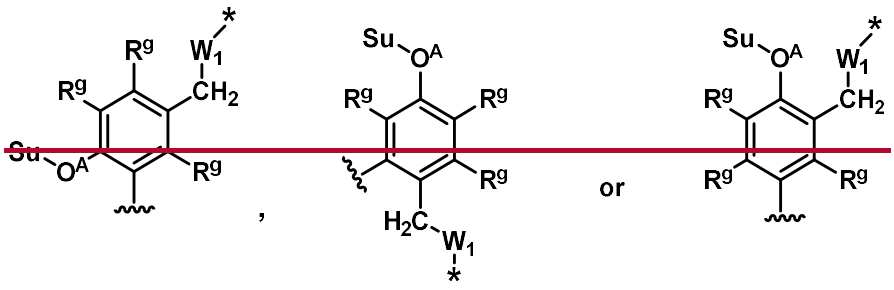
A is a C_{2-20} alkylene optionally substituted with 1-3 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R^{b1};

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;

4. 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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, * C(=O)-O-, or * -O-C(=O)-;

~~~~ represents covalent attachment to A or M;

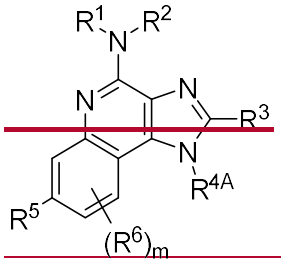
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;
~~~~

~~X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;~~

~~L is optionally substituted with a PEG Unit from PEG1 to PEG72;~~

~~5. each D has the structure of Formula (III):~~



~~(III)~~

~~or a pharmaceutically acceptable salt thereof;~~

~~wherein:~~

~~R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;~~

~~R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or~~

~~R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;~~

~~R^3 is selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the~~

group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^{4A} is (a) the point of covalent attachment to L or (b) C_1-C_6 alkyl substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

wherein when R^{4A} is (b) the C_1-C_6 alky, or a substituent thereof, is further substituted with the point of covalent attachment to L;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, and $-N(R^I)-S(O_2)R^K$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is i independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

18. An antibody drug conjugate (ADC) having the structure:

$$\mathbf{Ab\text{-}(L\text{-}D)_p}$$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula -M-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$-, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, or a triazole;

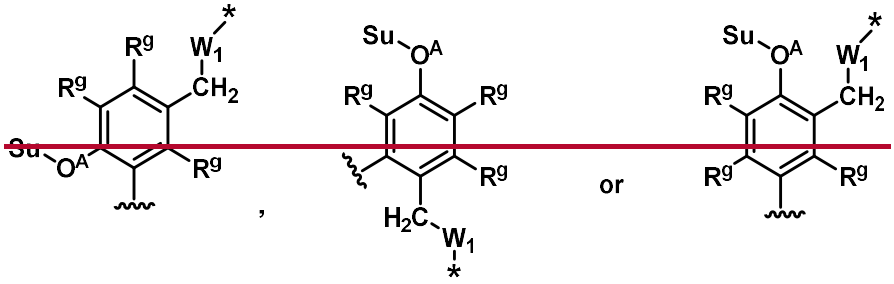
A is a C_{2-20} alkylene optionally substituted with 1-3 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R^{b1};

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, $-NR^{d1}R^{e1}$, $-(C_{1-6}\text{ alkylene})-NR^{d1}R^{e1}$, $-C(=O)NR^{d1}R^{e1}$, $-C(=O)(C_{1-6}\text{ alkyl})$, and $-C(=O)O(C_{1-6}\text{ alkyl})$;

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

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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, * C(=O) O , or * O-C(=O) ;

~~~~ represents covalent attachment to A or M;

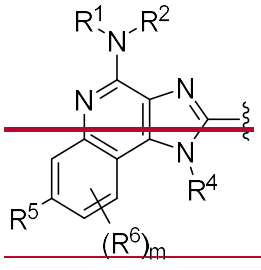
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof;

wherein:

~~~~ represents covalent attachment to L;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally

substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^4 is (a) $-OR^C$ or (b) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, and $-N(R^I)-S(O_2)R^K$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

19. An antibody drug conjugate (ADC) having the structure:

$$\mathbf{Ab\text{-}(L\text{-}D)_p}$$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula $-M-(A)_a-(W)_w-(Y)_y-(X)_x-$, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, or a triazole;

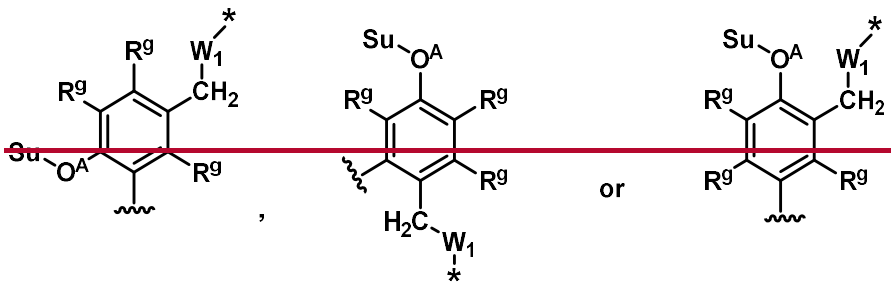
A is a C_{2-20} alkylene optionally substituted with 1-3 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R^{b1};

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;

6. 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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, * C(=O) O , or * O-C(=O) ;

~~~~ represents covalent attachment to A or M;

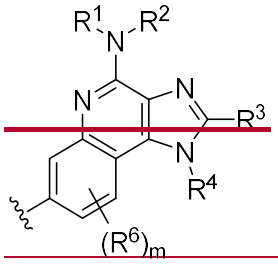
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (V):
~~~~



(V)

or a pharmaceutically acceptable salt thereof;

wherein:

---- represents covalent attachment to L;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) $-OR^C$ or (b) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D and R^E is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl.

20. An antibody drug conjugate (ADC) having the structure:

~~$Ab-(L-D)_p$~~

~~or a pharmaceutically acceptable salt thereof;~~

~~wherein:~~

~~Ab is an antibody;~~

~~each L is a linker;~~

~~wherein each D is conjugated to a linker;~~

~~wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ϵ-amino group of a lysine residue;~~

~~subscript p is an integer from 1 to 16;~~

~~L has the formula $-M-(A)_a-(W)_w-(Y)_y-(X)_x-$, wherein:~~

~~subscript a is 0 or 1;~~

~~subscript y is 0 or 1;~~

~~subscript w is 0 or 1;~~

~~subscript x is 0 or 1;~~

~~M is a succinimide, a hydrolyzed succinimide, an amide, or a triazole;~~

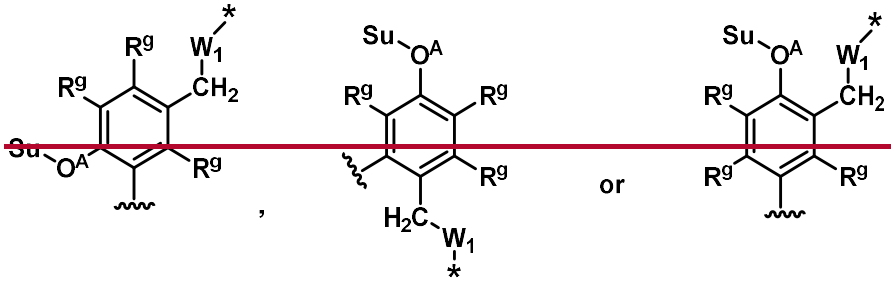
~~A is a C_{2-20} alkylene optionally substituted with 1-3 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R^{b1};~~

~~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;~~

~~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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;~~

W^1 is absent, * $C(=O)O$, or * $OC(=O)$;

~~~~ represents covalent attachment to A or M;

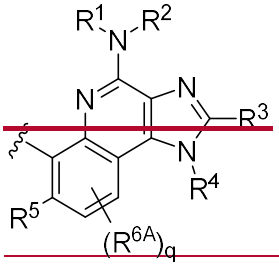
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof;

wherein:

~~~~ represents covalent attachment to L;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy,

~~C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;~~

~~R^4 is (a) $-OR^C$ or (b) C_1-C_6 alkyl optionally substituted with:~~

~~(i) 1-3 independently selected halogen;~~

~~(ii) $-OR^C$;~~

~~(iii) $-SR^C$;~~

~~(iv) $-NH-S(O_2)R^C$;~~

~~(v) $-OC(=O)R^C$;~~

~~(vi) $-CO_2H$;~~

~~(vii) C_1-C_6 alkoxycarbonyl;~~

~~(viii) $-C(=O)NR^DR^E$;~~

~~(ix) $-NR^DR^E$;~~

~~(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;~~

~~(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;~~

~~(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;~~

~~(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or~~

~~(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;~~

~~R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, and $-N(R^I)-S(O_2)R^K$;~~

~~each R^{6A} is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;~~

~~subscript q is 0, 1, or 2;~~

~~each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached,~~

form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

21. An antibody drug conjugate (ADC) having the structure:

$$\mathbf{Ab\text{-}(L\text{-}D)_p}$$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ϵ-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

L has the formula -M-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$-, wherein:

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

M is a succinimide, a hydrolyzed succinimide, an amide, or a triazole;

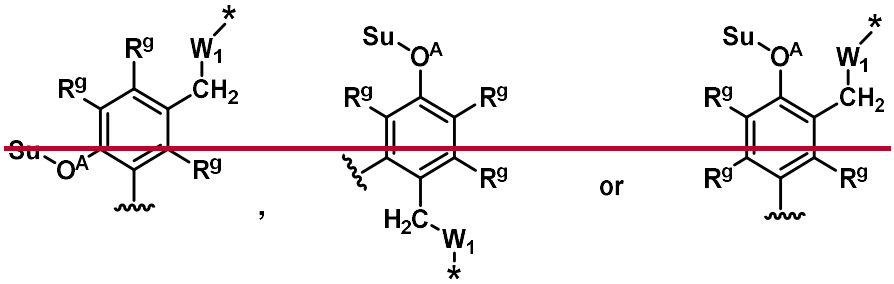
A is a C_{2-20} alkylene optionally substituted with 1-3 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R^{b1};

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, $-NR^{d1}R^{e1}$, $-(C_{1-6}\text{ alkylene})-NR^{d1}R^{e1}$, $-C(=O)NR^{d1}R^{e1}$, $-C(=O)(C_{1-6}\text{ alkyl})$, and $-C(=O)O(C_{1-6}\text{ alkyl})$;

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, $-NR^{d1}R^{e1}$, $-(C_{1-6}\text{ alkylene})-NR^{d1}R^{e1}$, $-C(=O)NR^{d1}R^{e1}$, $-C(=O)(C_{1-6}\text{ alkyl})$, and $-C(=O)O(C_{1-6}\text{ alkyl})$;

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

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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, * C(=O) O , or * O-C(=O) ;

~~~~ represents covalent attachment to A or M;

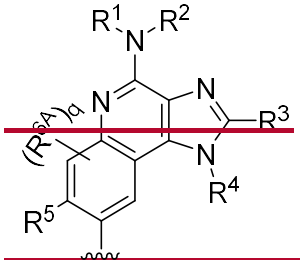
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (VII):



(VII)

or a pharmaceutically acceptable salt thereof;

wherein:

~~~~ represents covalent attachment to L;

~~R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;~~

~~R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$; or~~

~~R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;~~

~~R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;~~

~~R^4 is (a) $-OR^C$ or (b) C_1-C_6 alkyl optionally substituted with:~~

~~(i) 1-3 independently selected halogen;~~

~~(ii) $-OR^C$;~~

~~(iii) $-SR^C$;~~

~~(iv) $-NH-S(O_2)R^C$;~~

~~(v) $-OC(=O)R^C$;~~

~~(vi) $-CO_2H$;~~

~~(vii) C_1-C_6 alkoxycarbonyl;~~

~~(viii) $-C(=O)NR^DR^E$;~~

~~(ix) $-NR^DR^E$;~~

(x) -$[N(C_1$-C_6-alkyl)$R^D R^E]^+$;

(xi) -(phenyl)C_1-C_6-alkyl, wherein its C_1-C_6-alkyl is substituted with 5-10 membered heteroaryl, -$NR^D R^E$, -$[N(C_1$-C_6-alkyl)$R^D R^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6-alkoxy, -C(=O)$NR^D R^E$ or -CO_2H;

(xiii) -(5-10 membered heteroaryl)C_1-C_6-alkyl, wherein its C_1-C_6-alkyl is substituted with 5-10 membered heteroaryl, -$NR^D R^E$, -$[N(C_1$-C_6-alkyl)$R^D R^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, -$NR^D R^E$, C_1-C_6 alkoxy, -C(=O)$NR^D R^E$, or -CO_2H;

R^5 is selected from the group consisting of hydrogen, -C(=O)OR^F, -C(=O)$NR^G R^H$, -$S(O_2)NR^G R^H$, -$N(R^I)$-C(=O)R^J, and -$N(R^I)$-$S(O_2)R^K$;

each R^{6A} is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6-alkoxycarbonyl, C_1-C_6-haloalkyl, C_1-C_6-haloalkoxy, and -$NR^A R^B$;

subscript q is 0, 1, or 2;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6-alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6-alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl(C_1-C_6-alkyl)-, aryl, and aryl(C_1-C_6-alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6-alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, aryl, aryl(C_1-C_6-alkyl)-, and C_1-C_6-alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6-alkoxy, and C_3-C_8-cycloalkyl; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6-alkyl.

22. An antibody-drug conjugate (ADC) having the structure:

~~$Ab-(L-D)_p$~~

~~or a pharmaceutically acceptable salt thereof;~~

~~wherein:~~

~~Ab is an antibody;~~

~~each L is a linker;~~

~~wherein each D is conjugated to a linker;~~

~~wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ϵ-amino group of a lysine residue;~~

~~subscript p is an integer from 1 to 16;~~

~~L has the formula $-M-(A)_a-(W)_w-(Y)_y-(X)_x-$, wherein:~~

~~subscript a is 0 or 1;~~

~~subscript y is 0 or 1;~~

~~subscript w is 0 or 1;~~

~~subscript x is 0 or 1;~~

~~M is a succinimide, a hydrolyzed succinimide, an amide, or a triazole;~~

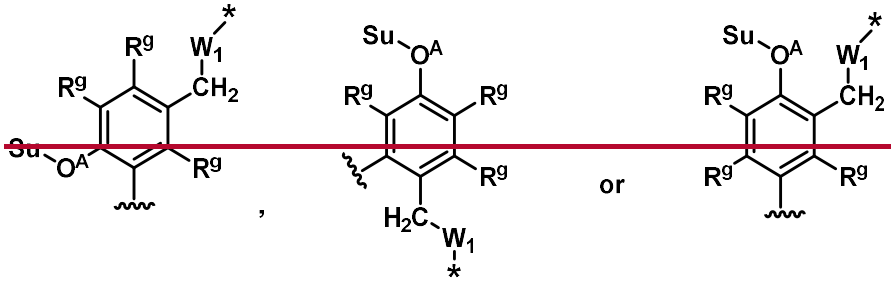
~~A is a C_{2-20} alkylene optionally substituted with 1-3 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R^{b1};~~

~~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;~~

~~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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;~~

W^1 is absent, * C(=O)-O , or * O-C(=O) ;

~~~~ represents covalent attachment to A or M;

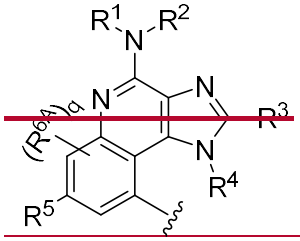
* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72;

each D has the structure of Formula (VIII):



(VIII)

or a pharmaceutically acceptable salt thereof;

wherein:

~~~~ represents covalent attachment to L;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy,

~~C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;~~

~~R^4 is (a) $-OR^C$ or (b) C_1-C_6 alkyl optionally substituted with:~~

~~(i) 1-3 independently selected halogen;~~

~~(ii) $-OR^C$;~~

~~(iii) $-SR^C$;~~

~~(iv) $-NH-S(O_2)R^C$;~~

~~(v) $-OC(=O)R^C$;~~

~~(vi) $-CO_2H$;~~

~~(vii) C_1-C_6 alkoxycarbonyl;~~

~~(viii) $-C(=O)NR^DR^E$;~~

~~(ix) $-NR^DR^E$;~~

~~(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;~~

~~(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;~~

~~(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;~~

~~(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or~~

~~(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;~~

~~R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, and $-N(R^I)-S(O_2)R^K$;~~

~~each R^{6A} is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;~~

~~subscript q is 0, 1, or 2;~~

~~each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached,~~

~~form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;~~

~~R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;~~

~~each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl), aryl, and aryl(C_1-C_6 alkyl); or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;~~

~~R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl), and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl; and~~

~~each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.~~

~~23.~~2. The ADC of claim 1~~ or 12~~, ~~wherein one R^X is R^5 and the remaining R^X are R^6; wherein R^5 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, -C(=O)OR^F, -C(=O)NR^GR^H, -S(O_2)NR^GR^H, -N(R^I)-C(=O)R^J, and -N(R^I)-S(O_2)R^K; and~~

~~each R^6 is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B; wherein no more than one R^6 is the point of covalent attachment to L.~~

wherein:

R^4 is C_1-C_6 alkyl substituted with -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -[N(C_1-C_6 alkyl)R^DR^E]$^+$, or 1-3 independently selected halogen; and

the C_1-C_6 alkyl of R^4, or a substituent thereof, is the point of covalent attachment to the linker,

R^5 is -C(=O)OR^F.

~~24.~~3. The ADC of any one of claims ~~1-23~~1-2, wherein subscript p is an integer from 1 to 8.

~~25. The ADC of any one of claims 1-23, wherein subscript p is an integer from 4 to 12.~~

~~26.~~4. The ADC of any one of claims ~~1-23~~1-2, wherein subscript p is an integer from 8 to 16.

~~27. The ADC of any one of claims 1-24, wherein subscript p is 2, 4, 6, or 8.~~

~~28. The ADC of any one of claims 1-27, wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ϵ-amino group of a lysine residue.~~

~~29.~~5. The ADC of any one of claims ~~1-27~~1-4, wherein each L is covalently attached to Ab via an ϵ-amino group of a lysine residue, or wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue.

~~30. The ADC of any one of claims 1-2, 12-13, or 23, wherein R^1 is the point of covalent attachment to the linker.~~

~~31. The ADC of any one of claims 1-2, 12-13, or 23, wherein R^2 is the point of covalent attachment to the linker.~~

~~32. The ADC of any one of claims 1-2, 12-13, or 23, wherein R^3 is the point of covalent attachment to the linker.~~

~~33. The ADC of any one of claims 1-2, 12-13, or 23, wherein R^4 is the point of covalent attachment to the linker.~~

~~34.~~6. The ADC of any one of claims ~~1-2, 12-13, or 23~~1-5, wherein the C_1-C_6 alkyl of R^4, or a substituent thereof, is the point of covalent attachment to the linker.

~~35. The ADC of any one of claims 1-2, 12-13, or 23, wherein a substituent of the C_1-C_6 alkyl of R^4 is the point of covalent attachment to the linker.~~

~~36. The ADC of any one of claims 1-2, 12-13, or 23, wherein R^5 is the point of covalent attachment to the linker.~~

~~37. The ADC of any one of claims 1-2, 12-13, or 23, wherein one R^6 is the point of covalent attachment to the linker.~~

~~38.~~7. The ADC of any one of claims ~~1-2, 12-13, or 23~~1-6, wherein one of R^A, ~~and~~ R^B , R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, and R^K is the point of covalent attachment to the linker.

~~39. The ADC of any one of claims 1-2, 12-13, 23, or 38, wherein R^A is the point of covalent attachment to the linker.~~

~~40. The ADC of any one of claims 1-2, 12-13, 23, or 38, wherein R^B is the point of covalent attachment to the linker.~~

~~41. The ADC of any one of claims 1-2, 12-13, or 23, wherein R^C is the point of covalent attachment to the linker.~~

42. The ADC of any one of claims 1-2, 12-13, or 23, wherein one of R^D, R^E, R^G, and R^H is the point of covalent attachment to the linker.

43. The ADC of any one of claims 1-2, 12-13, 23, or 42, wherein R^D is the point of covalent attachment to the linker.

44. The ADC of any one of claims 1-2, 12-13, 23 or 42, wherein R^E is the point of covalent attachment to the linker.

45. The ADC of any one of claims 1-2, 12-13, 23 or 42, wherein R^G is the point of covalent attachment to the linker.

46. The ADC of any one of claim 1-2, 12-13, 23 or 42, wherein R^H is the point of covalent attachment to the linker.

47. The ADC of claim 2 or 13, wherein R^F is the point of covalent attachment to the linker.

48. The ADC of claim 2 or 13, wherein one of R^I, R^J, and R^K is the point of covalent attachment to the linker.

49. The ADC of any one of claims 2, 13, or 48, wherein R^I is the point of covalent attachment to the linker.

50. The ADC of any one of claims 2, 13, or 48, wherein R^J is the point of covalent attachment to the linker.

51. The ADC of any one of claims 2, 13, or 48, wherein R^K is the point of covalent attachment to the linker.

52. The ADC of any one of claims 1-29 or 31-51, wherein R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B.

53. The ADC of any one of claims 1-29 or 31-52, wherein R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with one substituent selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano,

~~oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B.~~

~~54.~~8. The ADC of any one of claims ~~1-29 or 31-53~~1-7, wherein R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is unsubstituted.

~~55. The ADC of any one of claims 1-29 or 31-54, wherein R^1 is selected from the group consisting of hydrogen and C_1-C_6 alkyl.~~

~~56. The ADC of any one of claims 1-29 or 31-55, wherein R^1 is hydrogen~~

~~57. The ADC of any one of claims 1-29 or 31-56, wherein R^1 is an unsubstituted C_1-C_6 alkyl.~~

~~58. The ADC of any one of claims 1-11 or 31-51, wherein R^1 is selected from the group consisting of C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, and C_1-C_6 thione; and wherein each C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B.~~

~~59. The ADC of any one of claims 1-11, 31-51, or 58, wherein R^1 is selected from the group consisting of C_1-C_6 alkoxythiocarbonyl and C_1-C_6 carbamoyl; and wherein each C_1-C_6 alkoxythiocarbonyl and C_1-C_6 carbamoyl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B.~~

~~60. The ADC of any one of claims 1-2, 4, 6-13, 15, 17-30, or 32-59, wherein R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B.~~

~~61. The ADC of any one of claims 1-2, 4, 6-13, 15, 17-30, or 32-60, wherein R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with one substituent selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B.~~

~~62.~~9. The ADC of any one of claims ~~1-2, 4, 6-13, 15, 17-30, or 32-60~~1-8, wherein R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl are unsubstituted.

~~63.~~10. The ADC of any one of claims ~~1-2, 4, 6-13, 15, 17-30, or 32-62~~1-9, wherein R^1 and R^2 ~~is~~ are each independently selected from the group consisting of hydrogen and unsubstituted C_1-C_6 alkyl.

~~64. The ADC of any one of claims 1-2, 4, 6-13, 15, 17-30, or 32-63, wherein R^2 is hydrogen~~

~~65. The ADC of any one of claims 1-2, 4, 6-13, 15, 17-30, or 32-63, wherein R^2 is unsubstituted C_1-C_6 alkyl.~~

~~66. The ADC of any one of claims 1-2, 4, 6-13, 15, 17-30, or 32-64, wherein R^1 and R^2 are both hydrogen.~~

~~67. The ADC of any one of claims 1-2, 4, 6-13, 15, 17-30, 32-56, or 60-63, wherein R^1 and R^2 are both unsubstituted C_1-C_6 alkyl.~~

~~68. The ADC of any one of claims 1-2, 4, 6, 12-13, 15, 17, or 32-51, wherein R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl.~~

~~69. The ADC of any one of claims 1-2, 4, 6, 12-13, 15, 17, 32-51, or 68, wherein R^1 and R^2, taken together with the nitrogen atom to which they are attached, form an unsubstituted 3-6 membered heterocyclyl.~~

~~70. The ADC of any one of claims 1-6, 8-17, 19-31, or 33-69, wherein R^3 is selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6~~

~~cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with one substituent selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$.~~

~~71. The ADC of any one of claims 1-6, 8-17, 19-31, or 33-70, wherein R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle are unsubstituted.~~

~~72.~~11. The ADC of any one of claims ~~1-6, 8-17, 19-31, or 33-71~~1-10, wherein R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and C_1-C_6 alkanoyloxy; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and C_1-C_6 alkanoyloxy are unsubstituted.

~~73. The ADC of any one of claims 1-6, 8-17, 19-31, or 33-72, wherein R^3 is selected from the group consisting of hydrogen, unsubstituted C_1-C_6 alkyl, unsubstituted C_2-C_6 alkenyl, and unsubstituted C_2-C_6 alkynyl.~~

~~74.~~12. The ADC of any one of claims ~~1-6, 8-17, 19-31, or 33-73~~1-11, wherein R^3 is an unsubstituted C_1-C_6 alkyl or C_1-C_6 alkyl substituted with C_1-C_6 alkoxy.

~~75. The ADC of any one of claims 1-6, 8-17, 19-31, or 33-74, wherein R^3 is n-butyl.~~

~~76. The ADC of any one of claims 1-6, 8-17, 19-31, or 33-70, wherein R^3 is C_1-C_6 alkyl substituted with C_1-C_6 alkoxy.~~

~~77.~~13. The ADC of any one of claims ~~1-3, 5, 7-14, 16, 18-32 or 36-76~~1-12, wherein R^4 is C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.

~~78. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32 or 36-77, wherein R^4 is C_1-C_6 alkyl substituted with:~~

~~(i) 1-3 independently selected halogen;~~

~~(ii) $-OR^C$;~~

~~(iii) $-SR^C$;~~

~~(iv) $-NH\text{-}S(O_2)R^C$;~~

~~(v) $-OC(=O)R^C$;~~

~~(vi) $-CO_2H$;~~

~~(vii) C_1-C_6 alkoxycarbonyl;~~

~~(viii) $-C(=O)NR^DR^E$;~~

~~(ix) $-NR^DR^E$;~~

~~(x) $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$;~~

~~(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;~~

~~(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;~~

~~(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or~~

~~(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, $(C_1$-$C_6)$alkoxycarbonyl, or $-CO_2H$.~~

~~79. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32 or 36-78, wherein R^4 is C_1-C_6 alkyl substituted with:~~

~~(ix) $-NR^DR^E$;~~

~~(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;~~

~~(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;~~

~~(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;~~

~~(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or~~

~~(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, $(C_1$-$C_6)$alkoxycarbonyl, or $-CO_2H$.~~

~~80.~~14. The ADC of any one of claims ~~1-3, 5-14, 16-30 or 34-79~~1-13, wherein R^4 is C_1-C_6 alkyl substituted with $-OR^C$.

~~81. The ADC of any one of claims 1-3, 5-14, 16-30 or 34-79, wherein R^4 is C_1-C_6 alkyl substituted with $-NR^DR^E$.~~

~~82. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32 or 36-79, wherein R^4 is C_1-C_6 alkyl substituted with $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$.~~

~~83. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32 or 36-79, wherein R^4 is C_1-C_6 alkyl substituted with -(phenyl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen.~~

~~84. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, wherein R^4 is C_1-C_3 alkyl substituted with -(phenyl)C_1-C_3 alkyl, wherein the C_1-C_3 alkyl of the -(phenyl)C_1-C_3 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen.~~

~~85. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, 83, or 84, wherein R^4 is C_1-C_3 alkyl substituted with -(phenyl)C_1-C_3 alkyl, wherein the C_1-C_3 alkyl of the -(phenyl)C_1-C_3 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen.~~

~~86. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, or 83-85, wherein R^4 is $-CH_2$-(phenyl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen.~~

~~87.~~15. The ADC of any one of claims ~~1-3, 5, 7-14, 16, 18-32, 36-79, or 83-86~~1-13, wherein R^4 is $-CH_2$-(phenyl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with $-NR^DR^E$ or $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$.

~~88. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, or 83-87, wherein R^4 is $-CH_2$-(phenyl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with $-NR^DR^E$.~~

~~89. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, or 83-87, wherein R^4 is $-CH_2$-(phenyl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$.~~

~~90. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, or 36-79, wherein R^4 is C_1-C_6 alkyl substituted with phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$.~~

~~91. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, or 90, wherein R^4 is $-CH_2$-phenyl, wherein the phenyl is substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$.~~

~~92. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, or 36-79, wherein R^4 is C_1-C_6 alkyl substituted with -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen.~~

~~93. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, or 92, wherein R^4 is C_1-C_3 alkyl substituted with -(5-10 membered heteroaryl)C_1-C_3 alkyl, wherein the C_1-C_3 alkyl of the -(5-10 membered heteroaryl)C_1-C_3 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen.~~

~~94. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, 92, or 93, wherein R^4 is C_1-C_3 alkyl substituted with -(5-6 membered heteroaryl)C_1-C_3 alkyl, wherein the C_1-C_3 alkyl of the -(5-6 membered heteroaryl)C_1-C_3 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen.~~

95. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, or 92-94, wherein R^4 is $-CH_2$-(5-6 membered heteroaryl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen.

96. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, or 92-95, wherein R^4 is $-CH_2$-(5-6 membered heteroaryl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with $-NR^DR^E$ or $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$.

97. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, or 92-96, wherein R^4 is $-CH_2$-(5-6 membered heteroaryl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with $-NR^DR^E$.

98. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, or 92-96, wherein R^4 is $-CH_2$-(5-6 membered heteroaryl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$.

99. The ADC of any one of claims 94-98, wherein the 5-6 membered heteroaryl is pyridinyl, pyrimidinyl, or pyrazinyl.

100. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, or 36-79, wherein R^4 is C_1-C_6 alkyl substituted with 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.

101. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, or 100, wherein R^4 is C_1-C_3 alkyl substituted with 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.

102. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, 36-79, 100, or 101, wherein R^4 is $-CH_2$-(5-10 membered heteroaryl), wherein the 5-10 membered heteroaryl is optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.

103. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, or 36-79 or 100-102, wherein R^4 is $-CH_2$-(5-6 membered heteroaryl), wherein the 5-6 membered heteroaryl is optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.

104. The ADC of claim 103, wherein the 5-6 membered heteroaryl is pyridinyl, pyrimidinyl, or pyrazinyl.

105. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, or 36-76, wherein R^4 is $-OR^C$.

~~106. The ADC of any one of claims 1-3, 5, 7-14, 16, 18-32, or 36-79, wherein R^4 is an unsubstituted C_1-C_6 alkyl.~~

~~107. The ADC of any one of claims 1-3, 5, 7-11, or 23-76, wherein R^4 is $-S(=O)_2R^C$; $-C(=O)NR^DR^E$; $-C(=O)OR^C$, $-C(=O)SR^C$, $-C(=S)R^C$, or $-PO_3R^C$.~~

~~108. The ADC of any one of claims 1-3, 5, 7-11, 23-76, or 107, wherein R^4 is $-C(=O)NR^DR^E$ or $-C(=O)OR^C$.~~

~~109. The ADC of any one of claims 1-3, 5, 7-11, or 23-32, or 36-108, wherein neither of R^1 and R^4 is substituted with the solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide.~~

~~110. The ADC of any one of claims 1-3, 5, 7-11, or 23-32, or 36-108, wherein one of R^1 and R^4 is substituted with the solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide.~~

~~111.~~16. The ADC of any one of claims ~~1-3, 5, 7-11, or 23-32, 36-108, or 110~~1-7 or 9-15, wherein R^1 is substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide.

~~112. The ADC of any one of claims 1-3, 5, 7-11, or 23-32, 36-108, 110, or 111, wherein the solubilizing group (S_b) is a C_5-C_9 monosaccharide.~~

~~113. The ADC of any one of claims 1-3, 5, 7-11, or 23-32, 36-108, or 110-112, wherein the solubilizing group (S_b) is a C_5-C_6 monosaccharide.~~

~~114. The ADC of any one of claims 4, 6, 15, 17 or 52-78, wherein R^{4A} is the point of covalent attachment to L.~~

~~115. The ADC of any one of claims 4, 6, 15, 17 or 52-78, wherein R^{4A} is C_1-C_6 alkyl substituted with:~~

~~(i) 1-3 independently selected halogen;~~

~~(ii) $-OR^C$;~~

~~(iii) $-SR^C$;~~

~~(iv) $-NH-S(O_2)R^C$;~~

~~(v) $-OC(=O)R^C$;~~

~~(vi) $-CO_2H$;~~

~~(vii) C_1-C_6 alkoxycarbonyl;~~

~~(viii) $-C(=O)NR^DR^E$;~~

(ix) $-NR^DR^E$;

(x) $-[N(C_1-C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1-C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1-C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.

116. The ADC of any one of claims 4, 6, 15, 17, 52-76, or 115, wherein R^{4A} is C_1-C_6 alkyl substituted with:

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1-C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1-C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1-C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.

117. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115, or 116, wherein R^{4A} is C_1-C_6 alkyl substituted with:

(ix) $-NR^DR^E$;

(x) $-[N(C_1-C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1-C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, -C(=O)NR^DR^E or -CO_2H;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -$[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, -NR^DR^E, C_1-C_6 alkoxy, -C(=O)NR^DR^E, -SR^C, (C_1-C_6)alkoxycarbonyl, or -CO_2H.

118. The ADC of any one of claims 4, 6, 15, 17, 52-76, or 115-117, wherein R^{4A} is C_1-C_6 alkyl substituted with -NR^DR^E.

119. The ADC of any one of claims 4, 6, 15, 17, 52-76, or 115-117, wherein R^{4A} is C_1-C_6 alkyl substituted with -$[N(C_1$-C_6 alkyl)$R^DR^E]^+$.

120. The ADC of any one of claims 4, 6, 15, 17, 52-76, or 115-117, wherein R^{4A} is C_1-C_6 alkyl substituted with -(phenyl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -$[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen.

121. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, or 120, wherein R^{4A} is C_1-C_3 alkyl substituted with -(phenyl)C_1-C_3 alkyl, wherein the C_1-C_3 alkyl of the -(phenyl)C_1-C_3 alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -$[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen.

122. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, 120, or 121 wherein R^{4A} is C_1-C_3 alkyl substituted with -(phenyl)C_1-C_2 alkyl, wherein the C_1-C_3 alkyl of the -(phenyl)C_1-C_3 alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -$[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen.

123. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, or 120-122, wherein R^{4A} is -CH_2-(phenyl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, or -$[N(C_1$-C_6 alkyl)$R^DR^E]^+$.

124. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, or 120-123, wherein R^{4A} is -CH_2-(phenyl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with -NR^DR^E or -$[N(C_1$-C_6 alkyl)$R^DR^E]^+$.

125. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, or 120-124, wherein R^{4A} is -CH_2-(phenyl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with -NR^DR^E.

~~126. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, or 120-124, wherein R^{4A} is $-CH_2$-(phenyl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$.~~

~~127. The ADC of any one of claims 4, 6, 15, 17, 52-76, or 115-117, wherein R^{4A} is C_1-C_6 alkyl substituted with phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$.~~

~~128. The ADC of any one of claims 4, 6, 15, 17, 52-76, or 115-117, wherein R^{4A} is $-CH_2$-phenyl, wherein the phenyl is substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$.~~

~~129. The ADC of any one of claims 4, 6, 15, 17, 52-76, or 115-117, wherein R^{4A} is C_1-C_6 alkyl substituted with -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen.~~

~~130. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, or 129, wherein R^{4A} is C_1-C_3 alkyl substituted with -(5-10 membered heteroaryl)C_1-C_3 alkyl, wherein the C_1-C_3 alkyl of the -(5-10 membered heteroaryl)C_1-C_3 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen.~~

~~131. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, 129, or 130, wherein R^{4A} is C_1-C_3 alkyl substituted with -(5-6 membered heteroaryl)C_1-C_3 alkyl, wherein the C_1-C_3 alkyl of the -(5-6 membered heteroaryl)C_1-C_3 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen.~~

~~132. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, or 129-131, wherein R^{4A} is $-CH_2$-(5-6 membered heteroaryl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen.~~

~~133. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, or 129-132, wherein R^{4A} is $-CH_2$-(5-6 membered heteroaryl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with $-NR^DR^E$ or $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$.~~

~~134. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, or 129-132, wherein R^{4A} is $-CH_2$-(5-6 membered heteroaryl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with $-NR^DR^E$.~~

~~135. The ADC of any one of claims 4, 6, 15, 17, 52-76, 115-117, or 129-132, wherein R^{4A} is $-CH_2$-(5-6 membered heteroaryl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$.~~

~~136. The ADC of any one of claims 131-135, wherein the 5-6 membered heteroaryl is pyridinyl, pyrimidinyl, or pyrazinyl.~~

~~137. The ADC of any one of claims 4, 6, 15, 17, 52-76, 116, or 117, wherein R^{4A} is C_1-C_6 alkyl substituted with 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.~~

~~138. The ADC of any one of claims 4, 6, 15, 17, 52-76, 116, 117, or 137 wherein R^{4A} is C_1-C_3 alkyl substituted with 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.~~

~~139. The ADC of any one of claims 4, 6, 15, 17, 52-76, 116, 117, 137, or 138 wherein R^{4A} is $-CH_2$-(5-10 membered heteroaryl), wherein the 5-10 membered heteroaryl is optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.~~

~~140. The ADC of any one of claims 4, 6, 15, 17, 52-76, 116, 117, or 137-139, wherein R^{4A} is $-CH_2$-(5-6 membered heteroaryl), wherein the 5-6 membered heteroaryl is optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.~~

~~141. The ADC of claim 140, wherein the 5-6 membered heteroaryl is pyridinyl, pyrimidinyl, or pyrazinyl.~~

~~142.~~17. The ADC of any one of claim ~~2-7, 9-11, 13-18, 20-35, 37-46, or 48-141~~1-16, wherein R^5 is selected from the group consisting of $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, and $-N(R^I)-S(O_2)R^K$.

~~143.~~18. The ADC of any one of claims ~~2-7, 9-11, 13-18, 20-35, 37-46, or 48-141~~1-17, wherein R^5 is $-C(=O)OR^F$.

~~144. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, or 48-143, wherein R^F is selected from the group consisting of trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl), and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl.~~

~~145. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, or 48-144, wherein R^F is selected from the group consisting of trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and unsubstituted C_1-C_6 alkyl.~~

~~146. The ADC of any one of claims2-7, 9-11, 13-18, 20-35, 37-46, or 48-145, wherein R^F is selected from the group consisting of C_2-C_6 alkenyl, C_2-C_6 alkynyl, and unsubstituted C_1-C_6 alkyl.~~

~~147.~~19. The ADC of any one of claims ~~2-7, 9-11, 13-18, 20-35, 37-46, or 48-146,~~1-18 wherein R^F is selected from the group consisting of C_1-C_6 alkyl and hydrogen.

~~148. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, or 48-147, wherein R^F is methyl.~~

~~149. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, or 48-134, wherein R^F is hydrogen.~~

~~150. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, or 48-141, wherein R^5 is -C(=O)NR^GR^H.~~

~~151. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, or 48-141, wherein R^5 is -S(O_2)NR^GR^H.~~

~~152. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, 48-141, 150, or 151, wherein each R^G and R^H are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-.~~

~~153.~~20. The ADC of any one of claims ~~2-7, 9-11, 13-18, 20-35, 37-46, 48-141, or 150-152~~1-19, wherein each R^G and R^H are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

~~154. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, 48-141, 150, or 151, wherein R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl.~~

~~155. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, or 48-142, R^5 is -N(R^I)-C(=O)R^J.~~

~~156. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, 48-141, or 155, wherein R^I and R^J are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.~~

~~157. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, or 48-141, wherein R^5 is -N(R^I)-S(O_2)R^K.~~

~~158. The ADC of any one of claims 2-7, 9-11, 13-18, 20-35, 37-46, or 48-141, wherein R^5 is hydrogen.~~

~~159. The ADC of any one of claims 2-7, 9-11, 23-35, 37-46, or 48-141, wherein R^5 has:~~

~~i. a pka of at most about 7.0,~~

~~ii. a dipole moment of at least about 2.0 Debye, or~~

~~iii. i. and ii.~~

~~160. The ADC of any one of claims 2-7, 9-11, 23-35, 37-46, 48-141, or 159, wherein R^5 has a pka of at most about 5.0.~~

~~161. The ADC of any one of claims 2-7, 9-11, 23-35, 37-46, 48-141, 159, or 160, wherein R^5 is selected from the group consisting of -C(=O)OH, -NO_2, -CN, -CF_3, and -$S(O_3)H$.~~

~~162.~~21. The ADC of any one of claims ~~2-7, 9-11, 23-35, 37-46, 48-141, or 159-161~~1-20, wherein R^5 is -C(=O)OH.

~~163.~~22. The ADC of any one of claims ~~2-7, 9-11, 23-35, 37-46, 48-141, or 157~~1-21, wherein R^I and R^K are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

~~164. The ADC of any one of claims 2-8, 10-11, 13-19, 21-36 or 38-163, wherein each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B.~~

~~165.~~23. The ADC of any one of claims ~~2-8, 10-11, 13-19, 21-36 or 38-163~~1-22, wherein each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, and cyano.

~~166.~~24. The ADC of any one of claims ~~2-8, 10-11, 13-19, 21-36 or 38-163~~1-22, wherein subscript m is 0.

~~167. The ADC of any one of claims 2-8, 10-11, 13-19, 21-36 or 38-163, wherein subscript m is 1.~~

~~168. The ADC of any one of claims 2-8, 10-11, 13-19, 21-22, 24-36 or 38-163, wherein subscript m is 2.~~

~~169. The ADC of any one of claims 2-8, 10-11, 13-19, 21-22, 24-36 or 38-163, wherein subscript m is 3.~~

~~170. The ADC of any one of claims 9-11, 20-22, 24-36 or 38-159, wherein each R^{6A} is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano,~~

~~C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B.~~

~~171. The ADC of any one of claims 9-11, 20-22, 24-36 38-159, or 170, wherein each R^{6A} is independently selected from the group consisting of halogen, hydroxyl, nitro, and cyano.~~

~~172. The ADC of any one of claims 9-11, 20-22, 24-36 38-159, or 171, wherein subscript q is 0.~~

~~173. The ADC of any one of claims 9-11, 20-22, 24-36 38-159, or 171, wherein subscript q is 1.~~

~~174. The ADC of any one of claims 9-11, 20-22, 24-36 38-159, or 171, wherein subscript q is 2.~~

~~175.~~25. The ADC of any one of claims ~~1-37 or 41-174~~1-24, wherein each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

~~176. The ADC of any one of claims 1-37 or 41-175, wherein each R^A and R^B is hydrogen.~~

~~177. The ADC of any one of claims 1-37 or 41-175, wherein each R^A and R^B is an independently selected C_1-C_6 alkyl.~~

~~178. The ADC of any one of claims 1-37 or 41-175, wherein one of R^A and R^B is hydrogen and the other of R^A and R^B is C_1-C_6 alkyl.~~

~~179. The ADC of any one of claims 1-32, 36, 37, or 41-178, wherein R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen.~~

~~180.~~26. The ADC of any one of claims ~~1-32, 36, 37, or 41-179~~1-25, wherein R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl.

~~181. The ADC of any one of claims 1-32, 36, 37, or 41-180, wherein R^C is selected from the group consisting of hydrogen and C_1-C_{10} alkyl.~~

~~182. The ADC of any one of claims 1-32, 36, 37, or 41-181, wherein R^C is hydrogen.~~

~~183. The ADC of any one of claims 1-32, 36, 37, or 41-181, wherein R^C is C_1-C_{10} alkyl.~~

~~184. The ADC of any one of claims 1-41 or 45-183, wherein each R^D and R^E are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-.~~

~~185.~~27. The ADC of any one of claims ~~1-41 or 45-184~~1-26, wherein each R^D and R^E are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

~~186. The ADC of any one of claims 1-41 or 45-183, wherein R^D and R^E, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl.~~

~~187. The ADC of any one of claims 5-11, 16-22, or 24-186, wherein subscript x is 1.~~

~~188. The ADC of any one of claims 5-11, 16-22, or 24-187, wherein X is a C_1-C_6 alkylene.~~

~~189. The ADC of any one of claims 5-11, 16-22, or 24-188, wherein X is a C_1-C_3 alkylene.~~

~~190. The ADC of any one of claims 5-11, 16-22, or 24-187, wherein X is a 3-6 membered heteroalkylene.~~

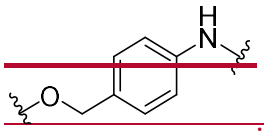
~~191. The ADC of any one of claims 5-11, 16-22, or 24-187, or 190 wherein X is a 3-4 membered heteroalkylene.~~

~~192. The ADC of any one of claims 5-11, 16-22, or 24-186, wherein subscript x is 0.~~

~~193. The ADC of any one of claims 5-11, 16-22, or 24-192, wherein subscript y is 1.~~

~~194. The ADC of any one of claims 5-11, 16-22, or 24-193, wherein Y is a self-immolative moiety.~~

~~195. The ADC of any one of claims 5-11, 16-22, 24-191, or 194 wherein Y is~~



.

~~196. The ADC of any one of claims 5-11, 16-22, 24-191, or 194, wherein Y is a non-cleavable moiety.~~

~~197. The ADC of any one of claims 5-11, 16-22, or 24-196, wherein Y is a cyclohexanecarboxyl, undecanoyl, caproyl, hexanoyl, butanoyl or propionyl group.~~

~~198. The ADC of any one of claims 5-11, 16-22, 24-191, or 194, wherein Y is PEG4 to PEG12.~~

~~199. The ADC of any one of claims 5-11, 16-22, or 24-198, wherein subscript y is 0.~~

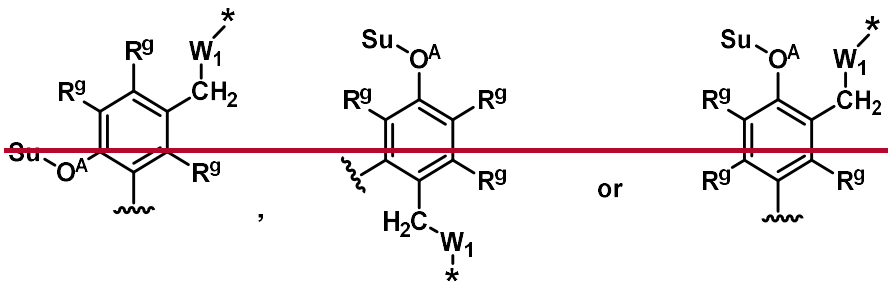
200. The ADC of any one of claims 5-11, 16-22, or 24-199, wherein subscript w is 1.

201. The compound of any one of claims 5-11, 16-22, or 24-200, wherein W is from 6-12 amino acids.

202. The compound of any one of claims 5-11, 16-22, or 24-201, wherein W is from 6-6 amino acids.

203. The compound of any one of claims 5-11, 16-22, or 24-202, wherein each amino acid in W is independently selected from the group consisting of alanine, glycine, lysine, serine, aspartic acid, aspartate methyl ester, *N,N*-dimethyl-lysine, phenylalanine, citrulline, valine-alanine, valine-citrulline, phenylalanine-lysine, and homoserine methyl ether.

204. The compound of any one of claims 5-11, 16-22, or 24-200, wherein W 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, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, *-C(=O)-O-, or *-O-C(=O)-;

~~~~ represents covalent attachment to A or M; and

* represents covalent attachment to X, Y, or D.

205. The compound of any one of claims 5-11, 16-22, or 24-200 or 204, wherein W^1 is absent.

206. The compound of any one of claims 5-11, 16-22, or 24-200 or 204, wherein W^1 is *-C(=O)-O-.

207. The compound of any one of claims 5-11, 16-22, or 24-200 or 204, wherein W^1 is *-O-C(=O)-.
~~~~

208. The compound of any one of claims 5-11, 16-22, or 24-200 or 204-207, wherein one R^g is halogen, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), $-CN$, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$, and the remaining R^g are hydrogen.

209. The compound of any one of claims 5-11, 16-22, or 24-200 or 204-207, wherein each R^g is hydrogen.

210. The ADC of any one of claims 5-11, 16-22, or 24-209, wherein subscript w is 0.

211. The ADC of any one of claims 5-11, 16-22, or 24-210, wherein subscript a is 1.

212. The ADC of any one of claims 5-11, 16-22, or 24-211, wherein A is C_{2-20} alkylene optionally substituted with 1-4 R^{a1}.

213. The ADC of any one of claims 5-11, 16-22, or 24-211, wherein A is C_{4-10} alkylene optionally substituted with 1-4 R^{a1}.

214. The ADC of any one of claims 5-11, 16-22, or 24-212, wherein A is C_{2-20} alkylene substituted with one R^{a1}.

215. The ADC of any one of claims 5-11, 16-22, or 24-213, wherein A is C_{4-10} alkylene substituted with one R^{a1}.

216. The ADC of any one of claims 5-11, 16-22, or 24-212, wherein A is C_{2-20} alkylene.

217. The ADC of any one of claims 5-11, 16-22, or 24-211, wherein A is C_{4-10} alkylene.

218. The ADC of any one of claims 5-11, 16-22, or 24-211, wherein A is a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1}.

219. The ADC of any one of claims 5-11, 16-22, 24-211 or 218, wherein A is a 4 to 12 membered heteroalkylene optionally substituted with 1-4 R^{b1}.

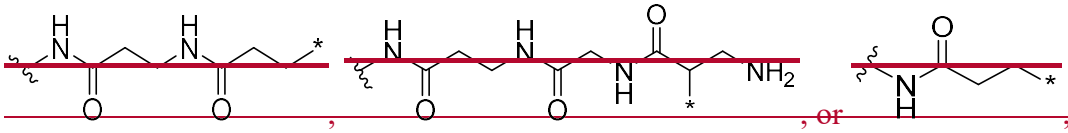
220. The ADC of any one of claims 5-11, 16-22, 24-211, 218, or 219, wherein A is a 2 to 40 membered heteroalkylene optionally substituted with one R^{b1}.

221. The ADC of any one of claims 5-11, 16-22, 24-211 or 218-220, wherein A is a 4 to 12 membered heteroalkylene optionally substituted with one R^{b1}.

222. The ADC of any one of claims 5-11, 16-22, 24-211 or 218, wherein A is a 2 to 40 membered heteroalkylene.

223. The ADC of any one of claims 5-11, 16-22, 24-211, 218, or 222, wherein A is a 4 to 12 membered heteroalkylene.

~~224. The ADC of any one of claims 5-11, 16-22, 24-211, wherein A is~~



~~, wherein~~

~~represents covalent attachment to W, and * represents covalent linkage to M.~~

~~225. The ADC of any one of claims 5-11, 16-22, 24-210, wherein subscript a is 0.~~

~~226. The ADC of any one of claims 5-11, 16-22, 24-225, wherein L is substituted with a PEG Unit from PEG1 to PEG72.~~

~~227. The ADC of any one of claims 5-11, 16-22, 24-224 or 226, wherein A is substituted with a PEG Unit from PEG1 to PEG72.~~

~~228. The ADC of any one of claims 5-11, 16-22, 24-225, wherein L is not substituted with a PEG Unit from PEG1 to PEG72.~~

~~229. The ADC of any one of claims 5-11, 16-22, 24-228, wherein M is a succinimide.~~

~~230. The ADC of any one of claims 5-11, 16-22, 24-228, wherein M is a hydrolyzed succinimide.~~

~~231. The ADC of any one of claims 5-11, 16-22, 24-228, wherein M is an amide.~~

~~232. The ADC of any one of claims 5-11, 16-22, 24-228, wherein M is a triazole.~~

~~233.~~28. The ADC of any one of claims ~~1-232~~1-27, wherein the antibody is a humanized antibody.

~~234.~~29. The ADC of any one of claims ~~1-233~~1-28, wherein the antibody is a monoclonal antibody.

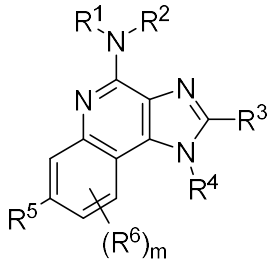
~~235. The ADC of any one of claims 1-234, wherein the antibody is fucosylated.~~

~~236. The ADC of any one of claims 1-235, wherein the antibody is afucosylated.~~

~~237.~~30. A composition comprising a distribution of the ADCs of any one of claims ~~1-236~~1-29, or a pharmaceutically acceptable salt thereof.

~~238. The composition of claim 237, further comprising at least one pharmaceutically acceptable carrier.~~

~~239.~~31. A compound of Formula (IX):



(IX)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $–NR^AR^B$;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $–NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen, $–NR^AR^B$, $–C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) $-OR^C$; (b) $-S(=O)_2R^C$; (c) $-C(=O)NR^DR^E$; (d) $-C(=O)OR^C$; (e) $-C(=O)SR^C$; (f) $-C(=S)R^C$; (g) $-PO_3R^C$; or (h) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is ~~selected from the group consisting of hydrogen,~~ $-C(=O)OR^F$~~, $-NO_2$, $-CN$, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)C(=O)R^J$, $-N(R^I)S(O_2)R^K$, and $-SO_3R^K$~~;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

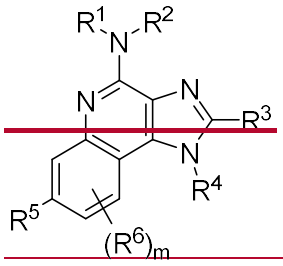
R^F is ~~selected from the group consisting of~~ hydrogen~~, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl~~;

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

~~when R^F is trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, or C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl; R^4 is -$[N(C_1$-C_6alkyl)$R^D R^E]^+$; -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with -$[N(C_1$-C_6 alkyl)$R^D R^E]^+$; or -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with -$[N(C_1$-C_6 alkyl)$R^D R^E]^+$;~~ and

each instance of R^1 and R^4 is optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide.

~~240. A compound of Formula (IX):~~



~~(IX)~~

~~or a pharmaceutically acceptable salt thereof;~~

~~wherein:~~

~~R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl,~~

~~halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;~~

~~R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$; or~~

~~R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;~~

~~R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;~~

~~R^4 is (a) $-OR^C$ or (b) C_1-C_6 alkyl substituted with:~~

~~(i) 1-3 independently selected halogen;~~

~~(ii) $-OR^C$;~~

~~(iii) $-SR^C$;~~

~~(iv) $-NH-S(O_2)R^C$;~~

~~(v) $-OC(=O)R^C$;~~

~~(vi) $-CO_2H$;~~

~~(vii) C_1-C_6 alkoxycarbonyl;~~

~~(viii) $-C(=O)NR^DR^E$;~~

~~(ix) $-NR^DR^E$;~~

~~(x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$;~~

~~(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;~~

~~(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;~~

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, or $-CO_2H$;

R^5 is $-C(=O)OR^F$;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-NR^AR^B$;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

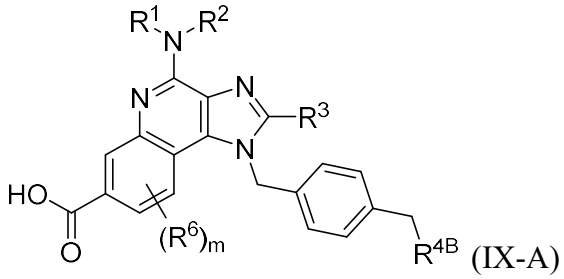
each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; and

when R^F is trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, or C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl; R^4 is $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$; -(phenyl)$C_1$-$C_6$ alkyl, wherein its C_1-C_6 alkyl is substituted with $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$; or -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$

~~241.~~32. The compound of ~~either claim 239 or 240~~claim 31, wherein the compound has the structure of Formula (IX-A):



(IX-A)

or a pharmaceutically acceptable salt thereof,
wherein:

R^1 is selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^2 is selected from the group consisting of hydrogen and C_1-C_6 alkyl; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_1-C_6 alkoxy, and C_1-C_6 alkylthio;

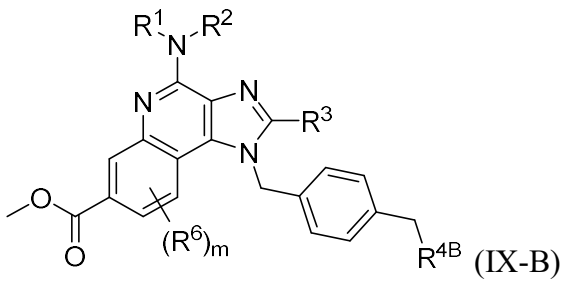
R^{4B} is selected from the group consisting of 5-10 membered heteroaryl, $-NR^DR^E$, and $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$;

R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy;

subscript m is 0 or 1; and

R^D and R^E are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl.

~~242.~~33. ~~The~~ A compound of ~~either claim 239 or 240, wherein the compound has the structure of~~ Formula (IX-B):



(IX-B)

or a pharmaceutically acceptable salt thereof;
wherein:

R^1 is selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^2 is selected from the group consisting of hydrogen and C_1-C_6 alkyl; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_1-C_6 alkoxy, and C_1-C_6 alkylthio;

R^{4B} is selected from the group consisting of ~~5-10 membered heteroaryl, -~~$-NR^DR^E$~~,~~ and $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$;

R^6 selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy;

subscript m is 0 or 1; and

R^D and R^E are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-~~; or R^D and R^E, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl~~.

~~243. The compound of any one of claims 239-242, wherein R^1 and R^2 are each independently selected C_1-C_6 alkyl.~~

~~244. The compound of any one of claims 239-243, wherein R^1 and R^2 are both methyl.~~

~~245. The compound of any one of claims 239-242, wherein one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is C_1-C_6 alkyl.~~

~~246. The compound of any one of claims 239-245, wherein one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is methyl.~~

~~247.~~34. The compound of any one of claims ~~239-242~~31-33, wherein R^1 and R^2 are (i) both hydrogen,

(ii) R^3 is C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_1-C_6 alkoxy, and C_1-C_6 alkylthio;

(iii) R^{4B} is $-NR^DR^E$;

(iv) R^D and R^E are each independently selected C_1-C_6 alkyl;

(v) subscript m is 0; or

(vi) a combination thereof.

~~248. The compound of any one of claims 239-242, wherein R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl.~~

~~249.~~35. The compound of any one of claims ~~239-248~~31-33, wherein R^3 is C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_1-C_6 alkoxy, and C_1-C_6 alkylthio.

~~250. The compound of any one of claims 239-249, wherein R^3 is C_1-C_6 alkyl substituted with one substituent selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_1-C_6 alkoxy, and C_1-C_6 alkylthio.~~

~~251. The compound of any one of claims 239-250, wherein R^3 is C_1-C_6 alkyl substituted with one substituent selected from the group consisting of hydroxyl and C_1-C_6 alkoxy.~~

~~252. The compound of any one of claims 239-249, wherein R^3 is an unsubstituted C_1-C_6 alkyl.~~

~~253. The compound of any one of claims 239-249, or 252, wherein R^3 is n-butyl.~~

~~254. The compound of any one of claims 239-252, wherein R^3 is hydrogen.~~

~~255. The compound of any one of claims 239-254, wherein R^{4B} is $-NR^DR^E$.~~

~~256. The compound of any one of claims 239-254, wherein R^{4B} is $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$.~~

~~257. The compound of any one of claims 239-256, wherein R^D and R^E are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-.~~

~~258. The compound of any one of claims 239-257, wherein R^D and R^E are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_2-C_6 alkenyl.~~

~~259. The compound of any one of claims 239-258, wherein R^D and R^E are each independently selected C_1-C_6 alkyl.~~

~~260. The compound of any one of claims 239-259, wherein R^D and R^E are both methyl.~~

~~261. The compound of any one of claims 239-258, wherein one of R^D and R^E is hydrogen and the other of R^D and R^E is C_1-C_6 alkyl.~~

~~262. The compound of any one of claims 239-258 or 261, wherein one of R^D and R^E is hydrogen and the other of R^D and R^E is methyl.~~

~~263. The compound of any one of claims 239-258, wherein R^D and R^E are both hydrogen.~~

~~264. The compound of any one of claims 239-257, wherein R^D and R^E, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl.~~

~~265. The compound of any one of claims 239-254, wherein R^{4B} is 5-10 membered heteroaryl.~~

~~266. The compound of any one of claims 239-265, wherein subscript m is 1.~~

~~267. The compound of any one of claims 239-266, wherein R^6 is selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy.~~

~~268. The compound of any one of claims 239-267, wherein R^6 is selected from the group consisting of halogen, hydroxyl, nitro, and cyano.~~

~~269. The compound of any one of claims 239-265, wherein subscript m is 0.~~

~~270. A composition comprising a compound of any one of claims 239-269, or a pharmaceutically acceptable salt thereof.~~

~~271.~~36. ~~A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the~~ Use of an antibody drug conjugate (ADC) according to ~~of~~ any one of claims ~~1-236~~1-29, a composition according to claim 30, or a compound of any one of claims 31-35 in the manufacture of a medicament for the treatment of cancer~~or a pharmaceutically acceptable salt thereof; or a therapeutically effective amount of the compound of any one of claims 239-269, or a pharmaceutically acceptable salt thereof~~.

~~272. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the composition of claim 237, 238, or 270.~~

~~273. A method of inducing an anti-tumor immune response in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the ADC of any one of claims 1-236, or a pharmaceutically acceptable salt thereof; or a therapeutically effective amount of the compound of any one of claims 239-269, or a pharmaceutically acceptable salt thereof.~~

~~274. A method of inducing an anti-tumor immune response in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the composition of claim 237, 238, or 270.~~

~~275.~~37. The ~~method of any one of claims 271-274~~use of claim 36, wherein the antibody of the ADC targets a surface antigen of a cell, and wherein the ADC is configured to internalize within ~~the~~ a cell upon binding of the antibody to ~~the~~ a surface antigen.

~~276. The method of any one of claims 271-275, wherein the ADC antibody (Ab) targets a tumor associated macrophage antigen.~~

~~277.~~38. The ~~method of any one of claims 271-276~~use of claim 37, wherein the surface antigen is EphA2.

~~278. The method of either claim 276 or 277, wherein the ADC is configured to internalize within the tumor associated macrophage.~~

~~279. The method of any one of claims 276-278, wherein the D of the ADC is configured to bind to a receptor inside of the tumor associated macrophage.~~

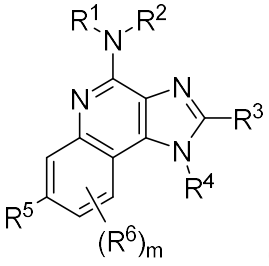
~~280. The method of any one of claims 276-279, wherein the D of the ADC is configured to bind to toll-like receptor 7, toll-like receptor 8, or toll-like receptor 7 and toll-like receptor 8.~~

~~281.~~39. The ~~method of any one of claims 276-280~~use of claim 37 or 38, wherein the linker (L) of the ADC is configured to undergo cleavage subsequent to internalizing within the ~~tumor associated macrophage~~cell.

40. An antibody drug conjugate (ADC) according to any one of claims 1-29, a composition according to claim 30, or a compound of any one of claims 31-35 for use in therapy.

~~282.~~41. A compound having the formula L^1-D, or a pharmaceutically acceptable salt thereof, wherein:

L^1 is a linker intermediate; and
D has the structure of Formula (X):



(X)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $–NR^AR^B$;

R^2 is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $–NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, $–NR^AR^B$, $–C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) the point of covalent attachment to L^1; (b) $-OR^C$; (c) $-S(=O)2R^C$; (d) $-C(=O)NR^DR^E$; (e) $-C(=O)OR^C$; (f) $-C(=O)SR^C$; (g) $-C(=S)R^C$; (h) $-PO_3R^C$; or (j) C_1-C_6 alkyl optionally substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) -OC(=O)R^C;

(vi) -CO_2H;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) -C(=O)NR^DR^E;

(ix) -NR^DR^E;

(x) -[N(C_1-C_6 alkyl)R^DR^E]$^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -[N(C_1-C_6 alkyl)R^DR^E]$^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, -C(=O)NR^DR^E or -CO_2H;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -[N(C_1-C_6 alkyl)R^DR^E]$^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, -NR^DR^E, C_1-C_6 alkoxy, -C(=O)NR^DR^E, -SR^C, (C_1-C_6)alkoxycarbonyl, or -CO_2H;

R^5 is ~~(a) the point of covalent attachment to L^1; or (b)~~ selected from the group consisting of ~~hydrogen,~~ -C(=O)OR^F, -NO_2, -CN, -CF_3 -C(=O)NR^GR^H, -S(O_2)NR^GR^H, -N(R^I)-C(=O)R^J, -N(R^I)-S(O_2)R^K, and SO_3R^K;

each R^6 is (a) the point of covalent attachment to L^1; or (b) independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and –NR^AR^B; wherein no more than one R^6 is the point of covalent attachment to L^1;

wherein when R^4 is (c), the C_1-C_6 alkyl, or a substituent thereof, may be further substituted with the point of covalent attachment to L^1;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is (a) the point of covalent attachment to L^1, (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^A and R^B is the point of covalent attachment to L^1;

R^C is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H are (a) the point of covalent attachment to L^1; or (b) independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^D, R^E, R^G, and R^H is the point of covalent attachment to L^1;

R^F is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

each R^I, R^J, and R^K is (a) the point of covalent attachment to L^1; or (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein only one of R^I, R^J, and R^K is the point of covalent attachment to L^1;

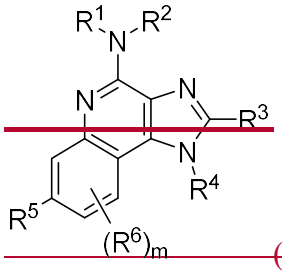
each instance of R^1 and R^4 is optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide;

wherein only one of R^1, R^2, R^3, R^4, R^5 R^A, R^6, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, and R^K is the point of covalent attachment to L^1; and

wherein Formula (X) has only one point of covalent attachment to L^1.

~~283. A compound having the formula L^1-D, or a pharmaceutically acceptable salt thereof, wherein:~~

~~L^1 is a linker intermediate; and~~
~~D is a compound of Formula (X):~~



~~(X)~~

~~or a pharmaceutically acceptable salt thereof;~~

~~wherein:~~

~~R^1 is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and~~

5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^2 is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^4 is (a) the point of covalent attachment to L^1; (b) $-OR^C$; or (c) C_1-C_6 alkyl substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH-S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$;

R^5 is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-NO_2$, $-CN$, $-CF_3$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)\text{-}C(=O)R^J$, $-N(R^I)\text{-}S(O_2)R^K$, and SO_3R^K;

each R^6 is (a) the point of covalent attachment to L^1; or (b) independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B; wherein no more than one R^6 is the point of covalent attachment to L^1;

wherein when R^4 is (c), the C_1-C_6 alkyl, or a substituent thereof, may be further substituted with the point of covalent attachment to L^1;

subscript m is 0, 1, 2, or 3;

each R^A and R^B is (a) the point of covalent attachment to L^1, (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^A and R^B is the point of covalent attachment to L^1;

R^C is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H are (a) the point of covalent attachment to L^1; or (b) independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl), aryl, and aryl(C_1-C_6 alkyl); or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl; wherein only one of R^D, R^E, R^G, and R^H is the point of covalent attachment to L^1;

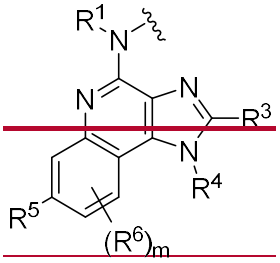
R^F is (a) the point of covalent attachment to L^1; or (b) selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

each R^I, R^J, and R^K is (a) the point of covalent attachment to L^1; or (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein only one of R^I, R^J, and R^K is the point of covalent attachment to L^1;

wherein only one of R^1, R^2, R^3, R^4, R^5 R^A, R^6, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, and R^K is the point of covalent attachment to L^1; and

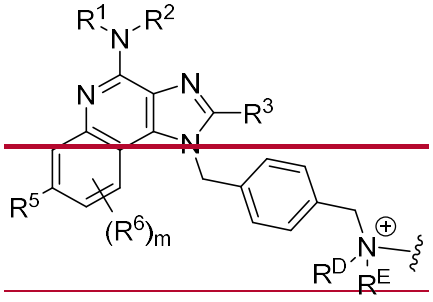
wherein Formula (X) has only one point of covalent attachment to L^1.

284. The compound of either claim 282 or 283, having the structure:



or a pharmaceutically acceptable salt thereof; wherein ~~~~ represents covalent attachment to L^1.

285. The compound of claim 284, having the structure:



or a pharmaceutically acceptable salt thereof; wherein ~~~~ represents covalent attachment to L^1.

286. The compound of any one of claims 282-285, wherein R^5 is $-C(=O)OR^F$.

287. The compound of any one of claims 282-286, wherein R^F is C_1-C_6 alkyl.

288. The compound of any one of claims 282-287, wherein R^F is methyl.

289. The compound of any one of claims 282-286, wherein R^F is hydrogen.

290. The compound of any one of claims 282-289, wherein subscript m is 0.

291. The compound of any one of claims 282-290, wherein R^3 is C_1-C_6 alkyl.

292. The compound of any one of claims 282-291, wherein R^3 is n-butyl.

293. The compound of any one of claims 282-292, wherein R^1 is hydrogen or C_1-C_6 alkyl.

294. The compound of any one of claims 282-293, wherein R^1 is hydrogen or methyl.

295. The compound of any one of claims 282-294, wherein R^1 is hydrogen.

296. The compound of any one of claims 282, 283, or 285-295, wherein R^2 is hydrogen or C_1-C_6 alkyl.

297. The compound of any one of claims 282, 283, or 285-296, wherein R^2 is hydrogen or methyl.

298. The compound of any one of claims 282, 283, or 285-297, wherein R^2 is hydrogen.

299. The compound of any one of claims 282, 283, or 285-298, wherein R^4 is C_1-C_6 alkyl substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH\text{-}S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.

300. The compound of any one of claims 282-284, or 286-299, wherein R^4 is C_1-C_6 alkyl substituted with:

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6-alkyl$)R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6-alkyl, wherein its C_1-C_6-alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6-alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6-alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6-alkyl, wherein its C_1-C_6-alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6-alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.

301. The compound of any one of claims 282-284, or 286-300, wherein R^4 is C_1-C_6 alkyl substituted with:

(ix) $-NR^DR^E$;

(x) $-[N(C_1$-C_6-alkyl$)R^DR^E]^+$; or

(xi) -(phenyl)C_1-C_6-alkyl, wherein its C_1-C_6-alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1$-C_6-alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen.

302. The compound of any one of claims 282-284, or 286-301, wherein R^4 is C_1-C_6 alkyl substituted with: $-NR^DR^E$.

303. The compound of any one of claims 282-284, or 286-301, wherein R^4 is C_1-C_6 alkyl substituted with $-[N(C_1$-C_6-alkyl$)R^DR^E]^+$.

304. The compound of any one of claims 282-284, or 286-301, wherein R^4 is C_1-C_6 alkyl substituted with: -(phenyl)C_1-C_6-alkyl, wherein its C_1-C_6-alkyl is substituted with $-NR^DR^E$ or $-[N(C_1$-C_6-alkyl$)R^DR^E]^+$.

305. The compound of any one of claims 282-284, or 286-298, wherein R^4 is the point of covalent attachment to L^1.

306. The compound of any one of claims 282-305, wherein R^D and R^E are independently C_1-C_6-alkyl.

307. The compound of any one of claims 282-306, wherein R^D and R^E are both methyl. The compound of any one of claims 282-308, wherein R^D and R^E, together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6-alkyl.

~~308. The compound of any one of claims 282-305 or 307, wherein R^D and R^E, together with the nitrogen atom to which they are attached form an unsubstituted 3-6 membered heterocyclyl.~~

~~309.~~42. The ~~compound~~ ADC of any one of claims ~~282-308~~1-29, wherein L^1 has the formula ~~M~~^{1}M-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$–;

subscript a is 0 or 1;

subscript y is 0 or 1;

subscript w is 0 or 1;

subscript x is 0 or 1;

wherein the sum of subscript a, subscript y, subscript w, and subscript x is greater than or equal to 1;

~~M^1~~ M is ~~a maleimido, azido, C_1-C_6 alkynyl, cycloalkynyl optionally substituted with 1 or 2 fluoro (e.g., cyclooctynyl or DIFO), sulfhydryl, succinimidyl esters (e.g., N-hydroxysuccinimidyl (NHS) or sulfo-NHS esters), 4-nitrophenyl esters, pentafluorophenyl esters, tetrafluorophenyl esters, anhydrides, acid chlorides, sulfonyl chlorides, isocyanates, isothiocyanates, alpha-haloketones, alpha-O-sulfonate (e.g., mesyl or tosyl) ketones, alkyl hydrazines, hydrazides, and hydroxylamines~~ a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, or a triazole;

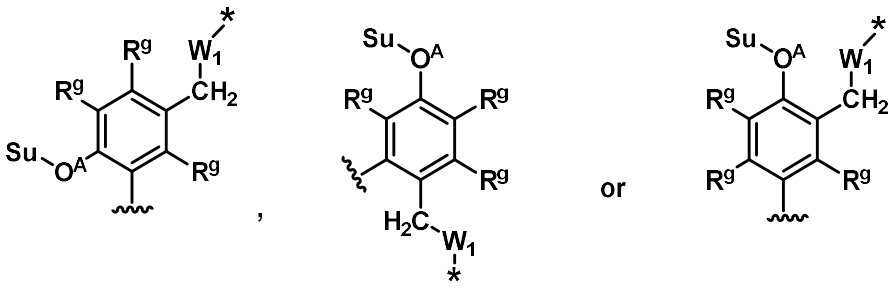
A is a C_{2-20} alkylene optionally substituted with 1-3 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R^{b1};

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;

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, C_1-C_6 alkoxy, $-N(C_1\text{-}C_6\text{ alkyl})_2$, $-NHC(=O)(C_1\text{-}C_6\text{ alkyl})$, -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W^1 is absent, *–C(=O)-O–, or *–O-C(=O)–;

~~~~ represents covalent attachment to A or M;

* represents covalent attachment to X, Y, or D;

Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

L is optionally substituted with a PEG Unit from PEG1 to PEG72.

~~310. An antibody drug conjugate (ADC) having the structure:~~

~~$Ab-(L-D)_p$~~

~~or a pharmaceutically acceptable salt thereof;~~

~~wherein:~~

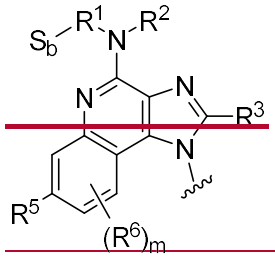
~~Ab is an antibody;~~

~~wherein each D is conjugated to a linker (L);~~

~~wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ε-amino group of a lysine residue;~~

~~subscript p is an integer from 1 to 16;~~

~~each D has the structure of Formula (XI):~~



~~(XI)~~

~~or a pharmaceutically acceptable salt thereof;~~

~~wherein:~~

~~~~~~ represents covalent attachment to L;

~~R^1 is a hydrolysable group selected from the group consisting of C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, and C_1-C_6 thione; wherein each C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, and C_1-C_6 thione, is optionally substituted with 1-3 substituents~~

~~independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;~~

~~R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B; or~~

~~R^1 and R^2, taken together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;~~

~~R^3 is selected from the group consisting of hydrogen, NR^AR^B, $C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B;~~

~~R^5 is selected from the group consisting of hydrogen, $C(=O)OR^F$, NO_2, CN, CF_3, $C(=O)NR^GR^H$, $S(O_2)NR^GR^H$, $N(R^I)C(=O)R^J$, $N(R^I)S(O_2)R^K$, and SO_3R^K;~~

~~each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NR^AR^B;~~

~~subscript m is 0, 1, 2, or 3;~~

~~each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;~~

~~R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;~~

~~each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl), aryl,~~

and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; and

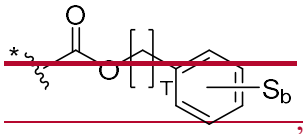
S_b is a solubilizing group selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide.

311. The ADC of claim 310, wherein R^1 is a hydrolysable group selected from the group consisting of C_1-C_6 alkoxycarbonyl and C_1-C_6 carbamoyl; wherein each C_1-C_6 alkoxycarbonyl and C_1-C_6 carbamoyl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and NR^AR^B.

312. The ADC of claim 310 or 311, wherein R^1 is a C_1-C_6 alkoxycarbonyl optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, and -NR^AR^B.

313. The ADC of any one of claims 310-312, wherein S_b is a solubilizing group selected from the group consisting of C_5-C_9 monosaccharide and C_{10}-C_{18} disaccharide.

314. The ADC of any one of claims 310-313, wherein R^1-S_b is



, wherein subscript T is 1-6.

315. The ADC of any one of claims 310-314, wherein R^2 is hydrogen or C_1-C_6 alkyl.

316. The ADC of any one of claims 310-315, wherein R^3 is selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle.

317. The ADC of any one of claims 310-316, wherein R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl.

~~318. The ADC of any one of claims 310-317, wherein R^5 comprises a pH of at most about 7.0, a dipole moment of at least about 2.0 Debye, or both.~~

~~319. The ADC of any one of claims 310-318, wherein R^5 is selected from the group consisting of -C(=O)OH, $-NO_2$, -CN, $-CF_3$, and $-S(O_3)H$.~~

~~320. The ADC of any one of claims 310-319, wherein R^5 is $-C(=O)OR^K$.~~

~~321. The ADC of any one of claims 310-320, wherein subscript m is 0.~~

~~322. The ADC of any one of claims 310-320, wherein the linker (L) comprises a cleavable group.~~

~~323. The ADC of claim 322, wherein the cleavable group comprises a glycosidic bond, peptide bond, carbamate, or quaternary amine.~~

43. An antibody drug conjugate (ADC) having the structure:

$Ab-(L-D)_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

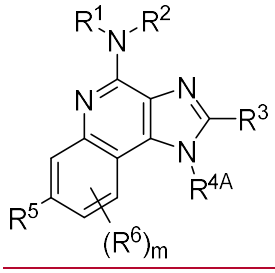
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ϵ-amino group of a lysine residue;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6 sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, C_1-C_6 amidine, C_1-C_6

sulfone, C_1-C_6 thione, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$; or

R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^3 is selected from the group consisting of hydrogen, $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_3-C_6 cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, and $-NR^AR^B$;

R^{4A} is (a) the point of covalent attachment to L or (b) C_1-C_6 alkyl substituted with:

(i) 1-3 independently selected halogen;

(ii) $-OR^C$;

(iii) $-SR^C$;

(iv) $-NH\text{-}S(O_2)R^C$;

(v) $-OC(=O)R^C$;

(vi) $-CO_2H$;

(vii) C_1-C_6 alkoxycarbonyl;

(viii) $-C(=O)NR^DR^E$;

(ix) $-NR^DR^E$;

(x) $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, -C(=O)NR^DR^E or -CO_2H;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -[N(C_1-C_6 alkyl)R^DR^E]$^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, -NR^DR^E, C_1-C_6 alkoxy, -C(=O)NR^DR^E, or -CO_2H;

wherein when R^{4A} is (b), the C_1-C_6 alkyl, or a substituent thereof, is further substituted with the point of covalent attachment to L;

R^5 is selected from the group consisting of -C(=O)OR^F, -NO_2, -CN, -CF_3 -C(=O)NR^GR^H, -S(O_2)NR^GR^H, -N(R^I)-C(=O)R^J, -N(R^I)-S(O_2)R^K, and -SO_3R^K;

each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and –NR^AR^B;

subscript m is 0, 1, 2, or 3;

each R^A and R^B independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen;

each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl optionally substituted with 1-3 independently selected C_1-C_6 alkyl;

R^F is selected from the group consisting of hydrogen, trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

R^1 is optionally substituted with a solubilizing group (S_b) selected from the group consisting of phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, and C_{15}-C_{27} trisaccharide; and

each R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

44. The ADC of claim 43, wherein R^{4A} is C_1-C_6 alkyl substituted with:

(ix) $-NR^DR^E$;

(x) $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$;

(xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

(xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; or

(xiv) 5-10 membered heteroaryl optionally substituted with halogen, $-NR^DR^E$, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$, $-SR^C$, (C_1-C_6)alkoxycarbonyl, or $-CO_2H$.

45. The ADC of claim 43 or 44, wherein R^{4A} is $–CH_2$-(phenyl)-(C_1-C_2 alkyl), wherein the C_1-C_2 alkyl is substituted with $-NR^DR^E$ or $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$.

46. The ADC of any one of claims 43-45, wherein R^D is the point of covalent attachment to the linker.