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, 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 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] 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;

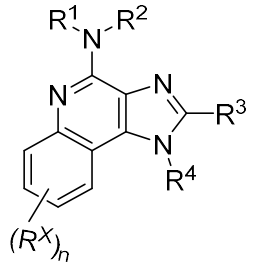
each L is a linker as defined herein;

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 the disclosure, each D has the structure of Formula (A):

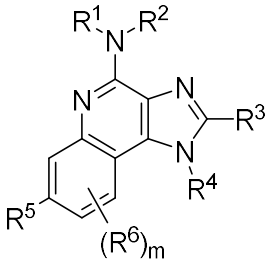


(A)

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 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:

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

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

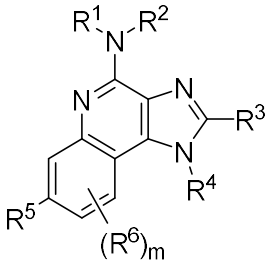
each L is a linker;

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_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 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;

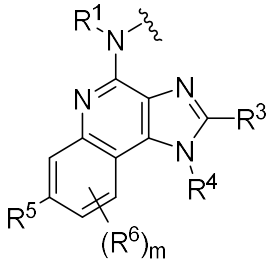
each R^I, R^J, and R^K is (a) the point of covalent attachment to L; or (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein only one of R^I, R^J, and R^K is the point of covalent attachment to L;

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

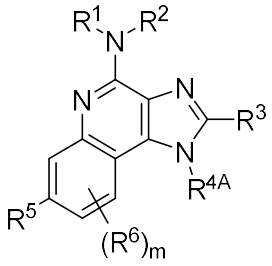


(II)

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 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;

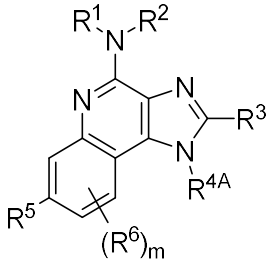
each L is a linker;

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;

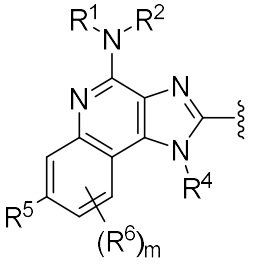
each R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_6 alkyl)-, aryl, and aryl(C_1-C_6 alkyl)-; or R^D and R^E, or R^G and R^H, together with the nitrogen atom to which they are attached,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

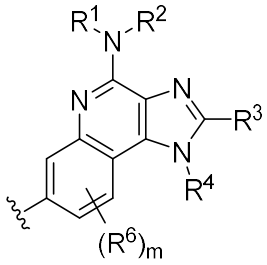


(IV)

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 the disclosure, each D has the structure of Formula (V):

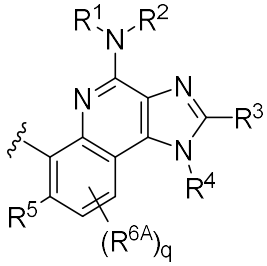


(V)

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 the disclosure, each D has the structure of Formula (VI):

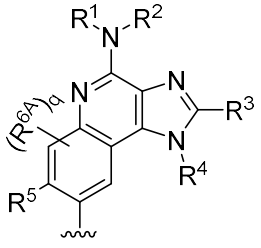


(VI)

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 the disclosure, each D has the structure of Formula (VII):

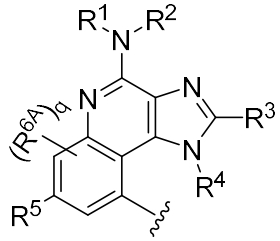


(VII)

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, each D has the structure of Formula (VIII):

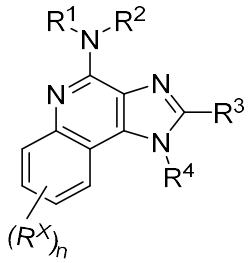


(VIII)

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, each D has the structure of Formula (A):

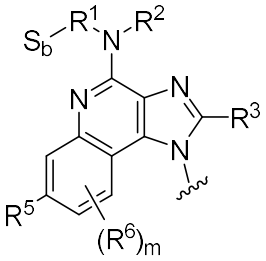


(A)

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, each D has the structure of Formula (XI):

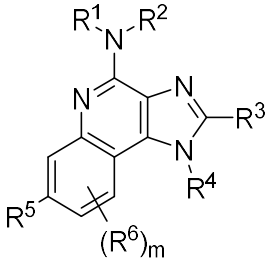


(XI)

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] The present disclosure provides compounds of Formula (IX):

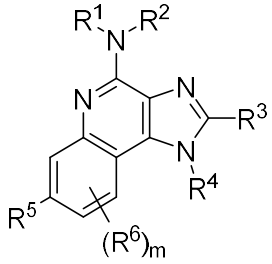


(IX)

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;

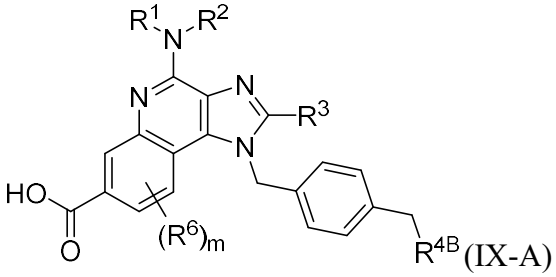
R^F is hydrogen;

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] The present disclosure provides compounds of Formula (IX-A):

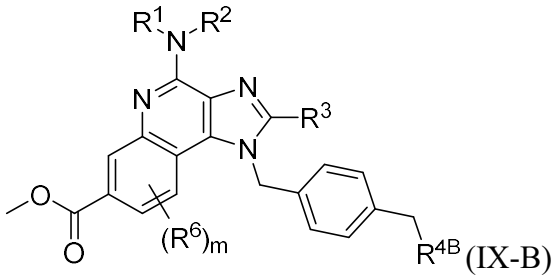


(IX-A)

or a pharmaceutically acceptable salt thereof,

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

[0021] The present disclosure provides compounds having the structure of Formula (IX-B):

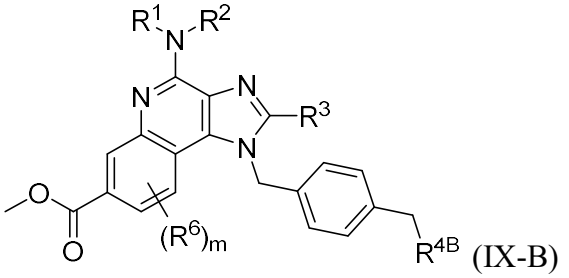


(IX-B)

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

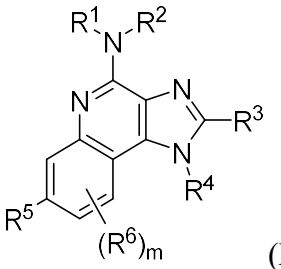
R^6 selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy;

subscript m is 0 or 1; and

[0022] R^D and R^E are independently selected from the group consisting of 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)-. The 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)

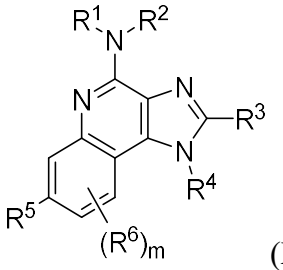
or a pharmaceutically acceptable salt thereof;

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

[0023] The 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):



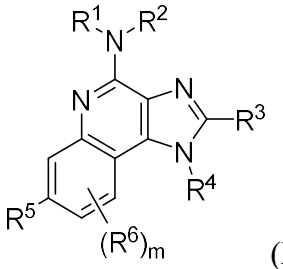
(X)

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

(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;

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

[0024] wherein Formula (X) has only one point of covalent attachment to L^1.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:

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

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

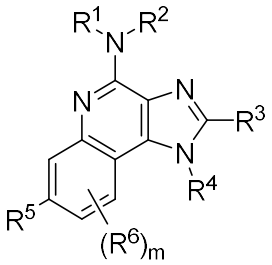
each L is a linker;

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_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 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.

2. The ADC of claim 1, 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, $-NR^DR^E$, $-[N(C_1\text{-}C_6\ \text{alkyl})R^DR^E]^+$, 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 $-C(=O)OR^F$.

3. The ADC of any one of claims 1-2, wherein subscript p is an integer from 1 to 8.

4. The ADC of any one of claims 1-2, wherein subscript p is an integer from 8 to 16.

5. The ADC of any one of claims 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.

6. The ADC of any one of claims 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.

7. The ADC of any one of claims 1-6, wherein one of 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 the linker.

8. The ADC of any one of claims 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.

9. The ADC of any one of claims 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.

10. The ADC of any one of claims 1-9, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen and unsubstituted C_1-C_6 alkyl.

11. The ADC of any one of claims 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.

12. The ADC of any one of claims 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.

13. The ADC of any one of claims 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 $-CO_2H$.

14. The ADC of any one of claims 1-13, wherein R^4 is C_1-C_6 alkyl substituted with $-OR^C$.

15. The ADC of any one of claims 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 $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$.

16. The ADC of any one of claims 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.

17. The ADC of any one of claim 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.

18. The ADC of any one of claims 1-17, wherein R^5 is -C(=O)OR^F.

19. The ADC of any one of claims 1-18 wherein R^F is selected from the group consisting of C_1-C_6 alkyl and hydrogen.

20. The ADC of any one of claims 1-19, wherein each R^G and R^H are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

21. The ADC of any one of claims 1-20, wherein R^5 is -C(=O)OH.

22. The ADC of any one of claims 1-21, wherein R^I and R^K are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

23. The ADC of any one of claims 1-22, wherein each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, and cyano.

24. The ADC of any one of claims 1-22, wherein subscript m is 0.

25. The ADC of any one of claims 1-24, wherein each R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

26. The ADC of any one of claims 1-25, wherein R^C is selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl.

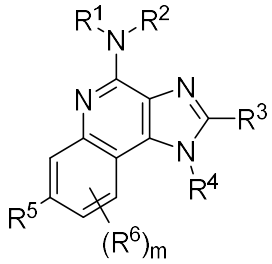
27. The ADC of any one of claims 1-26, wherein each R^D and R^E are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

28. The ADC of any one of claims 1-27, wherein the antibody is a humanized antibody.

29. The ADC of any one of claims 1-28, wherein the antibody is a monoclonal antibody.

30. A composition comprising a distribution of the ADCs of any one of claims 1-29, or a pharmaceutically acceptable salt thereof.

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 $-C(=O)OR^F$;

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;

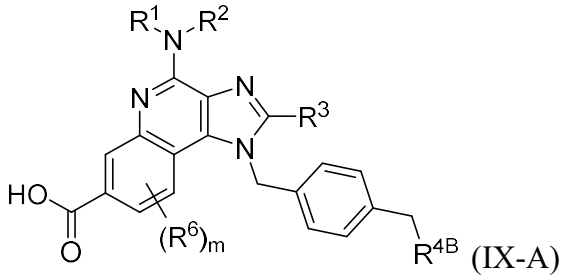
R^F is hydrogen;

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.

32. The compound of 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;

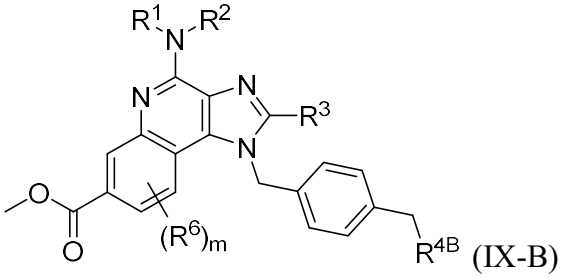
R^{4B} is selected from the group consisting of 5-10 membered heteroaryl, $-NR^DR^E$, and $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$;

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.

33. 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-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)-.

34. The compound of any one of claims 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.

35. The compound of any one of claims 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.

36. Use of 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 in the manufacture of a medicament for the treatment of cancer.

37. The 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 a cell upon binding of the antibody to a surface antigen.

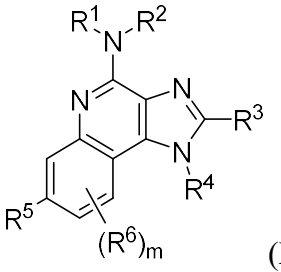
38. The use of claim 37, wherein the surface antigen is EphA2.

39. The use of claim 37 or 38, wherein the linker (L) of the ADC is configured to undergo cleavage subsequent to internalizing within the 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.

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

(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 $-CO_2H$;

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.

42. The ADC of any one of claims 1-29, wherein L^1 has the formula 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 is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, or a triazole;

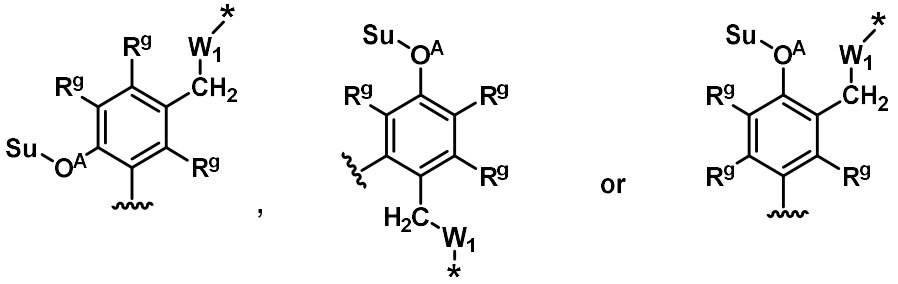
A is a C_{2-20} alkylene optionally substituted with 1-3 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R^{b1};

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.

43. 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;

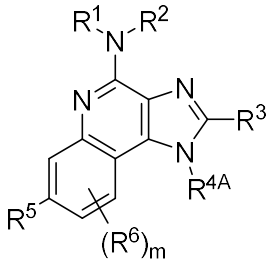
each L is a linker;

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

(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 $-CO_2H$;

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.