IMMUNOSTIMULATORY ANTI-PD-L1-DRUG CONJUGATES

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority from U.S. Provisional Application No. 63/394,912, filed August 3, 2022, which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in eXtensible Markup Language (XML) format and is hereby incorporated by reference in its entirety. Said XML copy, created on July 24, 2023, is named "438442-704021_SL.XML" and is 944 kilobytes in size.

INCORPORATION BY REFERENCE

[0003] 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

[0004] In addition to leveraging numerous disparate mechanisms for proliferation and expansion, tumors often affect local and systemic immunosuppression. While the majority of cells which express immunogenic antigens are rapidly cleared before neoplasia or tumorigenicity, tumor-mediated immunosuppression often blocks immune activity against cancer cells, and can allow tumors to spread unchecked. As many cytotoxic cancer therapies rely on immune activity for cancer cell clearance, immunosuppressive tumors can be resilient against conventional cancer therapies which do not also achieve immune reactivation, and therefore do not affect immune clearance. Accordingly, cancer therapies often require immune activating functions which can override tumor immunosuppression.

[0005] In spite of this need, most immunomodulatory therapies exhibit limited efficacies. While immunosuppressive tumor environments are often localized, many immunostimulatory therapies generate toxic systemic responses which can limit dosing below levels required for localized treatment efficacy. In particular, antibody-based treatments often affect antibody dependent cellular cytotoxicities (ADCCs), while untargeted immunostimulatory complexes can generate dangerous toxic inflammatory and cytokine responses. Furthermore, many immunostimulatory compounds target intracellular receptors present in both cancer and immune cells, such that treatments must balance requirements for tumor cell targeting and immune cell uptake.

[0006] Central among such immunostimulatory compouds, toll-like receptors (TLRs) play an important role in activitating the immune system against invading pathogens and against damaged cells with the potential to become tumorigenic (*see* Kaczanowska, et al., *J. Leukoc. Biol.* 2013; 93(6): 847-863). TLRs are a family of membrane bound proteins that, when activated, recuit adaptor proteins to propagate antigen-induced signals to modify cellular phenotype and activity. 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

[0007] 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, targeting payloads to these cancer sites can be essential for affecting immune reactivation. To achieve this end, in certain embodiments, the present disclosure provides antibody-drug conjugates (ADCs) configured to selectively activate immune responses within tumor microenvironments. In addition to delivering payloads to targeted cancer sites, ADCs of the present disclosure can be configured to release their payloads (e.g., TLR agonists) upon uptake by the cancer or cancer-associated cells, thereby targeting immune activation to cancer sites, and preventing off-target immune activation.

[0008] 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, 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.

[0009] 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.

[0010] Aspects of the present disclosure provide 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;

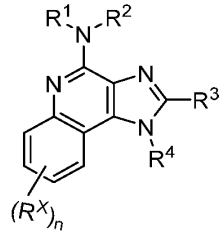
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide;

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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is optionally the point of covalent attachment to L;

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 selected from the group consisting of: the point of covalent attachment to L; hydrogen; -OR^C; -S(=O)$_2R^C$; -C(=O)NR^DR^E; -C(=O)OR^C; -C(=O)SR^C; -C(=S)R^C; -PO_3R^C; and -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 the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, -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, -NR^DR^E, -C(=O)NR^DR^E or -CO_2H;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the (-5-10 membered heteroaryl)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_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L;

each R^X is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) 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 instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, (b) the group consisting of hydrogen and C_1-C_6 alkyl; and (c) 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 at most one instance of R^A and R^B is the point of covalent attachment to L;

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

each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) 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)-; and

(c) 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;

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

wherein at most one of R^I, R^J, and R^K is the point of covalent attachment to L;

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

wherein Ab comprises a heavy chain variable region having at least 80% sequence identity to a first sequence and a light chain variable region having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20; the first sequence is SEQ ID NO: 44 and the second sequence is SEQ ID NO: 45; the first sequence is SEQ ID NO: 55 and the second sequence is SEQ ID NO: 56; the first sequence is SEQ ID NO: 69 and the second sequence is SEQ ID NO: 70; the first sequence is SEQ ID NO: 83 and the second sequence is SEQ ID NO: 84; the first sequence is SEQ ID NO: 97 and the second sequence is SEQ ID NO: 98; the first sequence is SEQ ID NO: 105 and the second sequence is SEQ ID NO: 106; the first sequence is SEQ ID NO:113 and the second sequence is SEQ ID NO: 114; the first sequence is SEQ ID NO: 121 and the second sequence is SEQ ID NO: 122; the first sequence is SEQ ID NO: 129 and the second sequence is SEQ ID NO: 130; the first sequence is SEQ ID NO: 137 and the second sequence is SEQ ID NO: 138; the first sequence is SEQ ID NO: 153 and the second sequence is SEQ ID NO: 154; the first sequence is SEQ ID NO: 161 and the second sequence is SEQ ID NO: 162; the first sequence is SEQ ID NO: 169 and the second sequence is SEQ ID NO: 170; the first sequence is SEQ ID NO: 177 and the second sequence is SEQ ID NO: 178; the first sequence is SEQ ID NO: 185 and the second sequence is SEQ ID NO: 186; the first sequence is SEQ ID NO: 193 and the second sequence is SEQ ID NO: 194; the first sequence is SEQ ID NO: 201 and the second sequence is SEQ ID NO: 202; the first sequence is SEQ ID NO: 209 and the second sequence is SEQ ID NO: 210; the first sequence is SEQ ID NO: 217 and the second sequence is SEQ ID NO: 218; the first sequence is SEQ ID NO: 225 and the second sequence is SEQ ID NO: 226; the first sequence is SEQ ID NO: 233 and the second sequence is SEQ ID NO: 234; the first sequence is SEQ ID NO: 241 and the second sequence is

SEQ ID NO: 242; the first sequence is SEQ ID NO: 249 and the second sequence is SEQ ID NO: 250; the first sequence is SEQ ID NO: 297 and the second sequence is SEQ ID NO: 298; the first sequence is SEQ ID NO: 307 and the second sequence is SEQ ID NO: 308; the first sequence is SEQ ID NO: 315 and the second sequence is SEQ ID NO: 316; the first sequence is SEQ ID NO: 323 and the second sequence is SEQ ID NO: 324; the first sequence is SEQ ID NO: 331 and the second sequence is SEQ ID NO: 332; the first sequence is SEQ ID NO: 339 and the second sequence is SEQ ID NO: 340; the first sequence is SEQ ID NO: 347 and the second sequence is SEQ ID NO: 348; the first sequence is SEQ ID NO: 355 and the second sequence is SEQ ID NO: 356; the first sequence is SEQ ID NO: 363 and the second sequence is SEQ ID NO: 364; the first sequence is SEQ ID NO: 371 and the second sequence is SEQ ID NO: 372; the first sequence is SEQ ID NO: 379 and the second sequence is SEQ ID NO: 380; the first sequence is SEQ ID NO: 387 and the second sequence is SEQ ID NO: 388; the first sequence is SEQ ID NO: 395 and the second sequence is SEQ ID NO: 396; the first sequence is SEQ ID NO: 403 and the second sequence is SEQ ID NO: 404; the first sequence is SEQ ID NO: 411 and the second sequence is SEQ ID NO: 412; the first sequence is SEQ ID NO: 419 and the second sequence is SEQ ID NO: 420; the first sequence is SEQ ID NO: 427 and the second sequence is SEQ ID NO: 428; the first sequence is SEQ ID NO: 435 and the second sequence is SEQ ID NO: 436; the first sequence is SEQ ID NO: 443 and the second sequence is SEQ ID NO: 444; the first sequence is SEQ ID NO: 451 and the second sequence is SEQ ID NO: 452; the first sequence is SEQ ID NO: 459 and the second sequence is SEQ ID NO: 460; the first sequence is SEQ ID NO: 467 and the second sequence is SEQ ID NO: 468; the first sequence is SEQ ID NO: 475 and the second sequence is SEQ ID NO: 476; the first sequence is SEQ ID NO: 483 and the second sequence is SEQ ID NO: 484; the first sequence is SEQ ID NO: 491 and the second sequence is SEQ ID NO: 492; the first sequence is SEQ ID NO: 501 and the second sequence is SEQ ID NO: 502; the first sequence is SEQ ID NO: 509 and the second sequence is SEQ ID NO: 510; the first sequence is SEQ ID NO: 517 and the second sequence is SEQ ID NO: 518; the first sequence is SEQ ID NO: 525 and the second sequence is SEQ ID NO: 526; the first sequence is SEQ ID NO: 533 and the second sequence is SEQ ID NO: 534; the first sequence is SEQ ID NO: 541 and the second sequence is SEQ ID NO: 542; the first sequence is SEQ ID NO: 549 and the second sequence is SEQ ID NO: 550; the first sequence is SEQ ID NO: 557 and the second sequence is SEQ ID NO: 558; the first sequence is SEQ ID NO: 565 and the second sequence is SEQ ID NO: 566; the first sequence is SEQ ID NO: 574 and the second sequence is SEQ ID NO: 574; the first sequence is SEQ ID NO: 581 and the second sequence is SEQ ID NO: 582; the first sequence is SEQ ID NO: 589 and the second sequence is SEQ ID NO: 590; the first sequence is SEQ ID NO: 597 and the second

sequence is SEQ ID NO: 598; the first sequence is SEQ ID NO: 605 and the second sequence is SEQ ID NO: 606; the first sequence is SEQ ID NO: 613 and the second sequence is SEQ ID NO: 614; the first sequence is SEQ ID NO: 621 and the second sequence is SEQ ID NO: 622; the first sequence is SEQ ID NO: 629 and the second sequence is SEQ ID NO: 630; the first sequence is SEQ ID NO: 637 and the second sequence is SEQ ID NO: 638; the first sequence is SEQ ID NO: 645 and the second sequence is SEQ ID NO: 646; the first sequence is SEQ ID NO: 653 and the second sequence is SEQ ID NO: 654; the first sequence is SEQ ID NO: 661 and the second sequence is SEQ ID NO: 662; the first sequence is SEQ ID NO: 669 and the second sequence is SEQ ID NO: 670; the first sequence is SEQ ID NO: 677 and the second sequence is SEQ ID NO: 678; the first sequence is SEQ ID NO: 685 and the second sequence is SEQ ID NO: 686; the first sequence is SEQ ID NO: 693 and the second sequence is SEQ ID NO: 694; the first sequence is SEQ ID NO: 701 and the second sequence is SEQ ID NO: 702; the first sequence is SEQ ID NO: 703 and the second sequence is SEQ ID NO: 704; the first sequence is SEQ ID NO: 711 and the second sequence is SEQ ID NO: 712; the first sequence is SEQ ID NO: 713 and the second sequence is SEQ ID NO: 714; the first sequence is SEQ ID NO: 715 and the second sequence is SEQ ID NO: 716; the first sequence is SEQ ID NO: 731 and the second sequence is SEQ ID NO: 732; the first sequence is SEQ ID NO: 739 and the second sequence is SEQ ID NO: 740; the first sequence is SEQ ID NO: 747 and the second sequence is SEQ ID NO: 748; the first sequence is SEQ ID NO: 755 and the second sequence is SEQ ID NO: 756; the first sequence is SEQ ID NO: 765 and the second sequence is SEQ ID NO: 766; the first sequence is SEQ ID NO: 773 and the second sequence is SEQ ID NO: 774; the first sequence is SEQ ID NO: 781 and the second sequence is SEQ ID NO: 782; the first sequence is SEQ ID NO: 789 and the second sequence is SEQ ID NO: 790; the first sequence is SEQ ID NO: 797 and the second sequence is SEQ ID NO: 798; the first sequence is SEQ ID NO: 805 and the second sequence is SEQ ID NO: 806; the first sequence is SEQ ID NO: 813 and the second sequence is SEQ ID NO: 814; the first sequence is SEQ ID NO: 821 and the second sequence is SEQ ID NO: 822; the first sequence is SEQ ID NO: 829 and the second sequence is SEQ ID NO: 830; the first sequence is SEQ ID NO: 837 and the second sequence is SEQ ID NO: 838; the first sequence is SEQ ID NO: 845 and the second sequence is SEQ ID NO: 846; the first sequence is SEQ ID NO: 853 and the second sequence is SEQ ID NO: 854; the first sequence is SEQ ID NO: 861 and the second sequence is SEQ ID NO: 862; the first sequence is SEQ ID NO: 869 and the second sequence is SEQ ID NO: 870; the first sequence is SEQ ID NO: 877 and the second sequence is SEQ ID NO: 878; the first sequence is SEQ ID NO: 885 and the second sequence is SEQ ID NO: 886; the first sequence is SEQ ID NO: 893 and the second sequence is SEQ ID NO: 894; the first sequence is SEQ ID NO: 900 and the

second sequence is SEQ ID NO: 901; the first sequence is SEQ ID NO: 909 and the second sequence is SEQ ID NO: 910; the first sequence is SEQ ID NO: 917 and the second sequence is SEQ ID NO: 918; the first sequence is SEQ ID NO: 925 and the second sequence is SEQ ID NO: 926; the first sequence is SEQ ID NO: 933 and the second sequence is SEQ ID NO: 934; the first sequence is SEQ ID NO: 941 and the second sequence is SEQ ID NO: 942; the first sequence is SEQ ID NO: 943 and the second sequence is SEQ ID NO: 944; the first sequence is SEQ ID NO: 951 and the second sequence is SEQ ID NO: 952; the first sequence is SEQ ID NO: 959 and the second sequence is SEQ ID NO: 960; the first sequence is SEQ ID NO: 967 and the second sequence is SEQ ID NO: 968; the first sequence is SEQ ID NO: 975 and the second sequence is SEQ ID NO: 976; the first sequence is SEQ ID NO: 983 and the second sequence is SEQ ID NO: 984; the first sequence is SEQ ID NO: 991 and the second sequence is SEQ ID NO: 992; the first sequence is SEQ ID NO: 993 and the second sequence is SEQ ID NO: 994; the first sequence is SEQ ID NO: 995 and the second sequence is SEQ ID NO: 996; the first sequence is SEQ ID NO: 1003 and the second sequence is SEQ ID NO: 1004; the first sequence is SEQ ID NO: 1011 and the second sequence is SEQ ID NO: 1012; the first sequence is SEQ ID NO: 1019 and the second sequence is SEQ ID NO: 1020; the first sequence is SEQ ID NO: 1027 and the second sequence is SEQ ID NO: 1028; the first sequence is SEQ ID NO: 1035 and 1036; or the first sequence is SEQ ID NO: 1043 and the second sequence is SEQ ID NO: 1044. In some cases, the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20; the first sequence is SEQ ID NO: 83 and the second sequence is SEQ ID NO: 84; the first sequence is SEQ ID NO: 97 and the second sequence is SEQ ID NO: 98; the first sequence is SEQ ID NO: 105 and the second sequence is SEQ ID NO: 106; the first sequence is SEQ ID NO:113 and the second sequence is SEQ ID NO: 114; the first sequence is SEQ ID NO: 121 and the second sequence is SEQ ID NO: 122; the first sequence is SEQ ID NO: 129 and the second sequence is SEQ ID NO: 130; the first sequence is SEQ ID NO: 137 and the second sequence is SEQ ID NO: 138; the first sequence is SEQ ID NO: 153 and the second sequence is SEQ ID NO: 154; the first sequence is SEQ ID NO: 161 and the second sequence is SEQ ID NO: 162; the first sequence is SEQ ID NO: 169 and the second sequence is SEQ ID NO: 170; the first sequence is SEQ ID NO: 177 and the second sequence is SEQ ID NO: 178; the first sequence is SEQ ID NO: 185 and the second sequence is SEQ ID NO: 186; the first sequence is SEQ ID NO: 193 and the second sequence is SEQ ID NO: 194; the first sequence is SEQ ID NO: 201 and the second sequence is SEQ ID NO: 202; the first sequence is SEQ ID NO: 209 and the second sequence is SEQ ID NO: 210; the first sequence is SEQ ID NO: 217 and the second sequence is SEQ ID NO: 218; the first sequence is SEQ ID NO: 225 and the second sequence is SEQ ID NO: 226; the first sequence is SEQ ID NO: 233 and the

second sequence is SEQ ID NO: 234; the first sequence is SEQ ID NO: 241 and the second sequence is SEQ ID NO: 242; the first sequence is SEQ ID NO: 249 and the second sequence is SEQ ID NO: 250; the first sequence is SEQ ID NO: 629 and the second sequence is SEQ ID NO: 630; the first sequence is SEQ ID NO: 637 and the second sequence is SEQ ID NO: 638; the first sequence is SEQ ID NO: 645 and the second sequence is SEQ ID NO: 646; the first sequence is SEQ ID NO: 653 and the second sequence is SEQ ID NO: 654; the first sequence is SEQ ID NO: 661 and the second sequence is SEQ ID NO: 662; the first sequence is SEQ ID NO: 669 and the second sequence is SEQ ID NO: 670; the first sequence is SEQ ID NO: 677 and the second sequence is SEQ ID NO: 678; the first sequence is SEQ ID NO: 685 and the second sequence is SEQ ID NO: 686; the first sequence is SEQ ID NO: 693 and the second sequence is SEQ ID NO: 694; the first sequence is SEQ ID NO: 701 and the second sequence is SEQ ID NO: 702; the first sequence is SEQ ID NO: 703 and the second sequence is SEQ ID NO: 704; the first sequence is SEQ ID NO: 711 and the second sequence is SEQ ID NO: 712; the first sequence is SEQ ID NO: 713 and the second sequence is SEQ ID NO: 714; the first sequence is SEQ ID NO: 715 and the second sequence is SEQ ID NO: 716; or the first sequence is SEQ ID NO: 1027 and the second sequence is SEQ ID NO: 1028. In some cases, the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20. In some cases, the heavy chain variable region has at least 90% sequence identity to the first sequence and the light chain variable region has at least 90% sequence identity to the second sequence. In some cases, the heavy chain variable region has at least 98% sequence identity to the first sequence and the light chain variable region has at least 98% sequence identity to the second sequence

[0011] Certain aspects of the present disclosure provide 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;

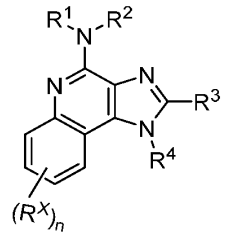
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide;

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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is optionally the point of covalent attachment to L;

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 selected from the group consisting of: the point of covalent attachment to L; hydrogen; $-OR^C$; $-S(=O)_2R^C$; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; $-C(=S)R^C$; $-PO_3R^C$; and -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 the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, $-NR^DR^E$, $-[N(C_1\text{-}C_6$ alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen;

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

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the (-5-10 membered heteroaryl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6$ 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_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L;

each R^X is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) 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 instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, (b) the group consisting of hydrogen and C_1-C_6 alkyl; and (c) 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 at most one instance of R^A and R^B is the point of covalent attachment to L;

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

each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) 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)-; and (c) 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;

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

wherein at most one of R^I, R^J, and R^K is the point of covalent attachment to L;

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

wherein Ab comprises a heavy chain having at least 80% sequence identity to a first sequence and a light chain having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 1 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 2 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 4 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 6 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 7 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 8 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ

ID NO: 9 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 46 and the second sequence is SEQ ID NO: 48; the first sequence is SEQ ID NO: 47 and the second sequence is SEQ ID NO: 48; the first sequence is SEQ ID NO: 57 and the second sequence is SEQ ID NO: 59; the first sequence is SEQ ID NO: 58 and the second sequence is SEQ ID NO: 59; the first sequence is SEQ ID NO: 60 and the second sequence is SEQ ID NO: 62; the first sequence is SEQ ID NO: 61 and the second sequence is SEQ ID NO: 62; the first sequence is SEQ ID NO: 71 and the second sequence is SEQ ID NO: 73; the first sequence is SEQ ID NO: 72 and the second sequence is SEQ ID NO: 73; the first sequence is SEQ ID NO: 74 and the second sequence is SEQ ID NO: 76; the first sequence is SEQ ID NO: 75 and the second sequence is SEQ ID NO: 76; the first sequence is SEQ ID NO: 85 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 86 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 88 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 89 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 251 and the second sequence is SEQ ID NO: 252; the first sequence is SEQ ID NO: 253 and the second sequence is SEQ ID NO: 254; the first sequence is SEQ ID NO: 255 and the second sequence is SEQ ID NO: 256; the first sequence is SEQ ID NO: 257 and the second sequence is SEQ ID NO: 258; the first sequence is SEQ ID NO: 259 and the second sequence is SEQ ID NO: 260; the first sequence is SEQ ID NO: 261 and the second sequence is SEQ ID NO: 262; the first sequence is SEQ ID NO: 263 and the second sequence is SEQ ID NO: 264; the first sequence is SEQ ID NO: 265 and the second sequence is SEQ ID NO: 266; the first sequence is SEQ ID NO: 267 and the second sequence is SEQ ID NO: 268; the first sequence is SEQ ID NO: 269 and the second sequence is SEQ ID NO: 270; the first sequence is SEQ ID NO: 271 and the second sequence is SEQ ID NO: 272; the first sequence is SEQ ID NO: 273 and the second sequence is SEQ ID NO: 274; the first sequence is SEQ ID NO: 275 and the second sequence is SEQ ID NO: 276; the first sequence is SEQ ID NO: 277 and the second sequence is SEQ ID NO: 278; the first sequence is SEQ ID NO: 279 and the second sequence is SEQ ID NO: 280; the first sequence is SEQ ID NO: 281 and the second sequence is SEQ ID NO: 282; the first sequence is SEQ ID NO: 283 and the second sequence is SEQ ID NO: 284; the first sequence is SEQ ID NO: 285 and the second sequence is SEQ ID NO: 286; the first sequence is SEQ ID NO: 287 and the second sequence is SEQ ID NO: 288; the first sequence is SEQ ID NO: 289 and the second sequence is SEQ ID NO: 290; the first sequence is SEQ ID NO: 299 and the second sequence is SEQ ID NO: 300; the first sequence is SEQ ID NO: 493 and the second sequence is SEQ ID NO: 494; the first sequence is SEQ ID NO: 717 and the second sequence is SEQ ID NO: 718; the first sequence is SEQ ID NO: 719 and the second sequence is SEQ ID NO: 720; the first sequence is SEQ ID NO: 721 and the second

sequence is SEQ ID NO: 722; the first sequence is SEQ ID NO: 723 and the second sequence is SEQ ID NO: 724; or the first sequence is SEQ ID NO: 757 and the second sequence is SEQ ID NO: 758. In some cases, the first sequence is SEQ ID NO: 1 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 2 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 4 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 6 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 7 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 8 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 9 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 85 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 86 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 88 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 89 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 251 and the second sequence is SEQ ID NO: 252; the first sequence is SEQ ID NO: 253 and the second sequence is SEQ ID NO: 254; the first sequence is SEQ ID NO: 255 and the second sequence is SEQ ID NO: 256; the first sequence is SEQ ID NO: 257 and the second sequence is SEQ ID NO: 258; the first sequence is SEQ ID NO: 259 and the second sequence is SEQ ID NO: 260; the first sequence is SEQ ID NO: 261 and the second sequence is SEQ ID NO: 262; the first sequence is SEQ ID NO: 263 and the second sequence is SEQ ID NO: 264; the first sequence is SEQ ID NO: 265 and the second sequence is SEQ ID NO: 266; the first sequence is SEQ ID NO: 267 and the second sequence is SEQ ID NO: 268; the first sequence is SEQ ID NO: 269 and the second sequence is SEQ ID NO: 270; the first sequence is SEQ ID NO: 271 and the second sequence is SEQ ID NO: 272; the first sequence is SEQ ID NO: 273 and the second sequence is SEQ ID NO: 274; the first sequence is SEQ ID NO: 275 and the second sequence is SEQ ID NO: 276; the first sequence is SEQ ID NO: 277 and the second sequence is SEQ ID NO: 278; the first sequence is SEQ ID NO: 279 and the second sequence is SEQ ID NO: 280; the first sequence is SEQ ID NO: 281 and the second sequence is SEQ ID NO: 282; the first sequence is SEQ ID NO: 283 and the second sequence is SEQ ID NO: 284; the first sequence is SEQ ID NO: 285 and the second sequence is SEQ ID NO: 286; the first sequence is SEQ ID NO: 287 and the second sequence is SEQ ID NO: 288; the first sequence is SEQ ID NO: 289 and the second sequence is SEQ ID NO: 290; the first sequence is SEQ ID NO: 717 and the second sequence is SEQ ID NO: 718; the first sequence is SEQ ID NO: 719 and the second sequence is SEQ ID NO: 720; the first sequence is SEQ ID NO: 721 and the second sequence is SEQ ID NO: 722; or the first sequence is SEQ ID NO: 723 and the second sequence is SEQ ID NO: 724. In some cases, the first sequence is SEQ ID NO: 1 and the second

sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 2 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 4 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 6 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 7 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 8 and the second sequence is SEQ ID NO: 10; or the first sequence is SEQ ID NO: 9 and the second sequence is SEQ ID NO: 10. In some cases, the heavy chain has at least 90% sequence identity to the first sequence and the light chain has at least 90% sequence identity to the second sequence. In some cases, the heavy chain has at least 98% sequence identity to the first sequence and the light chain has at least 98% sequence identity to the second sequence.

[0012] Various aspects of the present disclosure provide 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;

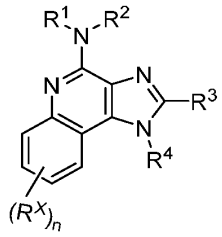
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide;

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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is optionally the point of covalent attachment to L;

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 selected from the group consisting of: the point of covalent attachment to L; hydrogen; -OR^C; -$S(=O)_2R^C$; -$C(=O)NR^DR^E$; -$C(=O)OR^C$; -$C(=O)SR^C$; -$C(=S)R^C$; -PO_3R^C; and -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 the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen;

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

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the (-5-10 membered heteroaryl)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 C_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L;

each R^X is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) 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 instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, (b) the group consisting of hydrogen and C_1-C_6 alkyl; and (c) 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 at most one instance of R^A and R^B is the point of covalent attachment to L;

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

each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) 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)-; and (c) 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;

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

wherein at most one of R^I, R^J, and R^K is the point of covalent attachment to L;

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

wherein Ab comprises a CDR-H1 comprising at least 80% sequence identity to a first sequence, a CDR-H2 comprising at least 80% sequence identity to a second sequence, a CDR-H3 comprising at least 80% sequence identity to a third sequence, a CDR-L1 comprising at least 80% sequence identity to a fourth sequence, a CDR-L2 comprising at least 80% sequence identity to a fifth sequence, and a CDR-L3 comprising at least 80% sequence identity to a sixth sequence, wherein the first, second, third, fourth, fifth, and sixth sequences are: SEQ ID NO: 13, 14, 15, 16, 17, and 18, respectively; SEQ ID NO: 21, 22, 23, 24, 25, and 26, respectively; SEQ ID NO: 38, 39, 40, 41, 42, and 43, respectively; SEQ ID NO: 49, 50, 51, 52, 53, and 54, respectively; SEQ ID NO: 63, 64, 65, 66, 67, and 68, respectively; SEQ ID NO: 77, 78, 79, 80, 81, and 82, respectively; SEQ ID NO: 91, 92, 93, 94, 95, and 96, respectively; SEQ ID NO: 99, 100, 101, 102, 103, and 104, respectively; SEQ ID NO: 107, 108, 109, 110, 111, and 112, respectively; SEQ ID NO: 115, 116, 117, 118, 119, and 120, respectively; SEQ ID NO: 123, 124, 125, 126, 127, and 128, respectively; SEQ ID NO: 131, 132, 133, 134, 135, and 136, respectively; SEQ ID NO: 139, 140, 141, 142, 143, and 144, respectively; SEQ ID NO: 147, 148, 149, 150, 151, and 152, respectively; SEQ ID NO: 155, 156, 157, 158, 159, and 160, respectively; SEQ ID NO: 163, 164, 165, 166, 167, and 168, respectively; SEQ ID NO: 171, 172, 173, 174, 175, and 176, respectively; SEQ ID NO: 179, 180, 181, 182, 183, and 184, respectively; SEQ ID NO: 187, 188, 189, 190, 191, and 192, respectively; SEQ ID NO: 195, 196, 197, 198, 199, and 200, respectively; SEQ ID NO: 203, 204, 205, 206, 207 and 208, respectively; SEQ ID NO: 211, 212, 213, 214, 215, and 216, respectively;

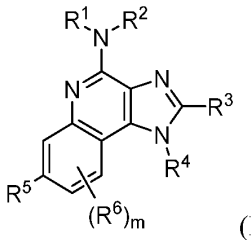
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157, 158, 159, and 160, respectively; SEQ ID NO: 163, 164, 165, 166, 167, and 168, respectively; SEQ ID NO: 171, 172, 173, 174, 175, and 176, respectively; SEQ ID NO: 179, 180, 181, 182, 183, and 184, respectively; SEQ ID NO: 187, 188, 189, 190, 191, and 192, respectively; SEQ ID NO: 195, 196, 197, 198, 199, and 200, respectively; SEQ ID NO: 203, 204, 205, 206, 207 and 208, respectively; SEQ ID NO: 211, 212, 213, 214, 215, and 216, respectively; SEQ ID NO: 219, 220, 221, 222, 223, and 224, respectively; SEQ ID NO: 227, 228, 229, 230, 231, and 232, respectively; SEQ ID NO: 235, 236, 237, 238, 239, and 240, respectively; SEQ ID NO: 243, 244, 245, 246, 247, and 248, respectively; SEQ ID NO: 623, 624, 625, 626, 627, and 628, respectively; SEQ ID NO: 631, 632, 633, 634, 635, and 636, respectively; SEQ ID NO: 639, 640, 641, 642, 643, and 644, respectively; SEQ ID NO: 647, 648, 649, 650, 651, and 652, respectively; SEQ ID NO: 655, 656, 657, 658, 659, and 660, respectively; SEQ ID NO: 663, 664, 665, 666, 667, and 668, respectively; SEQ ID NO: 671, 672, 673, 674, 675, and 676, respectively; SEQ ID NO: 679, 680, 681, 682, 683, and 684, respectively; SEQ ID NO: 687, 688, 689, 690, 691, and 692, respectively; SEQ ID NO: 695, 696, 697, 698, 699, and 700, respectively; SEQ ID NO: 705, 706, 707, 708, 709, and 710, respectively; or SEQ ID NO: 1021, 1022, 1023, 1024, 1025, and 1026, respectively. In some cases, the CDR-H1 comprises at most one mutation relative to the first sequence, the CDR-H2 comprises at most one mutation relative to the second sequence, the CDR-H3 comprises at most one mutation relative to the third sequence, the CDR-L1 comprises at most one mutation relative to the fourth sequence, the CDR-L2 comprises at most one mutation relative to the fifth sequence, and the CDR-L3 comprises at most one mutation relative to the sixth sequence. In some cases, the first, second, third, fourth, fifth, and sixth sequences are: SEQ ID NO: 13, 14, 15, 16, 17, and 18, respectively.

[0013] In some cases, Ab comprises an effector function-diminishing mutation. In some cases, the effector function diminishing mutation is selected from the group consisting of L234A/L235A, D265A/N297A, D270A, K322A, P329A, P329G, and combinations thereof. In some cases, the effector function diminishing mutation is L234A/L235A.

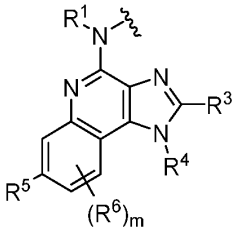
[0014] In some cases, each D has the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein R^5 is (a) the point of covalent attachment to L; or (b) 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 (a) the point of covalent attachment to L; or (b) 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; and m is 0, 1, 2, or 3.

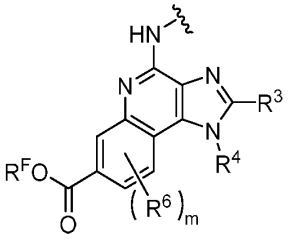
[0015] In some cases, each D has the structure of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein ~~~ is 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 -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 (a) the point of covalent attachment to L; or (b) 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; and m is 0, 1, 2, or 3.

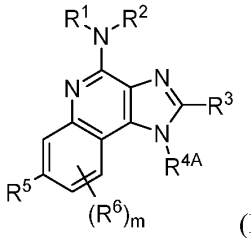
[0016] In some cases, each D has the structure of Formula (IIa):



(IIa)

or a pharmaceutically acceptable salt thereof, wherein each R^6 is independently selected from the group consisting of (a) the point of covalent attachment to L; or (b) 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, and m is 0, 1, 2, or 3.

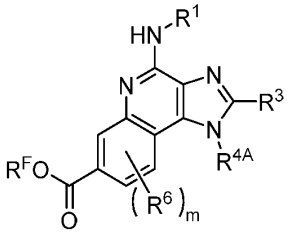
[0017] In some cases, each D has the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein R^{4A} is (a) the point of covalent attachment to L 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; (ix) -$[N(C_1\text{-}C_6\ \text{alkyl})R^DR^E]^+$; (x) -(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; (xi) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, -$C(=O)NR^DR^E$ or -CO_2H; (xii) -(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 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, the C_1-C_6 alkyl or a substituent thereof is 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 -$C(=O)OR^F$, -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 (a) the point of covalent attachment to L; or (b) 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; and m is 0, 1, 2, or 3.

[0018] In some cases, each D has the structure of Formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt thereof.

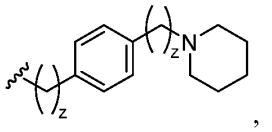
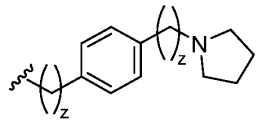
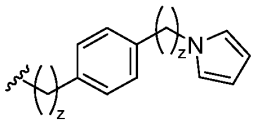
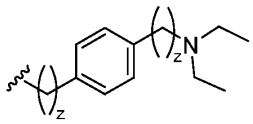
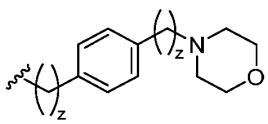
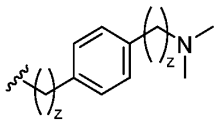
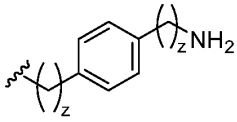
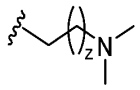
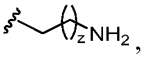
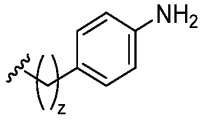
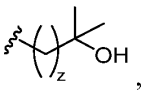
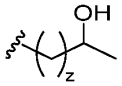
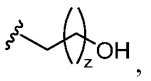
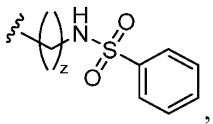
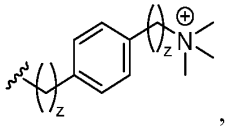
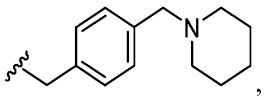
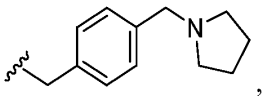
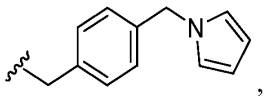
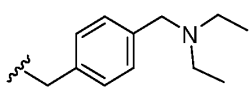
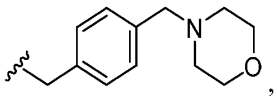
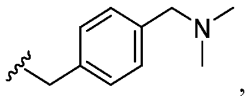
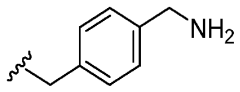
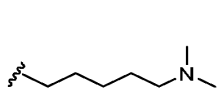
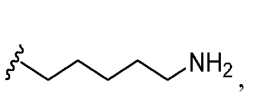
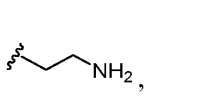
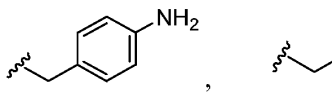
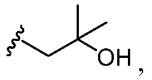
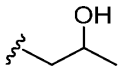
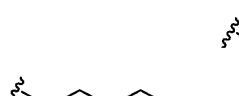
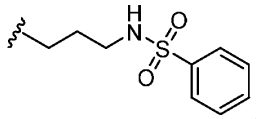
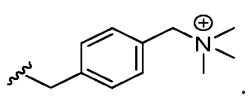
[0019] In some cases, R^1 or R^4 is the point of covalent attachment to L. In some cases, R^1 selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, phenyl, and 5-10 membered heteroaryl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6

alkoxythiocarbonyl, C_1-C_6 carbamoyl, phenyl, or 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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide. In some cases, R^1 selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, or phenyl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, C_1-C_6 alkoxy, –NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, and acylated C_5-C_9 monosaccharide. In some cases, R^1 is hydrogen or C_1-C_3 alkyl optionally substituted with a substituent selected from the group consisting of hydroxyl, halogen, and –NH_2. In some cases, R^1 is hydrogen or C_1-C_3 alkyl. In some cases, R^1 is hydrogen.

[0020] In some cases, R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, or phenyl 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. In some cases, R^2 is selected from the group consisting of hydrogen and C_1-C_3 alkyl, wherein the of C_1-C_3 alkyl 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. In some cases, R^2 is hydrogen or C_1-C_3 alkyl. In some cases, R^2 is hydrogen.

[0021] In some cases, R^3 is selected from the group consisting of –NR^AR^B, –C(=O)NR^AR^B, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl, and 5-10 membered heteroaryl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl, or 5-10 membered heteroaryl 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. In some cases, R^3 is C_1-C_5 alkyl optionally substituted with 1 substituent selected from the group consisting of hydroxyl, halogen, cyano, oxo, C_1-C_3 alkoxy, C_1-C_3 alkylthio, and -NR^AR^B. In some cases, R^3 is selected from the group consisting of butyl, -CH_2-O-CH_2CH_3, -CH_2-CH_2-O-CH_3, and -CH_2-NH-CH_2CH_3.

[0022] In some cases, R^4 is hydrogen; -C(=O)NR^DR^E; -C(=O)OR^C; -C(=O)SR^C; -C(=S)R^C; or C_1-C_6 alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) -O(C_1-C_6

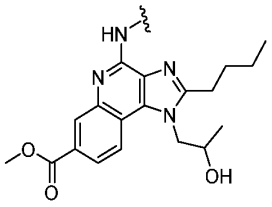
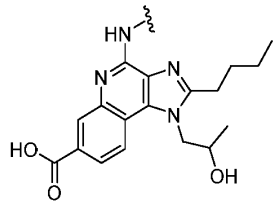
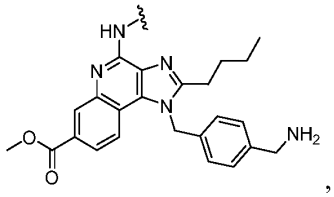
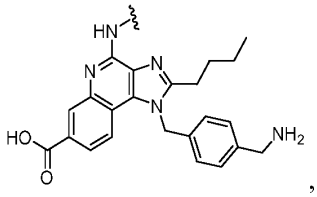
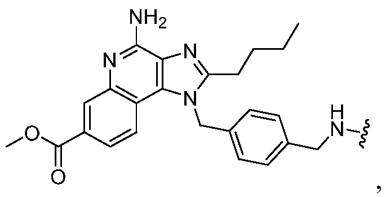
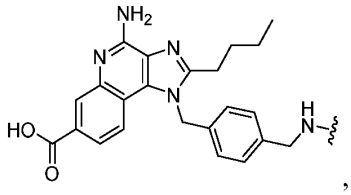
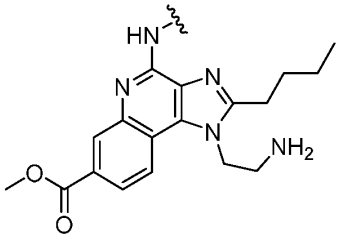
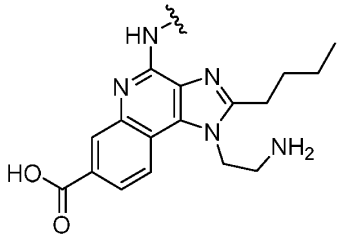
alkyl); (iii) -S(C_1-C_6 alkyl); (iv) -NH-S(O_2)R^C; (v) -OC(=O)R^C; (vi) -CO_2H; (vii) -C_1-C_6 alkoxycarbonyl; (viii) -C(=O)NR^DR^E; (ix) -NR^DR^E, wherein the R^D of -NR^DR^E is C_1-C_6 alkyl; (x) -[N(C_1-C_6 alkyl)R^DR^E]$^+$; (xi) -(phenyl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, -[N(C_1-C_6 alkyl)R^DR^E]$^+$, or 1-3 independently selected halogen; or (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, -NR^DR^E, -C(=O)NR^DR^E or -CO_2H. In some cases, R^4 is hydrogen or C_1-C_6 alkyl substituted with: (ix) -NR^DR^E, wherein the R^D of -NR^DR^E is C_1-C_6 alkyl; or (xi) -(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, 5-10 membered heterocycle, -[N(C_1-C_6 alkyl)R^DR^E]$^+$. In some cases, R^4 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , wherein each instance of subscript z is independently 1, 2, or 3. In some cases, R^4 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

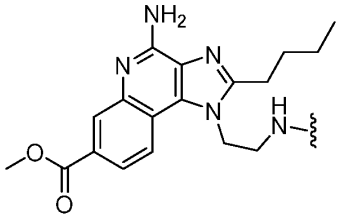
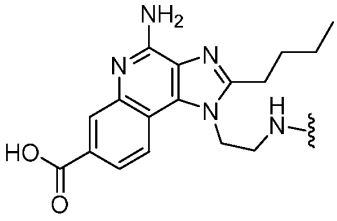
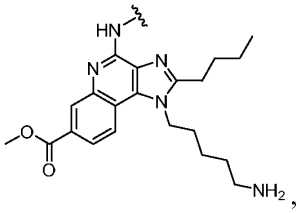
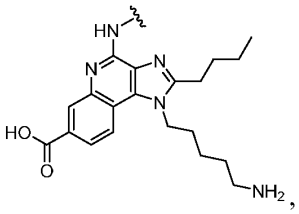
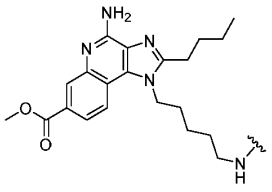
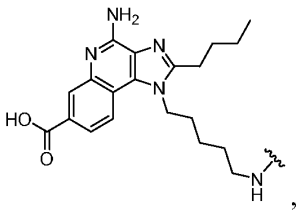
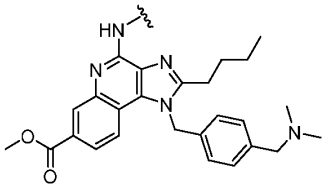
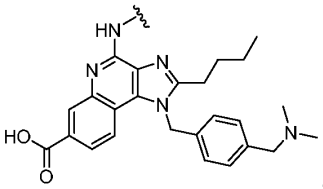
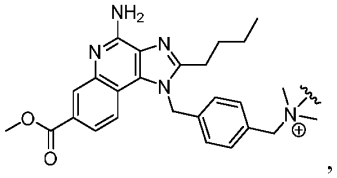
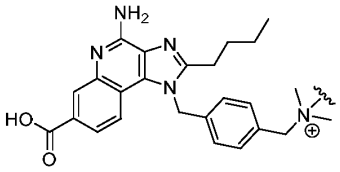
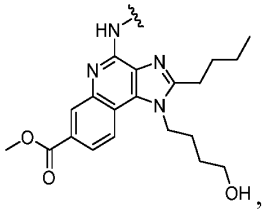
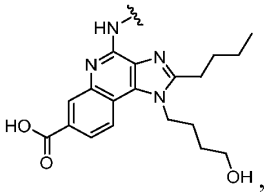
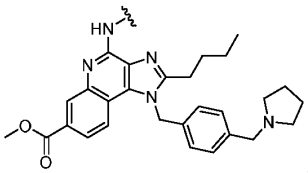
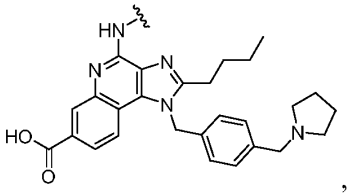
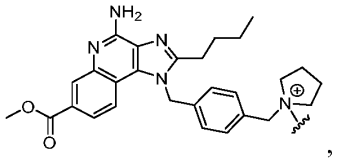
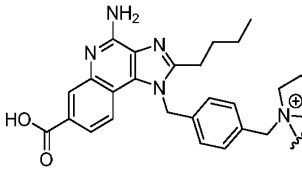
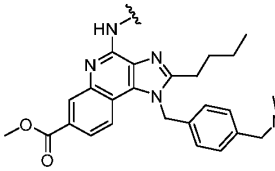
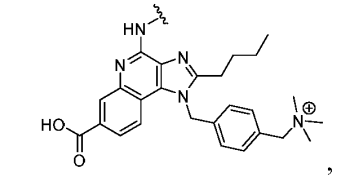
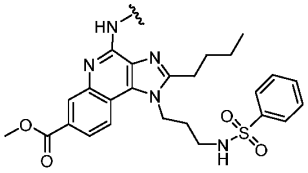
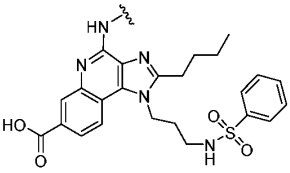
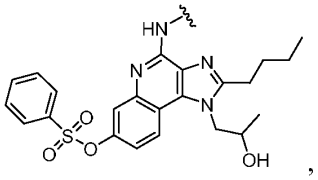
[0023] In some cases, R^5 is selected from the group consisting of hydrogen, -C(=O)OR^F, -S(O_2)NR^GR^H, -N(R^I)-C(=O)R^J, -N(R^I)-S(O_2)R^K, and SO_3R^K; and each R^6 is independently

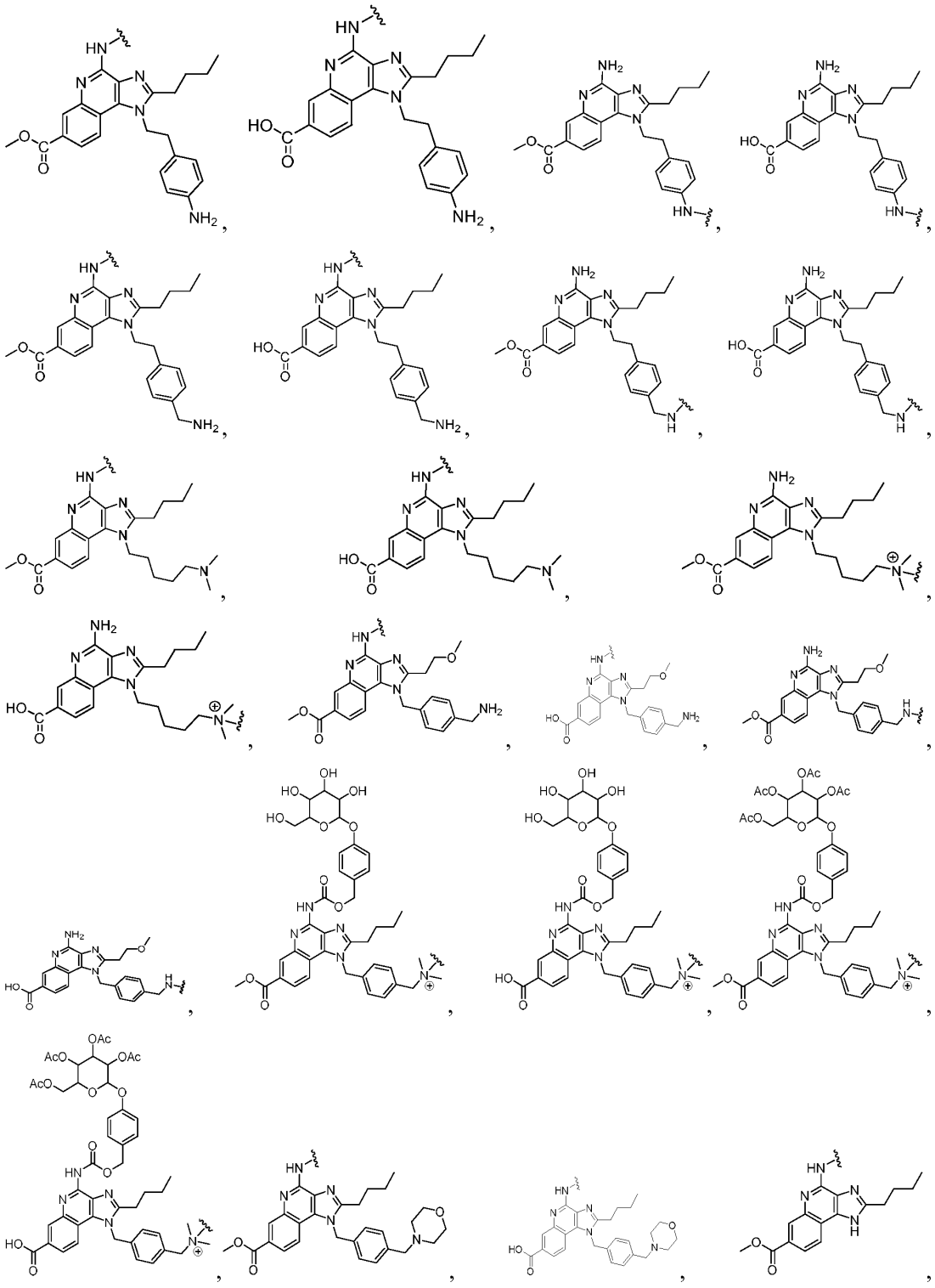
selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and $–NR^AR^B$. In some cases, R^5 is -C(=O)OH or -C(=O)O(C_1-C_3 alkyl); and each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and $–NR^AR^B$. In some cases, R^5 is -C(=O)OH or -C(=O)O(C_1-C_3 alkyl); and subscript m is zero. In some cases, R^5 has: (i) a pka of at most about 7.0; (ii) a dipole moment of at least about 2.0 Debye; or (i) and (ii).

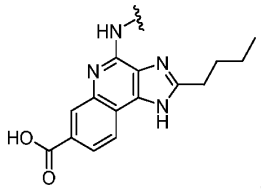
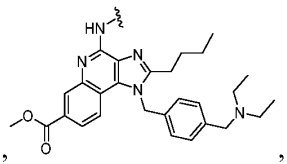
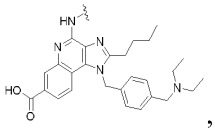
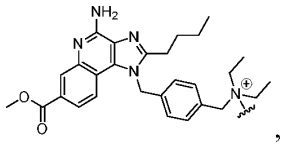
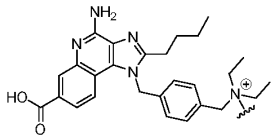
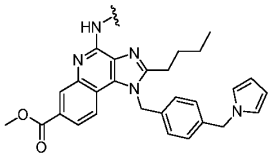
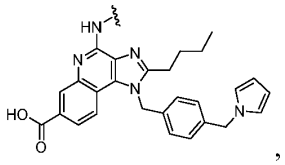
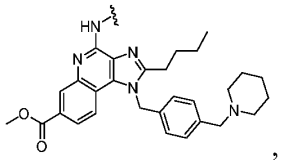
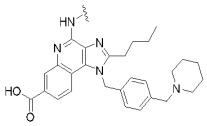
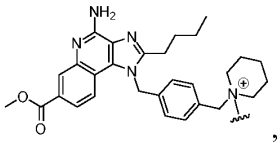
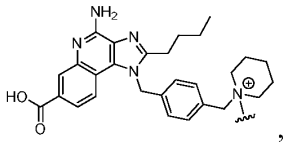
[0024] In some cases, each R^X is independently selected from the group consisting of hydrogen, -C(=O)OR^F, -C(=O)NR^GR^H, -S(O_2)NR^GR^H, -N(R^I)-C(=O)R^J, -N(R^I)-S(O_2)R^K, -S(O_3)R^K, halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $–NR^AR^B$. In some cases, subscript n is 1.

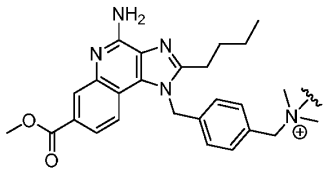
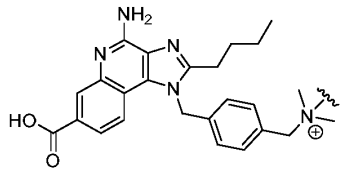
[0025] In some cases, each instance of R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_3 alkyl. In some cases, each instance of R^C is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl. In some cases, each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, C_4-C_6 cycloalkyl(C_1-C_3 alkyl)-, aryl, and aryl(C_1-C_3 alkyl). In some cases, each instance of R^F is independently selected from the group consisting of hydrogen, trifluoromethyl, and C_1-C_6 alkyl.

[0026] In some cases, each D is  ,  ,  ,  ,  ,  ,  ,  ,

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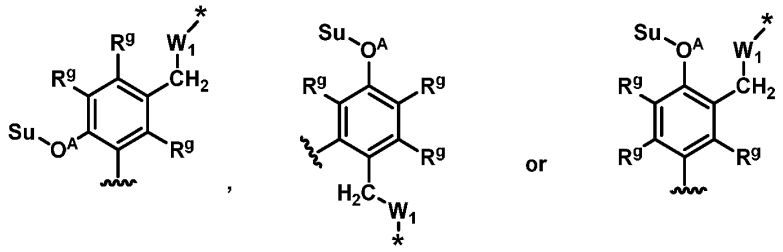










, or 

wherein ~~~ represents the point of covalent attachment to L. In some cases, each D is  or  , wherein ~~~ represents the point of covalent attachment to L. In some cases, Ab comprises a heavy chain with at least 80% sequence identity to SEQ ID NO: 3 or SEQ ID NO: 4 and a light chain with at least 80% sequence identity to SEQ ID NO: 5.

[0027] In some cases, the linker comprises a length of between 10 and 40 atoms as defined by the pathway between D and Ab through the fewest number of bonds. In some cases, the linker comprises a length of between 15 and 30 atoms as defined by the pathway between D and Ab through the fewest number of bonds. In some cases, the linker comprises a PEG Unit from PEG1 to PEG72, a monosaccharide, a disaccharide, a trisaccharide, an oligopeptide, or a combination thereof.

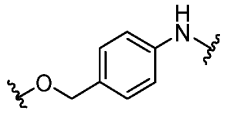
In some cases, L has the formula $–M-(A)_a-(W)_w-(Y)_y-(X)_x–$, wherein: subscript a is 0 or 1; subscript y is 0 or 1; subscript w is 0 or 1; subscript x is 0 or 1; M is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, a disulfide, a dihydropyridazine, or a triazole; A is a C_{2-20} 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:

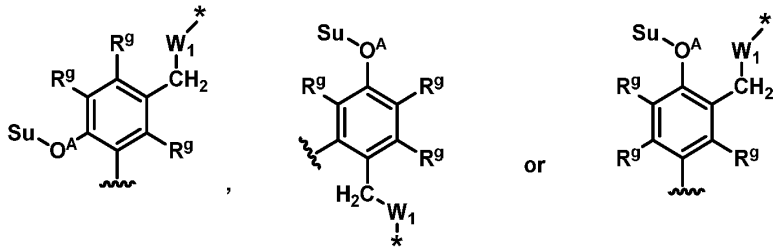


wherein Su is a Sugar moiety; $-O^A-$ represents the oxygen atom of a glycosidic bond; each R^g is independently hydrogen, halogen, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$; W^1 is absent, *–C(=O)-O–, or *–O-C(=O)–; ~~~ 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; and L is optionally substituted with a PEG Unit from PEG1 to PEG72.

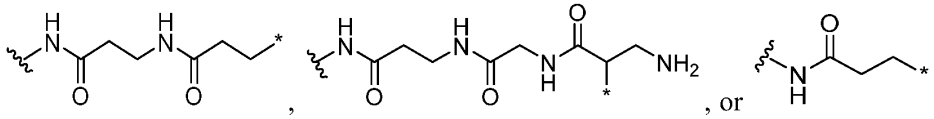
[0028] In some cases, subscript x is 1. In some cases, X is a C_1-C_6 alkylene. In some cases, X is a C_1-C_3 alkylene. In some cases, X is a 3-6 membered heteroalkylene. In some cases, X is a 3-4 membered heteroalkylene. In some cases, subscript x is 0.

[0029] In some cases, subscript y is 1. In some cases, Y is a self-immolative moiety. In some cases, Y is  . In some cases, Y is a non-cleavable moiety. In some cases, Y is a cyclohexanecarboxyl, undecanoyl, caproyl, hexanoyl, butanoyl or propionyl group. In some cases, Y is PEG4 to PEG12. In some cases, y is 0.

In some cases, subscript w is 1. In some cases, W is from 6-12 amino acids. In some cases, W is from 6-9 amino acids. In some cases, 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. In some cases, W has the structure:



wherein Su is a Sugar moiety; -OA- 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. In some cases, W^1 is absent. In some cases, W^1 is *-C(=O)-O-. In some cases, W^1 is *-O-C(=O)-. In some cases, 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. In some cases, each R^g is hydrogen. In some cases, w is 0.

[0030] In some cases, subscript a is 1. In some cases, A is C_2-$_{20}$ alkylene optionally substituted with 1-4 R^{a1}. In some cases, A is C_4-$_{10}$ alkylene optionally substituted with 1-4 R^{a1}. In some cases, A is C_2-$_{20}$ alkylene substituted with one R^{a1}. In some cases, A is C_4-$_{10}$ alkylene substituted with one R^{a1}. In some cases, A is C_2-$_{20}$ alkylene. In some cases, A is C_4-$_{10}$ alkylene. In some cases, A is a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1}. In some cases, A is a 4 to 12 membered heteroalkylene optionally substituted with 1-4 R^{b1}. In some cases, A is a 2 to 40 membered heteroalkylene optionally substituted with one R^{b1}. In some cases, A is a 4 to 12 membered heteroalkylene optionally substituted with one R^{b1}. In some cases, A is a 2 to 40 membered heteroalkylene. In some cases, A is a 4 to 12 membered heteroalkylene. In some cases, A is  wherein ~~~ represents covalent attachment to W, and * represents covalent linkage to M. In some cases, subscript a is 0.

[0031] In some cases, L is substituted with a PEG Unit from PEG1 to PEG72. In some cases, A is substituted with a PEG Unit from PEG1 to PEG72. In some cases, M is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, a disulfide, a dihydropyridazine, or a triazole.

[0032] Various aspects of the present disclosure provide a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an ADC of the present disclosure, or a pharmaceutically acceptable salt

thereof. In some cases, Ab of the ADC targets a cancer-associated antigen. In some cases, the ADC is configured to internalize within a cell. In some cases, the cell expresses the cancer-associated antigen. In some cases, the cell does not express the cancer-associated antigen. In some cases, the cell is an immune cell. In some cases, the immune cell is a $CD8^+$ T-cell, a $CD4^+$ T-Cell, a T-regulatory cell, a macrophage, or a natural killer cell. In some cases, the immune cell is a macrophage. In some cases, the immune cell expresses TLR7, TLR8, or TLR7 and TLR8. In some cases, the cancer cell does not express TLR7 or TLR8. In some cases, the immune cell expresses a surface protein which binds to the cancer-associated antigen. In some cases, the internalizing comprises endocytosis or micropinocytosis. In some cases, 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. In some cases, the linker (L) of the ADC is configured to undergo cleavage subsequent to internalizing within the immune cell.

BRIEF DESCRIPTION OF THE FIGURES

[0033] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0034] **FIGURE 1** illustrates the responses of human PBMCs from a single donor to selected small molecule TLR7/8 agonists.

[0035] **FIGURE 2** illustrates the average response of human PBMCs isolated from 3 donors to selected small molecule TLR7/8 agonists.

[0036] **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**).

[0037] **FIGURE 4** illustrates the responses of human immune cells to various small molecule TLR7/8 agonists.

[0038] **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**).

[0039] **FIGURE 6** illustrates the responses of human immune cells to various TLR7/8 agonists conjugated to a targeting antibody.

[0040] **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.

[0041] **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.

[0042] **FIGURE 9** illustrates the comparison of level of aggregation of various conjugated immunostimulatory ADCs.

[0043] **FIGURE 10** illustrates the anti-tumor responses of mice bearing CT26 tumors to treatment with **S8a** or **S8b** immune cell targeted antibody drug conjugates.

[0044] **FIGURE 11** illustrates the anti-tumor responses of mice bearing CT26 tumors to treatment with **S14a** or **S14b** immune cell targeted antibody drug conjugates.

[0045] **FIGURE 12** illustrates the anti-tumor responses of mice bearing MC38 tumors to treatment with **S8a**, **S8b**, **S18a** or **S18b** antibody drug conjugates.

[0046] **FIGURE 13** illustrates the anti-tumor responses of mice bearing CT26 tumors to treatment with **S18b** antibody drug conjugates with either a targeting or a non-targeting antibody.

[0047] **FIGURE 14** illustrates the anti-tumor responses of mice bearing Renca tumors to treatment with **S18a** free drug, and **S18a** and **S18b** antibody drug conjugates.

[0048] **FIGURE 15** illustrates cytokine responses of non-tumor bearing mice to treatment with **S18b** free drug and **S18b** antibody drug conjugates linked via N1 or C4 linkage.

[0049] **FIGURE 16** illustrates the cytokine response of non-tumor bearing mice to treatment with **S18b** free drug and **S18b** antibody drug conjugates linked via N1 or C4 linkage.

[0050] **FIGURE 17** illustrates the cytokine response of CT26-tumor bearing mice to treatment with **S18b** antibody drug conjugates linked via N1 or C4 linkage and with targeting or non-targeting antibody.

[0051] **FIGURE 18** illustrates the anti-tumor response of CT26-bearing mice to treatment with **S18b** antibody drug conjugates linked via N1 or C4 linkage and with targeting or non-targeting antibody.

[0052] **FIGURE 19** illustrates the cytokine response of Renca-tumor bearing mice to treatment with **S18b** drug conjugates linked via N1 or C4 linkage at 2 mg/kg dose.

[0053] **FIGURE 20** illustrates the anti-tumor response of Renca-bearing mice to treatment with **S18b** antibody drug conjugates linked via N1 or C4 linkage at 2 mg/kg dose.

[0054] **FIGURE 21** illustrates the activation of *in vitro* human immune cells in response to TLR7/8 antibody conjugates linked via N1 or C4 positions.

[0055] **FIGURE 22** illustrates the anti-tumor response of Renca-bearing mice to treatment with **S18b** antibody drug conjugates linked via N1 or C4 linkage at different dose levels.

[0056] **FIGURE 23** illustrates the cytokine response of Renca-tumor bearing mice to treatment with **S18b** antibody drug conjugates via N1 or C4 linkage at different dose levels.

[0057] **FIGURE 24** illustrates the *in vitro* assessment of TLR7 vs. TLR8 selectivity for various TLR7/8 small molecule agonists in HEK Blue hTLR7 and TLR8 cells.

[0058] **FIGURE 25** illustrate the *in vivo* assessment of TLR7 vs. TLR8 selectivity for various TLR7/8 small molecule agonists in C57BL/6 mice bearing subcutaneous MC38 tumors.

[0059] **FIGURE 26** illustrate the anti-tumor response of Renca-bearing mice to treatment with **S18a** antibody drug conjugates with different linkage sites and with or without a PEG group in the linker.

[0060] **FIGURE 27** illustrates the anti-tumor response of Renca-bearing mice to treatment with **S18a** antibody drug conjugates linked at the N1 or C4 positions, with different linker configurations, linkage sites and with or without a PEG group in the linker.

[0061] **FIGURE 28** provides tumor sizes in mice treated with targeted antibody-TLR7/8 agonist complexes.

[0062] **FIGURE 29** provides IL6 (top left), IL1b (top right), MIP1b (bottom left), and TNFα (bottom right) responses in human peripheral blood mononuclear cells (PBMCs) elicited with multiple imidazoquinoline complexes.

[0063] **FIGURE 30** summarizes cytokine responses in human immune cells following imidazoquinoline treatment. The top left panel summarizes IL6 levels following treatment, the top right panel summarizes TNFα levels following treatment, the bottom left panel summarizes MCP1 levels following treatment, and the bottom right panel summarizes IP10 levels following treatment.

[0064] **FIGURE 31** summarizes tumor size profiles over time post tumor implantation, in TLR7 positive and TLR7 knockout mice. The top left panel summarizes tumor growth in TLR7 positive mice, the bottom left panel summarizes tumor growth in TLR7 knockout mice, and the right panel summarizes tumor volumes on Day 36 post implantation for all mice.

[0065] **FIGURE 32** provides tumor sizes in mice bearing Renca tumors following treatment with TLR7/8 agonists.

[0066] **FIGURE 33** provides Renca tumor volumes in untreated mice, mice treated with an imidazoquinoline TLR agonist-coupled to a tumor targeted antibody or isotype control.

[0067] **FIGURE 34** summarizes Renca tumor volumes in untreated mice, mice treated with an imidazoquinoline TLR agonist C4-coupled to a tumor targeted antibody, or isotype control.

[0068] **FIGURE 35** summarizes CT26 tumor volumes in untreated mice, mice treated with an imidazoquinoline TLR agonist N1-coupled to a tumor targeted antibody, or isotype conrol.

[0069] **FIGURE 36** provides CT26 tumor volumes in untreated mice, mice treated with an imidazoquinoline TLR agonist C4-coupled to a tumor targeted antibody, or isotype control.

[0070] **FIGURE 37** summarizes 4T1 tumor volumes in untreated mice, mice treated with a bare EphA2-targeted antibody, and mice treated with a TLR7/8 agonist EphA2-targeted antibody conjugate.

[0071] **FIGURE 38** provides CT26 tumor volumes for untreated mice, mice treated with a tumor and immune targeting antibody alone, mice treated with a non-targeted isotype antibody conjugated to a TLR7/8 agonist, and mice treated with a TLR7/8 agonist conjugated to the tumor and immune targeting antibody.

[0072] **FIGURES 39A-F** provide cell survival rates for Hodgkin's lymphoma (**FIGURE 39A**), breast carcinoma (**FIGURE 39B**), pancreatic carcinoma (**FIGURE 39C**), lung carcinoma (**FIGURE 39D**), anaplastic large-cell lymphoma (**FIGURE 39E**), and CD30-positive anaplastic large T-cell lymphoma (**FIGURE 39F**) following treatment with an ADC consistent with the present disclosure.

[0073] **FIGURES 40A-D** summarize interleukin-6 (IL-6) induction in pancreatic carcinoma (**FIGURE 40A**), human lung squamous cell carcinoma (**FIGURE 40B**), and anaplastic large-cell lymphoma (**FIGURES 40C-D**) tumor cells following incubation with an ADC consistent with the present disclosure.

[0074] **FIGURES 41A-C** summarize IL-6 production by M0 (**FIGURE 41A**), M1 (**FIGURE 41B**), and M2 (**FIGURE 41C**) macrophage populations treated multiple ADCs, antibodies, and compounds consistent with the present disclosure.

[0075] **FIGURES 42A-F** summarizes immune activation responses in tumor and immune cell co-cultures following treatment with various ADCs and antibodies consistent with the present disclosure. **FIGURE 42A** provides CD69 levels in Karpas299 co-cultures following ADC and antibody treatment. **FIGURE 42B** provides CD69 levels in EBC-1 co-cultures following ADC and antibody treatment. **FIGURE 42C** provides IFN-γ levels in Karpas299 co-cultures following ADC and antibody treatment. **FIGURE 42D** provides IFN-γ levels in EBC-1 co-cultures following ADC and antibody treatment. **FIGURE 42C** provides CD86 levels in Karpas299 co-cultures following ADC and antibody treatment. **FIGURE 42D** provides CD86 levels in EBC-1 co-cultures cells following ADC and antibody treatment.

[0076] **FIGURE 43** summarizes frequencies of CD45+ PDL1+ immune cells and CD45- PDL1+ tumor cells from human non-small cell lung cancer tumors from multiple subjects.

[0077] **FIGURES 44A-B** summarize IL-6 and TNFα induction in the human non-small cell lung cancer tumors following ADC and antibody treatments consistent with the present disclosure.

[0078] **FIGURE 45** summarizes changes in tumor volume over 4 weeks of treatment with ADCs and antibodies consistent with the present disclosure.

[0079] **FIGURES 46A-C** provide tumor volume time courses following 2 mg/kg (**FIGURE 46A**), 1 mg/kg (**FIGURE 46B**), and 0.5 mg/kg (**FIGURE 46C**) doses of an ADC consistent with the present disclosure.

[0080] **FIGURES 47A-D** provide tumor growth responses of PDL1 positive tumors in untreated (**FIGURE 47A**), antibody-treated (**FIGURE 47B**), non-targeted ADC treated (**FIGURE 47C**), and targeted ADC treated (**FIGURE 47D**) mice.

[0081] **FIGURE 48** summarizes tumor growth inhibition for ADC and antibody-treated mice.

[0082] **FIGURES 49A-D** provide $CD4^+$ T-cell (**FIGURE 49A**), regulatory T-cell (**FIGURE 49B**), $CD8^+$ T-cell (**FIGURE 49C**), and macrophage (**FIGURE 49D**) populations in MC38 and Renca mouse tumors.

[0083] **FIGURES 50A-B** provide tumor growth responses of MC38 (**FIGURE 50A**) and Renca tumors (**FIGURE 50B**) implanted in mouse models treated with ADCs consistent with the present disclosure.

[0084] **FIGURE 51** is a set of plots of tumor growth responses and area under curve (AUC) values for two different tumor models treated with ADCs consistent with the present disclosure.

[0085] **FIGURE 52** is a series plots of cytokine responses in two tumor models following treatment with ADCs consistent with the present disclosure.

[0086] **FIGURE 53** is a group of plots of PDL1, CD4, CD8, F4/80 expression in two tumor models.

DETAILED DESCRIPTION

[0087] Many cancers are immunosuppressive, actively inhibiting immune cell proliferation, signaling, and activity to avoid detection and clearance. While certain TLR agonists can reactivate cancer-suppressed immune cells, TLR agonist treatments are often restricted by dose-limiting toxicities. Sustained TLR activation, even from mild agonist doses, can affect immune-related adverse events, including rheumatic and thyroid disorders, nausea, rashes, and general discomfort.

[0088] Circumventing toxicity-based dosing limitations commonly associated with TLR agonists, certain ADCs of the present disclosure elicit minimal cytokine responses from outside of target tumor sites. A surprising discovery disclosed herein is that broad TLR7/8 activation within tumor microenvironments can primarily activate immune cells without generating undesired responses from cancer and bystander cells. Leveraging this discovery, tumor-targeted

ADCs of the present disclosure can utilize appreciable concentrations of high potency TLR agonists to affect localized immune stimulation while avoiding dose-limiting systemic toxicities.

Definitions

[0089] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present application; other, suitable methods and materials known in the art in some aspects of this disclosure are also used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entireties. In case of conflict, the present specification, including definitions, will control. When trade names are used herein, the trade name includes the product formulation, the generic drug, and the active pharmaceutical ingredient(s) of the trade name product, unless otherwise indicated by context.

[0090] The terms "a," "an," or "the" as used herein not only include aspects with one member, but also include aspects with more than one member. For instance, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a linker" includes reference to one or more such linkers, and reference to "the cell" includes reference to a plurality of such cells.

[0091] The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation, for example, within experimental variability and/or statistical experimental error, and thus the number or numerical range may vary up to ±10% of the stated number or numerical range. In reference to an ADC composition comprising a distribution of ADCs as described herein, the average number of conjugated TLR agonist compounds to an antibody in the composition can be an integer or a non-integer, particularly when the antibody is to be partially loaded. Thus, the term "about" recited prior to an average drug loading value is intended to capture the expected variations in drug loading within an ADC composition.

[0092] The term "antibody" as used herein covers intact monoclonal antibodies, polyclonal antibodies, monospecific antibodies, multispecific antibodies (e.g., bispecific antibodies), including intact antibodies and antigen binding antibody fragments, and reduced forms thereof in which one or more of the interchain disulfide bonds are disrupted, that exhibit the desired biological activity and provided that the antigen binding antibody fragments have the requisite number of attachment sites for the desired number of attached groups, such as a linker (L), as described herein. In some aspects, the linkers are attached via a succinimide or hydrolyzed

succinimide to the sulfur atoms of cysteine residues of reduced interchain disulfide bonds and/or cysteine residues introduced by genetic engineering. The native form of an antibody is a tetramer and consists of two identical pairs of immunoglobulin chains, each pair having one light chain and one heavy chain. In each pair, the light and heavy chain variable domains (VL and VH) are together primarily responsible for binding to an antigen. The light chain and heavy chain variable domains consist of a framework region interrupted by three hypervariable regions, also called "complementarity determining regions" or "CDRs." The light chain and heavy chains also contain constant regions that may be recognized by and interact with the immune system. (*see*, e.g., Janeway *et al.*, 2001, *Immuno. Biology, 5th Ed.*, Garland Publishing, New York). An antibody includes any isotype (e.g., IgG, IgE, IgM, IgD, and IgA) or subclass (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) thereof. The antibody is derivable from any suitable species. In some aspects, the antibody is of human or murine origin, and in some aspects the antibody is a human, humanized or chimeric antibody. Antibodies can be fucosylated to varying extents or afucosylated.

[0093] An "intact antibody" is one which comprises an antigen-binding variable region as well as light chain constant domains (C_L) and heavy chain constant domains, C_H1, C_H2, C_H3 and C_H4, as appropriate for the antibody class. The constant domains are either native sequence constant domains (e.g., human native sequence constant domains) or amino acid sequence variants thereof.

[0094] An "antibody fragment" comprises a portion of an intact antibody, comprising the antigen-binding or variable region thereof. Antibody fragments of the present disclosure include at least one cysteine residue (natural or engineered) that provides a site for attachment of a linker and/or linker-drug compound. In some embodiments, an antibody fragment includes Fab, Fab′, or $F(ab')_2$.

[0095] As used herein the term "engineered cysteine residue" or "eCys residue" refers to a cysteine amino acid or a derivative thereof that is incorporated into a protein (e.g., an antibody) and which would otherwise not be present at its position within the protein. In those aspects one or more eCys residues can be incorporated into an antibody, and typically, the eCys residues are incorporated into either the heavy chain or the light chain of an antibody. Generally, incorporation of an eCys residue into an antibody is performed by mutagenizing a nucleic acid sequence of a parent antibody to encode for one or more amino acid residues with a cysteine or a derivative thereof. Suitable mutations include replacement of a desired residue in the light or heavy chain of an antibody with a cysteine or a derivative thereof, incorporation of an additional cysteine or a derivative thereof at a desired location in the light or heavy chain of an antibody, as well as adding

an additional cysteine or a derivative thereof to the N- and/or C-terminus of a desired heavy or light chain of an amino acid. Further information can be found in U.S. Pat. No. 9,000,130, the contents of which are incorporated herein in its entirety. Derivatives of cysteine (Cys) include but are not limited to beta-2-Cys, beta-3-Cys, homocysteine, and N-methyl cysteine.

[0096] In some embodiments, the antibodies of the present disclosure include those having one or more engineered cysteine (eCys) residues. In some embodiments, derivatives of cysteine (Cys) include, but are not limited to beta-2-Cys, beta-3-Cys, homocysteine, and N-methyl cysteine.

[0097] In some embodiments, the antibodies of the present disclosure include those having one or more engineered lysine (eLys)residues. In some embodients, one or more native lysine and/or eLys residues are activated prior to conjugation with a drug-linker intermediate (to form an ADC, as described herein). In some embodiments, the activation comprises contacting the antibody with a compound comprising a succinimydyl ester and a functional group selected from the group consisting of: maleimido, pyridyldisulfidem and iodoacetamido.

[0098] As used herein, an "antigen" can be an entity to which an antibody specifically binds.

[0099] The terms "specific binding" and "specifically binds" can refer to selective binding to a specific target. In reference to an antibody, these terms can denote binding to a specific antigen or epitope over a multitude of other antigens or epitopes. Typically, an antibody or antibody fragment binds with an affinity of at least about $1x10^{-7}$ M, for example, 10^{-8} M to 10^{-9} M, 10^{-10} M, 10^{-11} M, or 10^{-12} M and binds to the predetermined antigen with an affinity that is at least two-fold greater than its affinity for binding to a non-specific antigen (e.g., BSA, casein) other than the predetermined antigen or a closely related antigen.

[0100] The term "amino acid" as used herein can refer to natural and non-natural, and proteogenic amino acids. Exemplary amino acids include, but are not limited to alanine, arginine, aspartic acid, asparagine, histidine, glycine, glutamic acid, glutamine, phenylalanine, lysine, leucine, serine, tyrosine, threonine, isoleucine, proline, tryptophan, valine, cysteine, methionine, ornithine, β-alanine, citrulline, serine methyl ether, aspartate methyl ester, glutamate methyl ester, homoserine methyl ether, and *N,N*-dimethyl lysine.

[0101] "Percent (%) sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways

that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For example, the % sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % sequence identity to, with, or against a given amino acid sequence B) is calculated as follows: 100 times the fraction X/Y where X is the number of amino acid residues scored as identical matches by the sequence in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % sequence identity of A to B will not equal the % sequence identity of B to A.

[0102] A "sugar moiety" as used herein, refers to a monosaccharide group, for example, a pyranose or a furanose. A sugar moiety can comprise a hemiacetal or a carboxylic acid (from oxidation of the pendant $-CH_2OH$ group). In some embodiments, the sugar moiety is in the β-D conformation. In some embodiments, the sugar moiety is a glucose, glucuronic acid, or mannose group.

[0103] The term "inhibit" or "inhibition of" means to reduce by a measurable amount, or to prevent entirely (e.g., 100% inhibition).

[0104] As used herein, TLR7/8 can denote toll-like receptor 7 and toll-like receptor 8, just toll-like receptor, or just toll-like receptor 8. For example, a TLR7/8 ligand can be a TLR7 ligand, a TLR8 ligand, or a bifunctional TLR7 and TLR8 ligand.

[0105] A "TLR7/8 agonist" as defined herein includes any compound exhibiting selective TLR7/8 activity. Exemplary TLR7/8 agonists can exhibit activity (EC_{50}) against TLR7/8 of less than about 10 μM, less than about 5 μM, less than about 2 μM, less than about 1 μM, less than about 500 nM, less than about 250 nM, less than about 100 nM, or less than about 10 nM as measured in an assay as described herein. In some embodiments, a TLR7/8 agonist can exhibit selectivity for TLR7 over TLR8 of about 3.5-fold to about 25-fold, for example, about 3.5-fold to about 15-fold, about 10-fold to about 20-fold, about 15-fold to about 25-fold, about 3.5-fold to about 8-fold, about 5-fold to about 12-fold, about 8-fold to about 15-fold, about 12-fold to about 18-fold, about 15-fold to about 20-fold, or about 18-fold to about 25-fold. In some embodiments, a TLR7/8 agonist can exhibit selectivity for TLR8 over TLR7 of about 3.5-fold to about 25-fold, for example, about 3.5-fold to about 15-fold, about 10-fold to about 20-fold, about 15-fold to about 25-fold, about 3.5-fold to about 8-fold, about 5-fold to about 12-fold, about 8-fold to about

15-fold, about 12-fold to about 18-fold, about 15-fold to about 20-fold, or about 18-fold to about 25-fold.

[0106] The term "therapeutically effective amount" refers to an amount of an ADC, or a pharmaceutically acceptable salt thereof (as described herein) or a compound (as described herein, e.g. a compound of Formula (IX), or a pharmaceutically acceptable salt thereof), that is effective to treat a disease or disorder in a mammal. In the case of cancer, the therapeutically effective amount of the ADC or the compound provides one or more of the following biological effects: reduction of the number of cancer cells; reduction of tumor size; inhibition of cancer cell infiltration into peripheral organs; inhibition of tumor metastasis; inhibition, to some extent, of tumor growth; and/or relief, to some extent, of one or more of the symptoms associated with the cancer. For cancer therapy, efficacy, in some aspects, is measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

[0107] Unless otherwise indicated or implied by context, the term "substantial" or "substantially" refers to a majority, i.e., >50% of a population, of a mixture, or a sample, typically more than 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97 %, 98%, or 99%.

[0108] The terms "intracellularly cleaved" and "intracellular cleavage" refer to a metabolic process or reaction occurring inside a cell, in which the cellular machinery acts on the ADC or a fragment thereof, to intracellularly release free drug from the ADC, or other degradant products thereof. The moieties resulting from that metabolic process or reaction are thus intracellular metabolites.

[0109] The terms "cancer" and "cancerous" refer to or describe the physiological condition or disorder in mammals that is typically characterized by unregulated cell growth. A "tumor" comprises multiple cancerous cells.

[0110] "Subject" as used herein can refer to an individual to which an ADC or TLR7/8 agonist, as described herein, is administered. "Subject" as used herein can also refer to an individual from which a sample (e.g., a tumor resection) is collected. Examples of a "subject" include, but are not limited to, a mammal such as a human, rat, mouse, guinea pig, non-human primate, pig, goat, cow, horse, dog, cat, bird and fowl. Typically, a subject is a rat, mouse, dog, non-human primate, or human. In some aspects, the subject is a human.

[0111] The terms "treat" or "treatment," unless otherwise indicated or implied by context, refer to therapeutic treatment and prophylactic measures to prevent relapse, wherein the object is to inhibit an undesired physiological change or disorder, such as, for example, the development or spread of cancer. For purposes of the present disclosure, beneficial or desired clinical results

include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" in some aspects also means prolonging survival as compared to expected survival if not receiving treatment.

[0112] In the context of cancer, the term "treating" includes any or all of: inhibiting growth of cancer cells or of a tumor; inhibiting replication of cancer cells, lessening of overall tumor burden or decreasing the number of cancer cells, and ameliorating one or more symptoms associated with the disease.

[0113] The term "salt," as used herein, refers to organic or inorganic salts of a compound, such as a TLR7/8 agonist (e.g., a compound of Formula (IX)), Drug Unit (D) (e.g., a compound of any of Formulae (A), (I)-(VIII), (IIa), or (IIIa)), a linker, a drug-linker intermediate (e.g., a compound of Formula (X)), or an ADC, such as those described herein. In some aspects, the compound contains at least one amino group, and accordingly acid addition salts can be formed with the amino group. Exemplary salts include, but are not limited to, sulfate, trifluoroacetate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. A salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion, or other counterion. The counterion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a salt has one or more than one charged atom in its structure. In instances where there are multiple charged atoms as part of the salt, multiple counter ions can be present. Hence, a salt can have one or more charged atoms and/or one or more counterions. A "pharmaceutically acceptable salt" is one that is suitable for administration to a subject as described herein and in some aspects includes salts as described by P. H. Stahl and C. G. Wermuth, editors, Handbook of Pharmaceutical Salts: Properties, Selection and Use, Weinheim/Zürich:Wiley-VCH/VHCA, 2002, the list for which is specifically incorporated by reference in its entirety. In some embodiments, the ADCs described herein are present in the form of a pharmaceutically acceptable salt. In some embodiments, the compounds described herein are present in the form of a pharmaceutically acceptable salt.

[0114] The term "tautomer," as used herein refers to compounds whose structures differ markedly in arrangement of atoms, but which exist in easy and rapid equilibrium, and it is to be

understood that compounds provided herein may be depicted as different tautomers, and when compounds have tautomeric forms, all tautomeric forms are intended to be within the scope of the disclosure, and the naming of the compounds does not exclude any tautomer.

[0115] The term "optionally substituted," refers to an indicated group being either substituted or unsubstituted.

[0116] The term "alkyl" refers to an unsubstituted straight chain or branched, saturated hydrocarbon having the indicated number of carbon atoms (e.g., "C_1-C_4 alkyl," "C_1-C_6 alkyl," "C_1-C_8 alkyl," or "C_1-C_{10}" alkyl have from 1 to 4, 1 to 6, 1 to 8, or 1 to 10 carbon atoms, respectively) and is derived by the removal of one hydrogen atom from the parent alkane. Representative straight chain "C_1-C_8 alkyl" groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl; while branched C_1-C_8 alkyls include, but are not limited to, isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and 2-methylbutyl.

[0117] The term "alkylene" refers to a bivalent unsubstituted saturated branched or straight chain hydrocarbon of the stated number of carbon atoms (e.g., a C_1- C_6 alkylene has from 1 to 6 carbon atoms) and having two monovalent centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of the parent alkane. Alkylene groups can be substituted with 1-6 fluoro groups, for example, on the carbon backbone (as –CHF– or –CF_2–) or on terminal carbons of straight chain or branched alkylenes (such as –CHF_2 or –CF_3). Alkylene groups include but are not limited to: methylene (-CH_2-), ethylene (-CH_2CH_2-), n-propylene (-$CH_2CH_2CH_2$-), n-propylene (-$CH_2CH_2CH_2$-), n-butylene (-$CH_2CH_2CH_2CH_2$-), difluoromethylene (-CF_2-), tetrafluoroethylene (-CF_2CF_2-), and the like.

[0118] The term "alkenyl" refers to an unsubstituted straight chain or branched, hydrocarbon having at least one carbon-carbon double bond and the indicated number of carbon atoms (e.g., "C_2-C_8 alkenyl" or "C_2-C_{10}" alkenyl have from 2 to 8 or 2 to 10 carbon atoms, respectively). When the number of carbon atoms is not indicated, the alkenyl group has from 2 to 6 carbon atoms.

[0119] The term "alkynyl" refers to an unsubstituted straight chain or branched, hydrocarbon having at least one carbon-carbon triple bond and the indicated number of carbon atoms (e.g., "C_2-C_8 alkynyl" or "C_2-C_{10}" alkynyl have from 2 to 8 or 2 to 10 carbon atoms, respectively). When the number of carbon atoms is not indicated, the alkynyl group has from 2 to 6 carbon atoms.

[0120] The term "heteroalkyl" refers to a stable straight or branched chain saturated hydrocarbon having the stated number of total atoms and at least one (e.g., 1 to 15) heteroatom selected from the group consisting of O, N, Si and S. The carbon and heteroatoms of the heteroalkyl group can be oxidized (e.g., to form ketones, N-oxides, sulfones, and the like) and the nitrogen atoms can be quaternized. The heteroatom(s) can be placed at any interior position of the

heteroalkyl group and/or at any terminus of the heteroalkyl group, including termini of branched heteroalkyl groups), and/or at the position at which the heteroalkyl group is attached to the remainder of the molecule. Heteroalkyl groups can be substituted with 1-6 fluoro groups, for example, on the carbon backbone (as –CHF– or –CF_2–) or on terminal carbons of straight chain or branched heteroalkyls (such as –CHF_2 or –CF_3). Examples of heteroalkyl groups include, but are not limited to, -CH_2-CH_2-O-CH_3, -CH_2-CH_2-NH-CH_3, -CH_2-CH_2-N(CH_3)$_2$, -C(=O)-NH-CH_2-CH_2-NH-CH_3, -C(=O)-N(CH_3)-CH_2-CH_2-N(CH_3)$_2$, -C(=O)-NH-CH_2-CH_2-NH-C(=O)-CH_2-CH_3, -C(=O)-N(CH_3)-CH_2-CH_2-N(CH_3)-C(=O)-CH_2-CH_3, -O-CH_2-CH_2-CH_2-NH(CH_3), -O-CH_2-CH_2-CH_2-N(CH_3)$_2$, -O-CH_2-CH_2-CH_2-NH-C(=O)-CH_2-CH_3, -O-CH_2-CH_2-CH_2-N(CH_3)-C(=O)-CH_2-CH_3, -CH_2-CH_2-CH_2-NH(CH_3), -O-CH_2-CH_2-CH_2-N(CH_3)$_2$, -CH_2-CH_2-CH_2-NH-C(=O)-CH_2-CH_3, -CH_2-CH_2-CH_2-N(CH_3)-C(=O)-CH_2-CH_3, -CH_2-S-CH_2-CH_3, -CH_2-CH_2-S(O)-CH_3, -NH-CH_2-CH_2-NH-C(=O)-CH_2-CH_3, -CH_2-CH_2-S(O)$_2$-CH_3, -CH_2-CH_2-O-CF_3, and -Si(CH_3)$_3$. Up to two heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3 and –CH_2-O-Si(CH_3)$_3$. A terminal polyethylene glycol (PEG) moiety is a type of heteroalkyl group.

[0121] The term "acyl" refers to an alkyl, haloalkyl, alkenyl, alkynyl, aryl cycloalkyl, heteroaryl, or heterocyclyl group, as defined herein, connected to the remainder of the compound by a C=O (carbonyl) group.

[0122] The term "carboxamido" refers to a –C(=O)NRR' group, wherein R and R' are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl cycloalkyl, heteroaryl, and heterocyclyl, as defined herein.

[0123] The term "heteroalkylene" refers to a bivalent unsubstituted straight or branched group derived from heteroalkyl (as defined herein). Examples of heteroalkylene groups include, but are not limited to, -CH_2-CH_2-O-CH_2-, -CH_2-CH_2-O-CF_2-, -CH_2-CH_2-NH-CH_2-, -C(=O)-NH-CH_2-CH_2-NH-CH_2- -C(=O)-N(CH_3)-CH_2-CH_2-N(CH_3)-CH_2-, -C(=O)-NH-CH_2-CH_2-NH-C(=O)-CH_2-CH_2-, -C(=O)-N(CH_3)-CH_2-CH_2-N(CH_3)-C(=O)-CH_2-CH_2-, -O-CH_2-CH_2-CH_2-NH-CH_2-, -O-CH_2-CH_2-CH_2-N(CH_3)-CH_2-, -O-CH_2-CH_2-CH_2-NH-C(=O)-CH_2-CH_2-, -O-CH_2-CH_2-CH_2-N(CH_3)-C(=O)-CH_2-CH_2-, -CH_2-CH_2-CH_2-NH-CH_2-, -CH_2-CH_2-CH_2-N(CH_3)-CH_2-, -CH_2-CH_2-CH_2-NH-C(=O)-CH_2-CH_2-, -CH_2-CH_2-CH_2-N(CH_3)-C(=O)-CH_2-CH_2-, -CH_2-CH_2-NH-C(=O)-, -CH_2-CH_2-N(CH_3)-CH_2-, -CH_2-CH_2-N^+(CH_3)$_2$-, -NH-CH_2-CH_2(NH_2)-CH_2-, and -NH-CH_2-CH_2($NHCH_3$)-CH_2-. A bivalent polyethylene glycol (PEG) moiety is a type of heteroalkylene group.

[0124] The term "alkoxy" refers to an alkyl group, as defined herein, which is attached to a molecule via an oxygen atom. For example, alkoxy groups include, but are not limited to methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy and n-hexoxy.

[0125] The term "alkylthio" refers to an alkyl group, as defined herein, which is attached to a molecule via a sulfur atom. For example, alkythio groups include, but are not limited to thiomethyl, thioethyl, thio-n-propyl, thio-iso-propyl, and the like.

[0126] The term "haloalkyl" refers to an unsubstituted straight chain or branched, saturated hydrocarbon having the indicated number of carbon atoms (e.g., "C_1-C_4 alkyl," "C_1-C_6 alkyl," "C_1-C_8 alkyl," or "C_1-C_{10}" alkyl have from 1 to 4, 1 to 6, 1 to 8, or 1 to 10 carbon atoms, respectively) wherein at least one hydrogen atom of the alkyl group is replaced by a halogen (e.g., fluoro, chloro, bromo, or iodo). When the number of carbon atoms is not indicated, the haloalkyl group has from 1 to 6 carbon atoms. Representative C_{1-6} haloalkyl groups include, but are not limited to, trifluoromethyl, 2,2,2-trifluoroethyl, and 1-chloroisopropyl.

[0127] The term "haloalkoxy" refers to a haloalkyl group, as defined herein, which is attached to a molecule via an oxygen atom. For example, haloalkoxy groups include, but are not limited to trifluoromethoxy, 2,2,2-trifluoroethoxy, and 1,1,1-trifluoro2-methylpropoxy.

[0128] The term "cycloalkyl" refers to a cyclic, saturated or partially unsaturated hydrocarbon having the indicated number of carbon atoms (e.g., "C_{3-8} cycloalkyl" or "C_{3-6}" cycloalkyl have from 3 to 8 or 3 to 6 carbon atoms, respectively). When the number of carbon atoms is not indicated, the cycloalkyl group has from 3 to 6 carbon atoms. Cycloalkyl groups include bridged, fused, and spiro ring systems, and bridged bicyclic systems where one ring is aromatic and the other is unsaturated. Representative "C_{3-6} cycloalkyl" groups include, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0129] The term "aryl" refers to an unsubstituted monovalent carbocyclic aromatic hydrocarbon group of 6-10 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Aryl groups include, but are not limited to, phenyl, naphthyl, anthracenyl, biphenyl, and the like.

[0130] The term "heterocycle" refers to a saturated or partially unsaturated ring or a multiple condensed ring system, including bridged, fused, and spiro ring systems. Heterocycles can be described by the total number of atoms in the ring system, for example a 3-10 membered heterocycle has 3 to 10 total ring atoms. The term includes single saturated or partially unsaturated rings (e.g., 3, 4, 5, 6 or 7-membered rings) from about 1 to 6 carbon atoms and from about 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. The ring may be substituted with one or more (e.g., 1, 2 or 3) oxo groups and the sulfur and nitrogen atoms may also be present in their oxidized forms. Such rings include but are not limited to azetidinyl, tetrahydrofuranyl and piperidinyl. The term "heterocycle" also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) wherein a single heterocycle

ring (as defined above) can be condensed with one or more heterocycles (e.g., decahydronapthyridinyl), carbocycles (e.g., decahydroquinolyl) or aryls. The rings of a multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the point of attachment of a multiple condensed ring system (as defined above for a heterocycle) can be at any position of the multiple condensed ring system including a heterocycle, aryl and carbocycle portion of the ring. It is also to be understood that the point of attachment for a heterocycle or heterocycle multiple condensed ring system can be at any suitable atom of the heterocycle or heterocycle multiple condensed ring system including a carbon atom and a heteroatom (e.g., a nitrogen). Exemplary heterocycles include, but are not limited to aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydrofuranyl, dihydrooxazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,2,3,4-tetrahydroquinolyl, benzoxazinyl, dihydrooxazolyl, chromanyl, 1,2-dihydropyridinyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, and 1,4-benzodioxanyl.

[0131] The term "heteroaryl" refers to an aromatic hydrocarbon ring system with at least one heteroatom within a single ring or within a fused ring system, selected from the group consisting of O, N and S. The ring or ring system has 4n +2 electrons in a conjugated π system where all atoms contributing to the conjugated π system are in the same plane. In some embodiments, heteroaryl groups have 5-10 total ring atoms and 1, 2, or 3 heteroatoms (referred to as a "5-10 membered heteroaryl"). Heteroaryl groups include, but are not limited to, imidazole, triazole, thiophene, furan, pyrrole, benzimidazole, pyrazole, pyrazine, pyridine, pyrimidine, and indole.

[0132] The term "hydroxyl" refers to an –OH group.

[0133] The term "cyano" refers to a –CN group.

[0134] The term "carboxy" refers to a –C(=O)OH group.

[0135] The term "oxo" refers to a =O group.

[0136] The term "alkanoyl" refers to an alkyl group, as defined herein, connected to the remainder of the molecule by a -C(=O) group. Exemplary alkanoyl groups include, but are not limited to acetyl, n-propanoyl, and n-butanoyl.

[0137] The term "alkanoyloxy" refers to an alkyl group, as defined herein, connected to the remainder of the molecule by an -OC(=O) group. Exemplary alkanoyloxy groups include, but are not limited to acetoxy, n-propanoyloxy, and n-butanoyloxy.

[0138] The term "alkoxycarbonyl" refers to an alkoxy group, as defined herein, connected to a -C(=O)- group via the oxygen atom of the alkoxy (i.e., an alkyl ester group).

[0139] The term "alkoxythiocarbonyl" refers to an alkoxy group, as defined herein, connected to a C(=S)- group via the oxygen atom of the alkoxy (i.e., an alkyl thioester group).

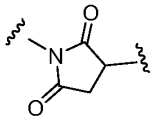
[0140] The term "carbamoyl", as defined herein, refers to $-C(=O)-N(R)_2$, wherein 'R' denotes variable substitution.

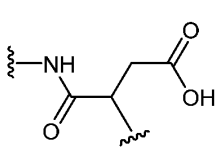
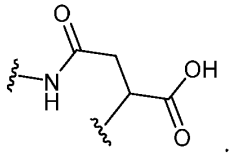
[0141] The term "amidine", as defined herein, refers to $C(=N)-N(R)_2$, wherein 'R' denotes variable substitution.

[0142] The term "sulfone", as defined herein, refers to $-S(=O)_2-R$, wherein 'R' denotes variable substitution.

[0143] The term "thione", as defined herein, refers to -C(=S)-R, wherein 'R' denotes variable substitution.

[0144] The terms "arylalkyl" and "cycloalkylalkyl" refer to an aryl group or a cycloalkyl group (as defined herein) connected to the remainder of the molecule by an alkyl group, as defined herein. Exemplary arylalkyl groups include, but are not limited to benzyl and phenethyl. Exemplary cycloalkylalkyl groups include, but are not limited to cyclopropylmethyl, cyclobutylmethyl, cyclopentylethyl, and cyclohexylethyl.

[0145] The term "succinimide" as used as part of an antibody-drug conjugate (ADC) can refer to  .

[0146] The term "hydrolyzed succinimide" can refer to a succinimide in which the imide hydrolyzes to form a carboxylic acid and an amide. Examples of hydrolyzed succinimides include  and  .

[0147] As used herein, the term "hydrolysable group" refers to a moiety which undergoes spontaneous hydrolytic cleavage under specific conditions. For example, a hydrolysable group may be inert in neutral and basic solutions, but may undergo hydrolytic cleavage in days, hours, minutes, or seconds under acidic conditions. In some cases, a hydrolysable group is configured to undergo hydrolytic cleavage in a particular physiological environment, such as blood (e.g., peripheral blood) or oxidative (e.g., lysosomal) or reductive (e.g., cytoplasmic) intracellular compartments. In some cases, a hydrolysable group is configured for catalytic cleavage, for example by enzymes present in a specific organism (e.g., humans) or tissues (e.g., metabolically active tissues such as liver, kidney, or brain). A hydrolysable group can be configured for cleavage

by a range of enzymes, or by a specific enzyme. For example, a hydrolysable group can comprise an oligopeptide of the sequence arginine-arginine-valine-arginine, for which human furin may have high cleavage activity. A hydrolysable group can be configured for cleavage within a particular environment, such as endosomes or lysozomes of human cells. In such cases, the hydrolysable group may be stable outside of the environment in which it is configured for cleavage. For example, a hydrolysable group may be stable in circulation within peripheral blood, but hydrolytically cleave upon uptake into a cell. Examples of hydrolysable groups include organophosphates such as phosphate esters, thiophosphates, and dithiophosphates, carbamates, carbonates, thioesters, quaternary amines, ureas, disulfides, organosulfates, diorganosulfates, certain amides and esters, and peptides with protease cleavage sites.

[0148] It will be appreciated by those skilled in the art that compounds described herein having a chiral center may exist in and be isolated in optically active and racemic forms.

[0149] As used herein, the term "free drug" refers to a biologically active species that is not covalently attached to an antibody. Accordingly, free drug refers to a compound as it exists immediately upon cleavage from the ADC. The release mechanism can be via a cleavable linker in the ADC, or via intracellular conversion or metabolism of the ADC. In some aspects, the free drug will be protonated and/or may exist as a charged moiety. The free drug is a pharmacologically active species which is capable of exerting the desired biological effect. In some embodiments, the pharamacologically active species is the parent drug alone. In some embodiments, the pharamacologically active species is the parent drug bonded to a component or vestige of the ADC (e.g., a component of the linker, succinimide, hydrolyzed succinimide, and/or antibody that has not undergone subsequent intracellular metabolism). In some embodiments, free drug refers to a compound of any one of Formulae (A), (I)-(VIII), (IIa), or (IIIa), or a pharmaceutically acceptable salt thereof, as described herein, for example, wherein one or more of X, Y, W, A, and M are absent. In some embodiments, free drug refers to a compound of Formula (IX). In some embodiments, free drug refers to a compound of Formula (X). In some embodiments, free drug refers to a compound, or a pharmaceutically acceptable salt thereof, disclosed in U.S. Publ. No. 2017/0217960, which is incorporated by reference in its entirety.

[0150] As used herein, the term "Drug Unit" refers to the free drug that is conjugated to an antibody in an ADC, as described herein.

Antibody Drug Conjugates (ADCs)

[0151] Aspects of the present disclosure provide an antibody drug conjugate (ADC) with a TLR7/8 payload. As many cells express TLR7 and TLR8 (including epithelial and myeloid cells), localizing the effects of TLR7/8 agonists to specified disease sites can be important for treatment

efficacy. To this end, many of the ADCs disclosed herein are configured to release their payloads within target disease sites. In many cases, the ADCs affect immune cell activation within tumor suppressive microenvironments, thereby avoiding systemic cytokine and antibody-dependent toxicities often elicited by free antibodies and TLR7/8 agonists.

[0152] Some embodiments provide 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 consistent with the present disclosure;

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 is a TLR7/8 agonist.

[0153] Some embodiments provide 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 consistent with the present disclosure;

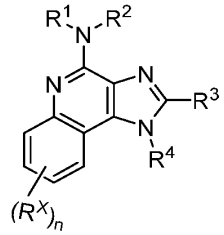
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

subscript p is an integer from 1 to 16;

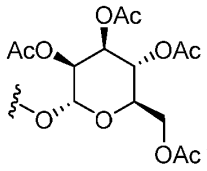
each D has the structure of Formula (A):



(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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide (e.g., 

), C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide;

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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is optionally the point of covalent attachment to L;

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 selected from the group consisting of: the point of covalent attachment to L; hydrogen; $-OR^C$; $-S(=O)_2R^C$; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; $-C(=S)R^C$; $-PO_3R^C$; and $-C_1$-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 the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, $-NR^DR^E$, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen;

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

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the (-5-10 membered heteroaryl)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_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L;

each R^X is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) 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 instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, (b) the group consisting of hydrogen and C_1-C_6 alkyl; and (c)

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 at most one instance of R^A and R^B is the point of covalent attachment to L;

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

each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of (a) the point of covalent attachment to L; (b) 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)-; and 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;

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

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

[0154] In some cases, the antibody drug conjugate (ADC) has the structure:

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

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

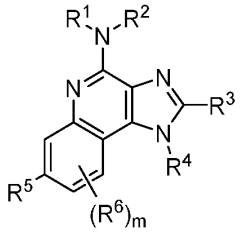
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide;

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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is optionally the point of covalent attachment to L;

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 selected from the group consisting of: the point of covalent attachment to L; hydrogen; $-OR^C$; $-S(=O)_2R^C$; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; $-C(=S)R^C$; $-PO_3R^C$; and -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 the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, $-NR^DR^E$, $-[N(C_1\text{-}C_6$ alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;

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

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the (-5-10 membered heteroaryl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6$ 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_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof is optionally 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 (a) the point of covalent attachment to L; or (b) 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 $-NR^AR^B$; and

m is 0, 1, 2, or 3;

each instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, (b) the group consisting of hydrogen and C_1-C_6 alkyl; and (c) 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 at most one instance of R^A and R^B is the point of covalent attachment to L;

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

each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) 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)-; and (c) 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;

each instance of R^F is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) 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;

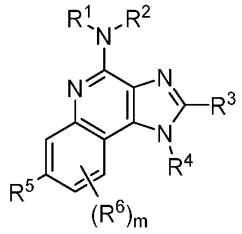
each instance of R^I, R^J, and R^K is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen and C_1-C_6 alkyl;

wherein at most one of R^I, R^J, and R^K is the point of covalent attachment to L;

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

[0155] In some cases, a structure of Formula (A) is a structure of Formula (I), Formula (II), Formula (IIa), Formula (III), Formula (IIIa), Formula (IV), Formula (V), Formula (VI), Formula (VII), or Formula (VIII). Accordingly, in some cases, D has the structure of Formula (I), Formula (II), Formula (IIa), Formula (III), Formula (IIIa), Formula (IV), Formula (V), Formula (VI), Formula (VII), or Formula (VIII) wherein R^1, R^2, R^3, R^4, R^{4A}, R^5, R^6, R^{6A}, R^X, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, n, m, q, and ~~~ are as defined herein.

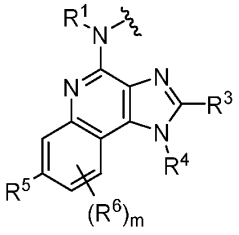
[0156] In some cases, each D has the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein each 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 are as defined herein, and wherein m is an integer equal to n-1 (e.g., if n is 3 then m is 2). In some cases, m is 0, 1, or 2. In some cases, m is 1 or 2. In some cases, m is 0 or 1. In some cases, m is 1. In some cases, m is 0.

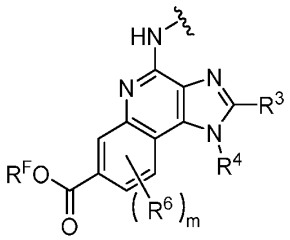
[0157] In some cases, each D has the structure of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein each of R^1, 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, R^K, and m are as defined herein, and ~~~ represents the point of covalent attachment to L.

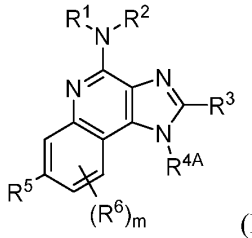
[0158] In some cases, each D has the structure of Formula (IIa):



(IIa)

or a pharmaceutically acceptable salt thereof, wherein each of R^3, R^4, R^6, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, m, and ~~~ are as defined herein. In some cases, m is 0 or 1. In some cases, m is 0.

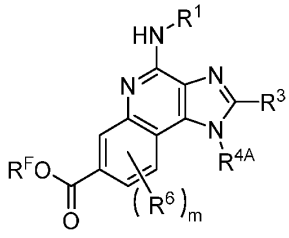
[0159] In some cases, each D has the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, $R4^A$, R^5, R^6, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, and m are as defined herein.

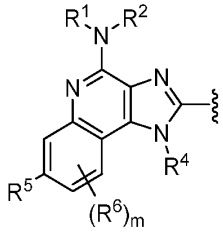
[0160] In some cases, each D has the structure of Formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^{4A}, R^6, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, and m are as defined herein.

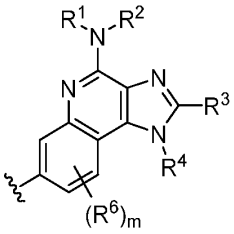
[0161] In some cases, each D has the structure of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, 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, R^K, m, and ~~~ are as defined herein.

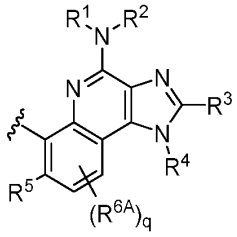
[0162] In some cases, each D has the structure of Formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^6, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, m, and ~~~ are as defined herein.

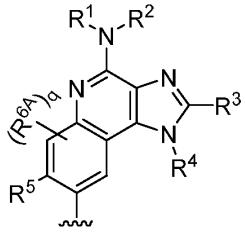
[0163] In some cases, each D has the structure of Formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, and ~~~ are as defined herein, each instance of 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 $-NR^AR^B$; and subscript q is 0, 1, or 2.

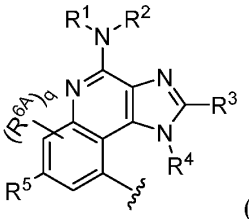
[0164] In some cases, each D has the structure of Formula (VII):



(VII)

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, R^{6A} R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, subscript q, and ~~~ are as defined herein.

[0165] In some cases, each D has the structure of Formula (VIII):



(VIII)

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, R^{6A} R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, subscript q, and ~~~ are as defined herein.

[0166] In some cases of Formulae (A) and (I), R^1, R^2, R^3, R^4, or an instance of R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, or R^K is the point of covalent attachment to L. In some cases of Formulae (A) and (I), R^1, R^3, R^4, or an instance of R^A or R^B is the point of covalent attachment to L. In some cases of Formulae (A) and (I), R^1, R^3, or R^4 is the point of covalent attachment to L. In some cases of Formulae (A) and (I), R^1 or R^4 is the point of covalent attachment to L. In some cases of Formulae (A) and (I), R^1 is the point of covalent attachment to L. In some cases of Formulae (A) and (I), R^2 is the point of covalent attachment to L. In some cases of Formulae (A) and (I), 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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is the point of covalent attachment to L. In some cases of Formulae (A) and (I), R^3 is the point of covalent attachment to L. In some cases of Formulae (A) and (I), R^4 is the point of covalent attachment to L. In some cases of Formulae (A) and (I), R^4 is C_1-C_6 alkyl, and the C_1-C_6 alkyl or a substituent thereof is further substituted with the point of covalent attachment to L. In some cases of Formulae (A) and (I), R^4 is C_1-C_6 alkyl, and the C_1-C_6 alkyl is further substituted with the point of covalent attachment to L. In some cases of Formulae (A) and (I), R^4 is C_1-C_6 alkyl (h), and a substituent of the C_1-C_6 alkyl is further substituted with the point of covalent attachment to L. In some cases of Formulae (A) and (I), R^4 comprises an instance of R^C, R^D, R^E, R^G, and/or R^H which is the point of covalent attachment to L. In some cases of Formula (A), one instance of R^x is the point of covalent attachment to L. In some cases of Formula (A), an instance of R^X contains an instance of R^A, R^B, R^F, R^G, R^H, R^I, R^J, or R^K which is the point of covalent attachment to L. In some cases of Formulae (A) and (I), an instance of R^1 or R^2 is substituted with $–NR^AR^B$, of which R^A or R^B is the point of covalent attachment to L. In some cases of Formula (A), an instance of R^X is $–NR^AR^B$, of which R^A or R^B is the point of covalent attachment to L.

[0167] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each L is covalently attached to Ab via a sulfur atom of a cysteine residue, an ϵ-amino group of a lysine residue, an imidazole of a histidine residue, a guanidinium of an arginine residue, a thiol of a methionine residue, a carboxylate of an aspartate or glutamate residue, a phenol of a tyrosine residue, or an indole of a tryptophan residue. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each L is covalently attached to Ab via a sulfur atom of a cysteine residue or an ϵ-amino group of a lysine residue. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each L is covalently attached to glycosylation of the Ab.

[0168] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 is selected from the group consisting of 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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, phenyl, and 5-10 membered heteroaryl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, phenyl, or 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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, 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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, or phenyl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, C_1-C_6 alkoxy, –NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, and acylated C_5-C_9 monosaccharide. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, or phenyl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, C_1-C_6 alkoxy, –NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, and acylated C_5-C_9 monosaccharide. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 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, oxiranyl, C_3-C_8 cycloalkyl, phenyl, 5-10 membered heteroaryl, C_1-C_6 alkoxy, and $-NR^AR^B$. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 selected from the group consisting of hydrogen and C_1-C_3 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, and $-NR^AR^B$. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 selected from the group consisting of hydrogen and C_1-C_3 alkyl optionally substituted with a substituent selected from the group consisting of hydroxyl, halogen, and $-NH_2$. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 selected from the group consisting of hydrogen and C_1-C_3 alkyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 is hydrogen.

[0169] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, phenyl, C_1-C_3 alkoxy,$-NR^AR^B$, C_5-C_9 monosaccharide, and acylated C_5-C_9 monosaccharide. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, C_1-C_3 alkoxy,$-NR^AR^B$, C_5-C_9 monosaccharide, and acylated C_5-C_9 monosaccharide. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, C_1-C_3 alkoxy, and $-NR^AR^B$. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 is substituted with 1-3 substituents. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 is substituted with 1 substituent. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 is substituted with at most one substituent. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 is not substituted.

[0170] In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is selected from the group consisting of 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

$-NR^AR^B$. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, 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_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 $-NR^AR^B$. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is selected from the group consisting of C_1-C_6 alkyl, 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_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 $-NR^AR^B$. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, or phenyl 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 $-NR^AR^B$. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, or phenyl is optionally substituted with a 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 $-NR^AR^B$. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and phenyl; wherein the of C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, or phenyl 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 $-NR^AR^B$. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is selected from the group consisting of hydrogen and C_1-C_6 alkyl, wherein the of C_1-C_6 alkyl 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 $-NR^AR^B$. In some cases of Formulae

(A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is selected from the group consisting of hydrogen and C_1-C_3 alkyl, wherein the of C_1-C_3 alkyl 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 $-NR^AR^B$. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is selected from the group consisting of hydrogen and C_1-C_3 alkyl, wherein the of C_1-C_3 alkyl is optionally substituted with a substituent independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, and $-NH_2$. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is hydrogen or C_1-C_3 alkyl. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is selected from the group consisting of hydrogen and C_1-C_3 alkyl. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is hydrogen.

[0171] In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, phenyl, C_1-C_3 alkoxy, and $-NR^AR^B$. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, C_1-C_3 alkoxy, and $-NR^AR^B$. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, C_1-C_3 alkoxy, and $-NR^AR^B$. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is substituted with 1-3 substituents. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is substituted with 1 substituent. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is substituted with at most one substituent. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^2 is not substituted.

[0172] In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), at least one of R^1 and R^2 is hydrogen. In some cases of Formulae (A) and (I), R^1 is the point of covalent attachment to L and R^2 is hydrogen. In some cases of Formulae (A), (I), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), R^1 and R^2 are hydrogen.

[0173] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is selected from the group consisting of $-NR^AR^B$, $-C(=O)NR^AR^B$, 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, 5-10 membered heteroaryl, and 3-12 membered heterocycle; wherein each 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, 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. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is C_1-C_6 alkyl 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 alkylthio, and -NR^AR^B. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is C_1-C_6 alkyl substituted with a 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 alkylthio, and -NR^AR^B. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is C_1-C_6 alkyl substituted with a substituent selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, and -NH_2.

[0174] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is selected from the group consisting of –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. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is selected from the group consisting of hydrogen, –NR^AR^B, –C(=O)NR^AR^B, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl, and 5-10 membered heteroaryl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl, or 5-10 membered heteroaryl 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. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is selected from the group consisting of –NR^AR^B, –C(=O)NR^AR^B, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl, and 5-10 membered heteroaryl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl, or 5-10 membered heteroaryl 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. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is selected from the group consisting of hydrogen, –NR^AR^B, C_1-C_6 alkyl, C_1-C_6 alkanoyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl or phenyl 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. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is selected from the group consisting of –NR^AR^B, C_1-C_6 alkyl, C_1-C_6 alkanoyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl or phenyl 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. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is selected from the group consisting of –NR^AR^B, C_1-C_6 alkyl, and C_1-C_6 alkanoyl; wherein the C_1-C_6 alkyl or C_1-C_6 alkanoyl 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. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is C_1-C_4 alkyl 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. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is C_1-C_4 alkyl optionally substituted with a 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. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is C_1-C_4 alkyl optionally substituted with a substituent selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, and -NH_2. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is C_1-C_4 alkyl optionally substituted with a substituent selected from the group consisting of hydroxyl, halogen, and -NH_2.

[0175] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is 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. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo,

phenyl, C_1-C_6 alkoxy, and -NR^AR^B. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is optionally substituted with a substituent selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, phenyl, C_1-C_6 alkoxy, and -NR^AR^B. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, cyano, oxo, C_1-C_6 alkoxy, and -NR^AR^B. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is optionally substituted with a substituent selected from the group consisting of hydroxyl, cyano, oxo, C_1-C_6 alkoxy, and -NR^AR^B. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is optionally substituted with a substituent selected from the group consisting of oxo, C_1-C_3 alkoxy, and -NR^AR^B. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is optionally substituted with a substituent selected from the group consisting of C_1-C_3 alkoxy, and -NHR^B. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is substituted one substituent. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is substituted with at most one substituent. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is unsubstituted.

[0176] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is C_1-C_5 alkyl optionally substituted with 1 substituent selected from the group consisting of hydroxyl, halogen, cyano, oxo, C_1-C_3 alkoxy, C_1-C_3 alkylthio, and -NR^AR^B. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is C_1-C_5 alkyl optionally substituted with 1 substituent selected from the group consisting of C_1-C_3 alkoxy and -NR^AR^B. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (V), (VI), (VII), and (VIII), R^3 is selected from the group consisting of butyl, -CH_2-O-CH_2CH_3, -CH_2-CH_2-O-CH_3, and -CH_2-NH-CH_2CH_3. In some cases, R^3 is hydrogen.

[0177] In some cases of Formulae (A), (I), R^4 is the point of covalent attachment to L; hydrogen; -OR^C; -$S(=O)_2R^C$; -$C(=O)NR^DR^E$; -$C(=O)OR^C$; -$C(=O)SR^C$; -$C(=S)R^C$; -PO_3R^C; or C_1-C_6 alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) -O(C_1-C_6 alkyl); (iii) -S(C_1-C_6 alkyl); (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, wherein the R^D of -NR^DR^E is C_1-C_6 alkyl; (x) -$[N(C_1$-C_6 alkyl)$R^DR^E]^+$; (xi) -(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, 5-10 membered heterocycle, -$[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, -NR^DR^E, -$C(=O)NR^DR^E$ or -CO_2H; wherein when R^4 is C_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof may be further substituted with the point of covalent

attachment to L. In some cases of Formulae (A) and (I), R^4 is hydrogen; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; $-C(=S)R^C$; or C_1-C_6 alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) $-O(C_1$-C_6 alkyl); (iii) $-S(C_1$-C_6 alkyl); (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) $-NR^DR^E$, wherein the R^D of $-NR^DR^E$ is C_1-C_6 alkyl; (x) $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$; (xi) $-$(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, 5-10 membered heterocycle, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen; or (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-NR^DR^E$, $-C(=O)NR^DR^E$ or $-CO_2H$; wherein when R^4 is C_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof may be further substituted with the point of covalent attachment to L.

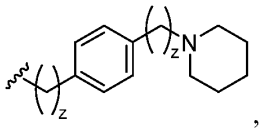
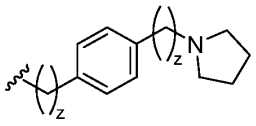
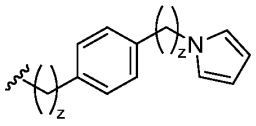
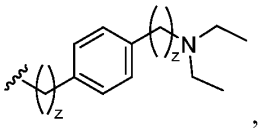
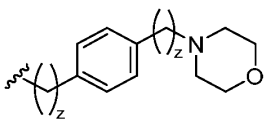
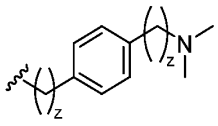
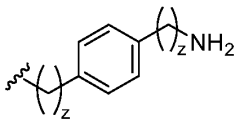
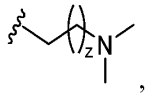
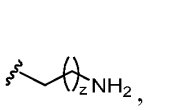
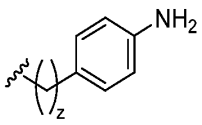
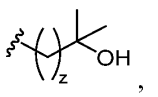
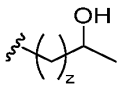
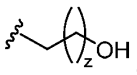
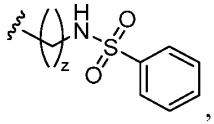
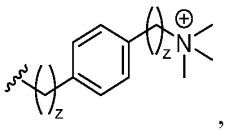
[0178] In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is hydrogen; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; $-C(=S)R^C$; or C_1-C_6 alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) $-O(C_1$-C_6 alkyl); (iii) $-S(C_1$-C_6 alkyl); (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) $-NR^DR^E$, wherein the R^D of $-NR^DR^E$ is C_1-C_6 alkyl; (x) $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$; (xi) $-$(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, 5-10 membered heterocycle, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen; or (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-NR^DR^E$, $-C(=O)NR^DR^E$ or $-CO_2H$. In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is hydrogen or C_1-C_6 alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) $-O(C_1$-C_6 alkyl); (iii) $-S(C_1$-C_6 alkyl); (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) $-NR^DR^E$, wherein the R^D of $-NR^DR^E$ is C_1-C_6 alkyl; (x) $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$; (xi) $-$(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, 5-10 membered heterocycle, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$, or 1-3 independently selected halogen; or (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-NR^DR^E$, $-C(=O)NR^DR^E$ or $-CO_2H$. In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is hydrogen or C_1-C_6 alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) $-O(C_1$-C_6 alkyl); (ix) $-NR^DR^E$, wherein the R^D of $-NR^DR^E$ is C_1-C_6 alkyl; (x) $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$; (xi) $-$(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, 5-10 membered heterocycle, $-[N(C_1$-C_6 alkyl$)R^DR^E]^+$; or (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-NR^DR^E$, $-C(=O)NR^DR^E$ or $-CO_2H$. In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is C_1-C_6 alkyl optionally substituted with: (ii) $-O(C_1$-C_6 alkyl); (ix) $-NR^DR^E$, wherein the R^D of $-NR^DR^E$ is C_1-C_6 alkyl; or

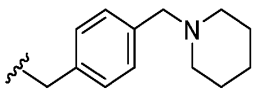
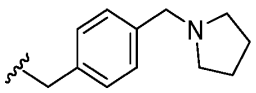
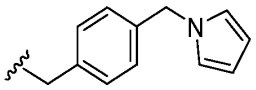
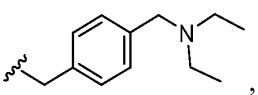
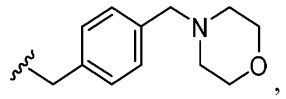
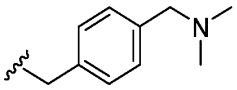
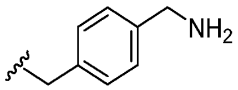
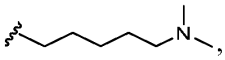
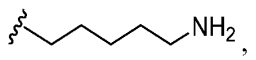
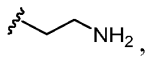
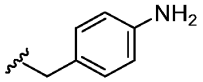
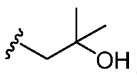
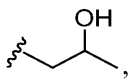
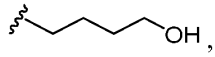
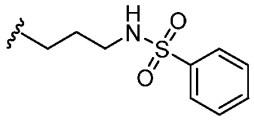
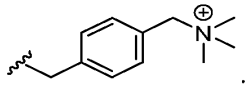
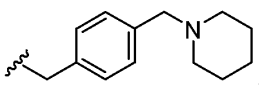
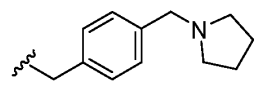
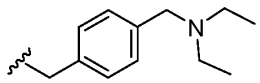
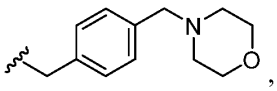
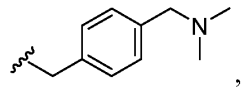
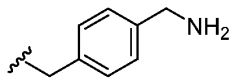
(xi) -(phenyl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, -[N(C_1-C_6 alkyl)R^DR^E]$^+$.

[0179] In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is C_1-C_6 alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) -O(C_1-C_6 alkyl); (ix) -NR^DR^E, wherein the R^D of -NR^DR^E is C_1-C_6 alkyl; (x) -[N(C_1-C_6 alkyl)R^DR^E]$^+$; (xi) -(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, 5-10 membered heterocycle, -[N(C_1-C_6 alkyl)R^DR^E]$^+$; or (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, -NR^DR^E, -C(=O)NR^DR^E or -CO_2H. In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is C_1-C_6 alkyl substituted with: (ii) -O(C_1-C_6 alkyl); (ix) -NR^DR^E, wherein the R^D of -NR^DR^E is C_1-C_6 alkyl; (x) -[N(C_1-C_6 alkyl)R^DR^E]$^+$; (xi) -(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, 5-10 membered heterocycle, -[N(C_1-C_6 alkyl)R^DR^E]$^+$; or (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, -NR^DR^E, -C(=O)NR^DR^E or -CO_2H. In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is C_1-C_6 alkyl substituted with: (ix) -NR^DR^E, wherein the R^D of -NR^DR^E is C_1-C_6 alkyl; or (xi) -(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, 5-10 membered heterocycle, -[N(C_1-C_6 alkyl)R^DR^E]$^+$.

[0180] In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is -C(=O)NR^DR^E; -C(=O)OR^C; -C(=O)SR^C; -C(=S)R^C; or 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, 5-10 membered heterocycle, -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, -NR^DR^E, -C(=O)NR^DR^E or -CO_2H; (xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the 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_1-C_6 alkyl, the C_1-C_6 alkyl.

[0181] In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is C_1-C_6 alkyl optionally substituted with: (ii) -OR^C; (iii) -SR^C; (iv) -NH-S(O_2)R^C; (ix) -NR^DR^E; (xi) -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, -NR^DR^E, or -[N(C_1-C_6 alkyl)R^DR^E]$^+$; or (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, -NR^DR^E, -C(=O)NR^DR^E or -CO_2H.

[0182] In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , wherein each instance of subscript z is independently 1, 2, or 3.

[0183] In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R^4 is selected from the group consisting of  ,  ,  ,  ,  , and  .

[0184] In some cases of Formulas (III) and (IIIa), and R^{4A} is (a) the point of covalent attachment to L 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) $-NR^DR^E$; (ix) $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$; (x) -(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; (xi) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$; or (xii) -(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 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, the C_1-C_6 alkyl or a substituent thereof is further substituted with the point of covalent attachment to L. In some cases of Formulas (III) and (IIIa), R^{4A} 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) $-NR^DR^E$; (ix) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$; (x) -(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; or (xi) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$; (xii) -(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 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 the C_1-C_6 alkyl or a substituent thereof is further substituted with the point of covalent attachment to L. In some cases of Formulas (III) and (IIIa), R^{4A} is C_1-C_6 alkyl substituted with: (ii) $-OR^C$; (iii) $-SR^C$; (iv) $-NH$-$S(O_2)R^C$; (ix) $-NR^DR^E$; (ix) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$; or (x) -(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; wherein the C_1-C_6 alkyl or a substituent thereof is further substituted with the point of covalent attachment to L. In some cases of Formulas (III) and (IIIa), R^{4A} is C_1-C_6 alkyl substituted with (ix) $-NR^DR^E$; (ix) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$; or (x) -(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; wherein the C_1-C_6 alkyl or a substituent thereof is further substituted with the point of covalent attachment to L.

[0185] In some cases of Formula (A), subscript n is 0, 1, or 2. In some cases of Formula (A), subscript n is 1. In some cases of Formula (A), subscript n is 0. In some cases of Formula (A), one instance of R^X is R^5 and the remaining instances of R^X are R^6. As used herein, the "remaining" R^X groups refers to 0 or subscript n-1 R^X groups, e.g., 0, 1, 2, or 3 R^X groups. Thus, when subscript n is 0, there are zero remaining R^X groups; when subscript n is 1, there are also zero remaining R^X groups; when subscript n is 2, there is 1 remaining R^X group; when subscript n is 3, there are 2 remaining R^X groups; when subscript n is 4, there are 3 remaining R^X groups.

[0186] In some cases of Formulae (A) and (I), R^5 is (a) the point of covalent attachment to L; or (b) 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. In some cases of Formulae (A) and (I), R^5 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, -C(=O)OR^F, -$S(O_2)NR^GR^H$, -$N(R^I)$-C(=O)R^J, -$N(R^I)$-$S(O_2)R^K$, and SO_3R^K. In some cases of Formulae (A) and (I), R^5 is selected from the group consisting of hydrogen, -C(=O)OR^F, -$S(O_2)NR^GR^H$, -$N(R^I)$-C(=O)R^J, -$N(R^I)$-$S(O_2)R^K$, and SO_3R^K. In some cases of Formulae (A) and (I), R^5 is -C(=O)OR^F. In some cases of Formulae (A) and (I), R^5 is -C(=O)OH or -C(=O)O(C_1-C_3 alkyl); and each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and –NR^AR^B. In some cases of Formulae (A) and (I), R^5 is -C(=O)OH or -$C(=O)OCH_3$.

[0187] In some cases of Formulae (A) and (I), each R^6 is independently selected from the group consisting of (a) the point of covalent attachment to L; or (b) 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. In some cases of Formulae (A) and (I), each R^6 is independently selected from the group consisting of (a) the point of covalent attachment to L; or (b) the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and –NR^AR^B; wherein no more than one R^6 is the point of covalent attachment to L. In some cases of Formulae (A) and (I), each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and –NR^AR^B; wherein no more than one R^6 is the point of covalent attachment to L. In some cases of Formulae (A) and (I), each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and –NR^AR^B.

[0188] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), 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. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), R^5 is selected from the group consisting of hydrogen, -C(=O)OR^F, -$S(O_2)NR^GR^H$, -$N(R^I)$-C(=O)R^J, -$N(R^I)$-$S(O_2)R^K$, and SO_3R^K. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), R^5 is -C(=O)OR^F. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), R^5 is -C(=O)OH or -C(=O)O(C_1-C_3 alkyl), each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and –NR^AR^B.

[0189] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), 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 $-NR^AR^B$. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and $-NR^AR^B$. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and $-NR^AR^B$. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and $-NR^AR^B$.

[0190] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), R^5 is -C(=O)OH or -C(=O)O(C_1-C_3 alkyl); and each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and $-NR^AR^B$. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), R^5 is -C(=O)OH or -C(=O)O(C_1-C_3 alkyl); and subscript m is zero. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), R^5 is -C(=O)OH; and subscript m is zero. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), R^5 is -C(=O)OCH_3; and subscript m is zero. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), subscript m is 0, 1, or 2. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), subscript m is 1 or 2. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), subscript m is 0 or 1. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), subscript m is 1. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), and (IV), subscript m is zero.

[0191] In some cases of Formulae (A) and (I), one instance of R^6 is the point of covalent attachment to L and the other R^6, if any, are 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 $-NR^AR^B$.

[0192] In some embodiments disclosed herein, R^5 is acidic, negatively charged, and/or highly polar (e.g., comprises a dipole moment of at least about 2.0 Debye). A surprising observation disclosed herein (e.g., as demonstrated in Example 37) is that C7 imidazoquinoline functionalization (R^5) can enhance toll-like receptor activation. It is contemplated that the importance of this functionalization in certain imidazoquinolines may have been previously missed due to its tendency to decrease cellular uptake, potentially masking its potency when applied as a free drug. However, when used in tandem with an effective targeting and uptake system, such as an antibody as disclosed herein, imidazoquinolines with negative or highly polar C7 functionalizations can affect enhanced TLR7/8 responses. Without being limited by theory, it is posited that TLR7/8 binding may position the imidazoquinoline C7 proximal to charged or polar

protic residues, enabling strong hydrogen bonding interactions which enhance binding strength and agonist behavior.

[0193] Accordingly, in certain cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (VI), (VII), and (VIII), R^5 is negatively charged under physiological conditions and/or highly polar (e.g., comprises a dipole moment of at least about 2.0 Debye). in certain cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (VI), (VII), and (VIII), R^5 comprises a pKa of at most about 7.0. In certain cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (VI), (VII), and (VIII), R^5 comprises a pKa of at most about 6.0. In certain cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (VI), (VII), and (VIII), R^5 comprises a pKa of at most about 5.0. In certain cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (VI), (VII), and (VIII), R^5 comprises a pKa of at most about 4.0. In certain cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (VI), (VII), and (VIII), R^5 comprises a pKa of at most about 3.0. In certain cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (VI), (VII), and (VIII), R^5 comprises a pKa of at most about 2.0. In certain cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (VI), (VII), and (VIII), R^5 comprises a dipole moment of at least about 2.0 Debye (e.g., as calculated with density functional theory). In certain cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (VI), (VII), and (VIII), R^5 comprises a dipole moment of at least about 2.5 Debye. in certain cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (VI), (VII), and (VIII), R^5 comprises a dipole moment of at least about 3.0 Debye. In certain cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (VI), (VII), and (VIII), R^5 comprises a pka of at most about 7.0 or a dipole moment of at least 2.0 Debye.

[0194] In some cases of Formula (A), each R^X is independently selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)-C(=O)R^J$, $-N(R^I)-S(O_2)R^K$, $-S(O_3)R^K$, 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 $-NR^AR^B$. In some cases of Formula (A), one instance of R^X is the point of covalent attachment to L and all other instances of R^X, if any, are 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 $-NR^AR^B$.

[0195] In some cases of Formula (A), n is 0, 1, or 2. In some cases of Formula (A), n is 1 or 2. In some cases of Formula (A), n is 0 or 1. In some cases of Formula (A), n is 0. In many cases, n is 1.

[0196] In some cases of Formulae (A) and (I), each instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, and (b) independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In some cases of Formulae (A) and (I), each instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, and (b) independently selected from the group consisting of hydrogen and C_1-C_3 alkyl. In some cases of Formulae (A) and (I), each instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, and (b) independently selected from the group consisting of hydrogen and methyl. In some cases of Formulae (A) and (I), at most one instance of R^A and R^B is (a) the point of covalent attachment to L, and the remaining instances of R^A and R^B are hydrogen.

[0197] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_3 alkyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^A and R^B is independently selected from the group consisting of hydrogen and methyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), all instances of R^A and R^B are hydrogen.

[0198] In some cases of Formulae (A) and (I), each instance of R^C is independently selected from the group consisting of: (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen. In some cases of Formulae (A) and (I), each instance of R^C is independently selected from the group consisting of: (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen, phenyl, and C_1-C_4 alkyl optionally substituted with phenyl. In some cases of Formulae (A) and (I), each instance of R^C is independently selected from the group consisting of: (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen and C_1-C_4 alkyl. In some cases of Formulae (A) and (I), each instance of R^C is independently selected from the group consisting of: (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen and methyl.

[0199] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^C is independently selected from the group consisting of hydrogen, phenyl, and C_1-C_{10} alkyl optionally substituted with phenyl or 1-3 independently selected halogen. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^C is independently selected from the group consisting of hydrogen, phenyl, and C_1-

C_4 alkyl optionally substituted with phenyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^C is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^C is independently selected from the group consisting of hydrogen and methyl.

[0200] In some cases of Formulae (A) and (I), each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) 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)-. In some cases of Formulae (A) and (I), each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, C_4-C_6 cycloalkyl(C_1-C_3 alkyl)-, aryl, and aryl(C_1-C_3 alkyl)-. In some cases of Formulae (A) and (I), each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen and C_1-C_6 alkyl. In some cases of Formulae (A) and (I), each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen and methyl.

[0201] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of 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)-. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, C_4-C_6 cycloalkyl(C_1-C_3 alkyl)-, aryl, and aryl(C_1-C_3 alkyl)-. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen and methyl.

[0202] In some cases of Formulae (A) and (I), each instance of R^F is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen, trifluoromethyl, 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, and C_1-C_6 alkoxy. In some cases of Formulae (A) and (I), each instance of R^F is independently selected from the group consisting of (a) the point of covalent attachment to L; and

(b) the group consisting of hydrogen, trifluoromethyl, C_3-C_6 cycloalkyl, aryl, aryl(C_1-C_3 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1 substituent selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, and C_1-C_6 alkoxy. In some cases of Formulae (A) and (I), each instance of R^F is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen, trifluoromethyl, and C_1-C_6 alkyl. In some cases of Formulae (A) and (I), each instance of R^F is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen, trifluoromethyl, and C_1-C_3 alkyl. In some cases of Formulae (A) and (I), each instance of R^F is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen, trifluoromethyl, and methyl.

[0203] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^F is independently selected from the group consisting of hydrogen, trifluoromethyl, 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, and C_1-C_6 alkoxy. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^F is independently selected from the group consisting of hydrogen, trifluoromethyl, C_3-C_6 cycloalkyl, aryl, aryl(C_1-C_3 alkyl)-, and C_1-C_6 alkyl optionally substituted with 1 substituent selected from the group consisting of halogen, C_1-C_6 alkanoyloxy, and C_1-C_6 alkoxy. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^F is independently selected from the group consisting of hydrogen, trifluoromethyl, and C_1-C_6 alkyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^F is independently selected from the group consisting of hydrogen, trifluoromethyl, and C_1-C_6 alkyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^F is independently selected from the group consisting of hydrogen, trifluoromethyl, and C_1-C_3 alkyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^F is independently selected from the group consisting of hydrogen, trifluoromethyl, and methyl.

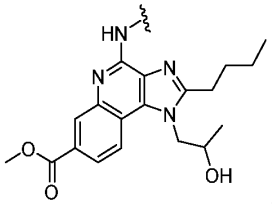
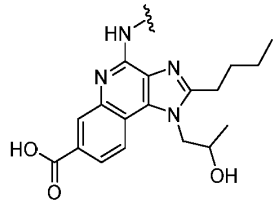
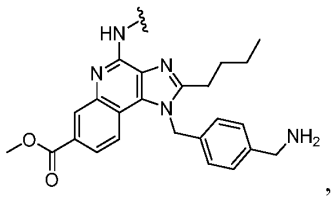
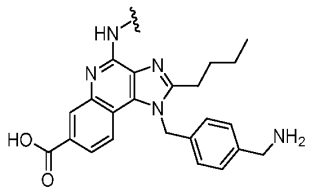
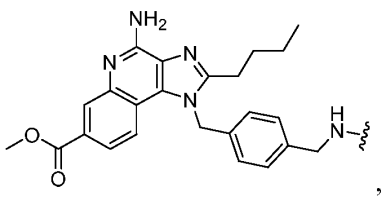
[0204] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), when R^F is trifluoromethyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, aryl(C_1-C_6 alkyl)-, or C_1-C_6 alkyl optionally substituted with 1-3 substituents independently selected 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^DR^E]$^+$; -(phenyl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with -[$N(C_1$-

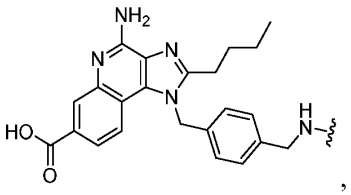
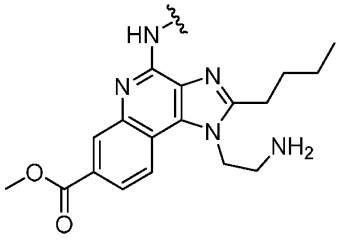
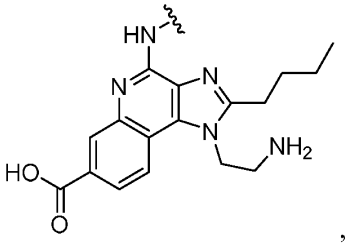
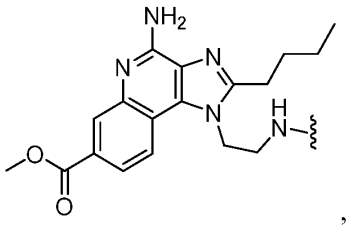
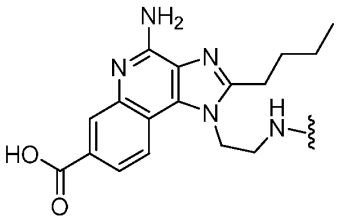
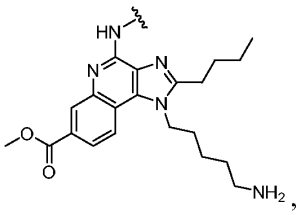
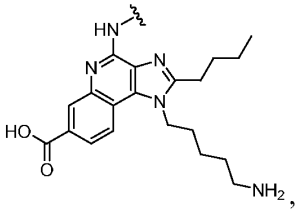
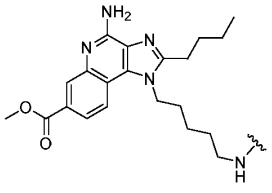
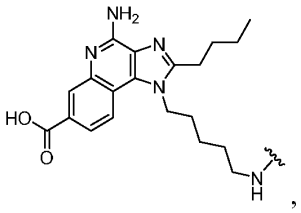
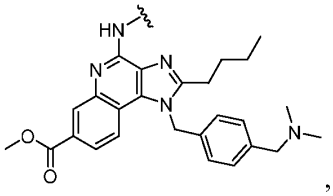
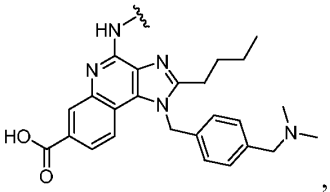
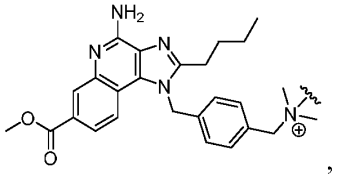
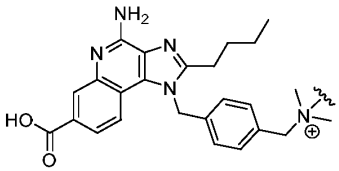
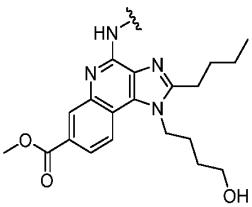
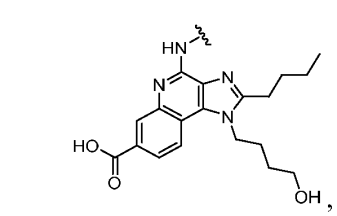
C_6 alkyl)$R^DR^E]^+$; or -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with -[N(C_1-C_6 alkyl)$R^DR^E]^+$.

[0205] In some cases of Formulae (A) and (I), each instance of R^I, R^J, and R^K is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen and C_1-C_3 alkyl. In some cases of Formulae (A) and (I), each instance of R^I, R^J, and R^K is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen and methyl. In some cases of Formulae (A) and (I), each instance of R^I, R^J, and R^K is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) hydrogen.

[0206] In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and C_1-C_3 alkyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^I, R^J, and R^K is independently selected from the group consisting of hydrogen and methyl. In some cases of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), and (VIII), each instance of R^I, R^J, and R^K is hydrogen.

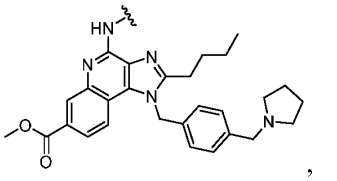
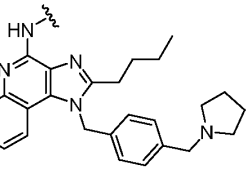
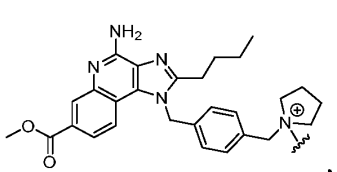
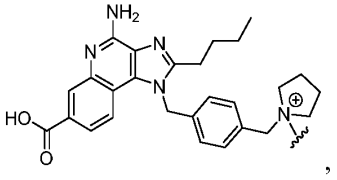
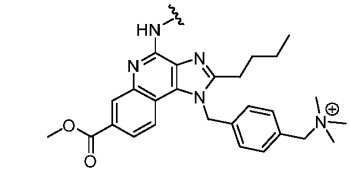
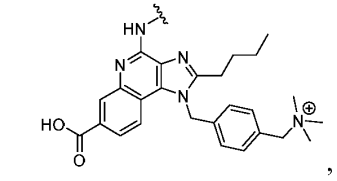
[0207] In some cases of Formulae (VI), (VII), and (VIII), each instance of R^{6A} is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 alkanoyloxy, C_1-C_6 alkoxycarbonyl, and $–NR^AR^B$. In some cases of Formulae (VI), (VII), and (VIII), each instance of R^{6A} is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxy, and $–NR^AR^B$. In some cases of Formulae (VI), (VII), and (VIII), each instance of R^{6A} is independently selected from the group consisting of C_1-C_6 alkyl and $–NR^AR^B$. In some cases of Formulae (VI), (VII), and (VIII), subscript q is 0 or 1. In some cases of Formulae (VI), (VII), and (VIII), subscript q is 0.

[0208] In some cases, each D is  ,  ,  ,  ,  ,


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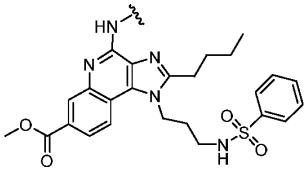
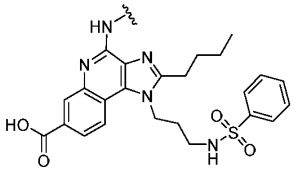
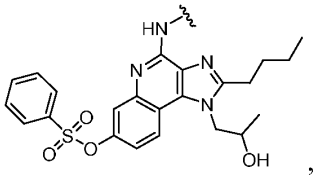
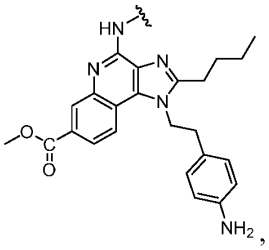
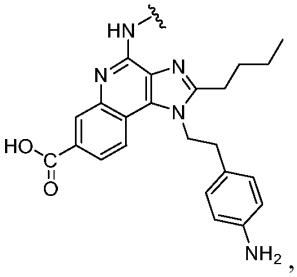
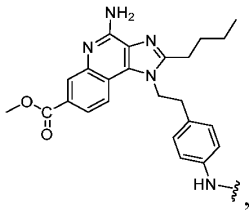
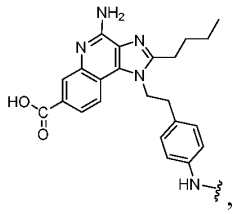
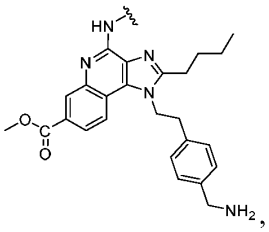
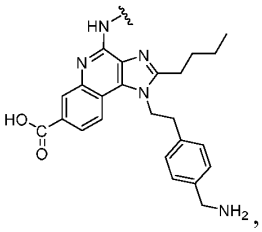
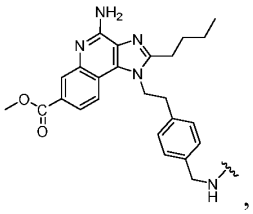
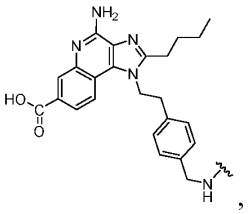
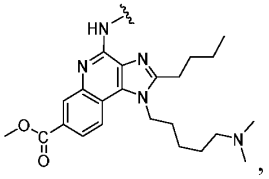
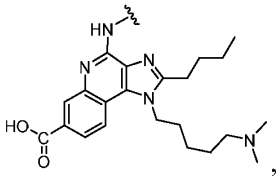
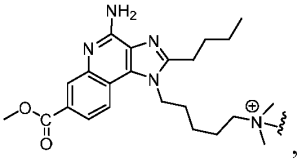
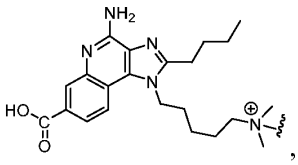
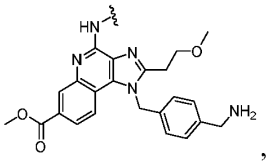
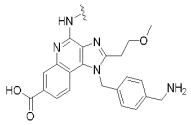
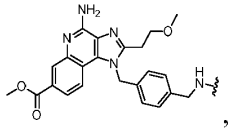
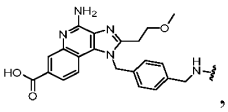
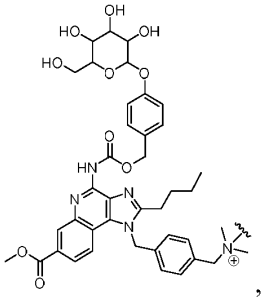
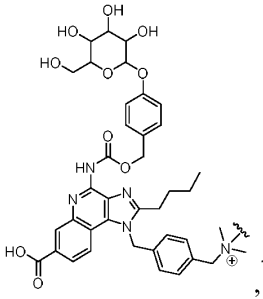
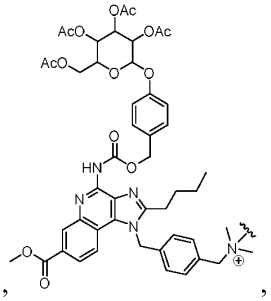
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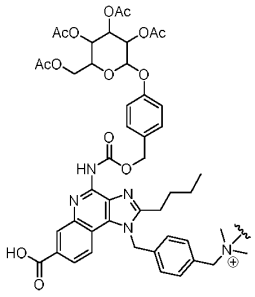
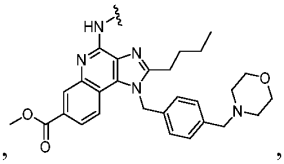
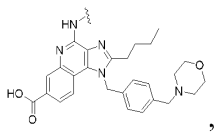
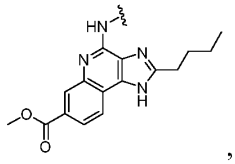
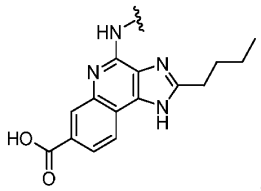
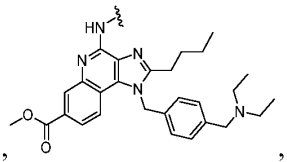
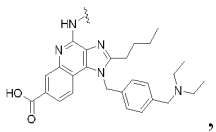
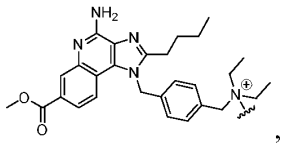
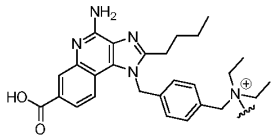
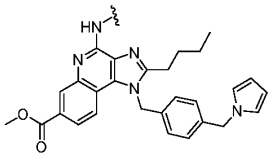
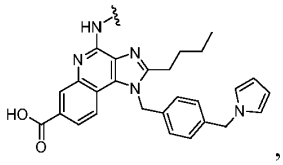
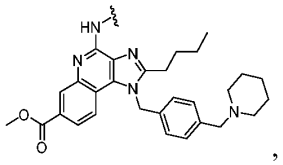
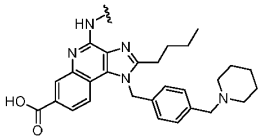
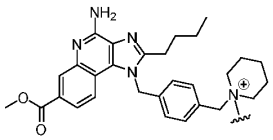
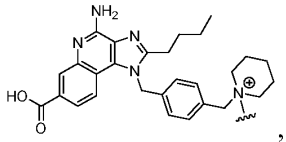
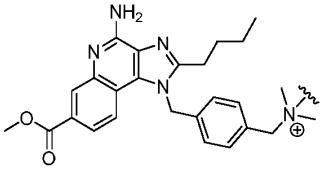
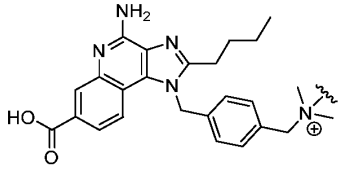
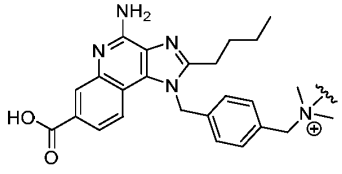
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, wherein ~~~ represents the point of covalent attachment to L. In some cases, each D is  or  , wherein ~~~ represents the point of covalent attachment to L. In some cases, each D is  , wherein ~~~ represents the point of covalent attachment to L.

[0209] In some embodiments, the ADC is capable of releasing (i) a component of the linker bound to D; (ii) a component of antibody bound to L-D; and/or (iii) the parent compound D as the free drug (as defined herein). In some embodiments, the free drug is released at the intended site of action targeted by the antibody. In some embodiments, the free drug is released within the

intended site of action targeted by the antibody. In some embodiments, the free drug is capable of binding to a toll-like receptor (TLR). In some embodiments, the binding of the free drug to a TLR exhibits an agonist effect on the TLR. In some embodiments, the binding of the free drug to a TLR exerts an immunostimulatory effect.

Antibodies

[0210] For many of the ADCs disclosed herein, the antibody targets an antigen associated with a clinically relevant disease state. Such antibodies can localize the ADCs to disease sites, thereby enabling targeted TLR7/8 agonist payload delivery and site-specific treatment. As untargeted TLR7/8 agonists can affect systemic immune-related toxicities, TLR7/8-mediated immune reactivation is often only feasible when the agonist payloads are delivered in a site-specific manner. Accordingly, targeted ADC antibodies disclosed herein can enable use of highly potent TLR7/8 agonists which would otherwise exhibit prohibitively high toxicities through systemic delivery. In some cases, the antibody further mediates cellular uptake to affect intracellular or subcellular TLR7/8 agonist delivery.

[0211] The term "monoclonal antibody" as used herein can refer to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population comprise identical sequences except for possible minor amounts of naturally occurring mutations. Often, Monoclonal antibodies are highly specific, being directed against a single antigenic site. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and is not to be construed as requiring production of the antibody by any particular method.

[0212] Useful polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of immunized animals. Useful monoclonal antibodies are homogeneous populations of antibodies to a particular antigenic determinant (e.g., a cancer or immune cell antigen, a protein, a peptide, a carbohydrate, a chemical, nucleic acid, or fragments thereof). A monoclonal antibody (mAb) to an antigen-of-interest can be prepared by using any technique known in the art which provides for the production of antibody molecules by continuous cell lines in culture.

[0213] Useful monoclonal antibodies include, but are not limited to, human monoclonal antibodies, humanized monoclonal antibodies, or chimeric human-mouse (or other species) monoclonal antibodies. The antibodies include full-length antibodies and antigen binding fragments thereof. Human monoclonal antibodies may be made by any of numerous techniques known in the art (*e.g.*, Teng *et al.*, 1983, *Proc. Natl. Acad. Sci. USA.* 80:7308-7312; Kozbor *et al.*, 1983, *Immunology Today* 4:72-79; and Olsson *et al.*, 1982, *Meth. Enzymol.* 92:3-16).

[0214] In some embodiments, an antibody includes a functionally active fragment, derivative or analog of an antibody that binds specifically to target cells (e.g., cancer cell antigens) or other antibodies bound to cancer cells or matrix. In this regard, "functionally active" means that the fragment, derivative or analog is able to bind specifically to target cells. To determine which CDR sequences bind the antigen, synthetic peptides containing the CDR sequences are typically used in binding assays with the antigen by any binding assay method known in the art (e.g., the Biacore assay) (*See*, *e.g.*, Kabat *et al.*, 1991, *Sequences of Proteins of Immunological Interest*, Fifth Edition, National Institute of Health, Bethesda, Md; Kabat E *et al.*, 1980, *J. Immunology* 125(3):961-969).

[0215] Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which are typically obtained using standard recombinant DNA techniques, are useful antibodies. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as for example, those having a variable region derived from a murine monoclonal and a constant region derived from a human immunoglobulin. *See*, e.g., U.S. Patent No. 4,816,567; and U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entireties. Humanized antibodies are antibody molecules from non-human species having one or more CDRs from the non-human species and a framework region from a human immunoglobulin molecule. *See*, e.g., U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in International Publication No. WO 87/02671; European Patent Publication No. 0 184 187; European Patent Publication No. 0 171 496; European Patent Publication No. 0 173 494; International Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Publication No. 012 023; Berter *et al.*, 1988, *Science* 240:1041-1043; Liu *et al.*, 1987, *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.*, 1987, *J. Immunol.* 139:3521-3526; Sun *et al.*, 1987, *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.*, 1987, *Cancer. Res.* 47:999-1005; Wood *et al.*, 1985, *Nature* 314:446-449; and Shaw *et al.*, 1988, *J. Natl. Cancer Inst.* 80:1553-1559; Morrison, 1985, *Science* 229:1202-1207; Oi *et al.*, 1986, *BioTechniques* 4:214; U.S. Patent No. 5,225,539; Jones *et al.*, 1986, *Nature* 321: 522-525; Verhoeyan *et al.*, 1988, *Science* 239:1534; and Beidler *et al.*, 1988, *J. Immunol.* 141:4053-4060; each of which is incorporated herein by reference in its entirety.

[0216] In some embodiments, an antibody is a completely human antibody. In some embodiments, an antibody is produced using transgenic mice that are incapable of expressing

endogenous immunoglobulin heavy and light chain genes, but which are capable of expressing human heavy and light chain genes.

[0217] In some embodiments, an antibody is an intact or fully-reduced antibody. The term 'fully-reduced' is meant to refer to an antibody in which all four inter-chain disulfide linkages have been reduced to provide eight thiols that can be attached to a linker (L).

[0218] Attachment to an antibody can be via thioether linkages from native and/or engineered cysteine residues, or from an amino acid residue engineered to participate in a cycloaddition reaction (such as a click reaction) with the corresponding linker intermediate. *See,* e.g., Maerle, et al., *PLOS One* 2019: 14(1); e0209860. In some embodiments, an antibody is an intact or fully-reduced antibody, or is an antibody bearing engineered an cysteine group that is modified with a functional group that can participate in, for example, click chemistry or other cycloaddition reactions for attachment of other components of the ADC as described herein (e.g., Diels-Alder reactions or other [3+2] or [4+2] cycloadditions). *See,* e.g., Agard, et al., *J. Am. Chem. Soc.* Vol. 126, pp. 15046-15047 (2004); Laughlin, et al., *Science*, Vol. 320, pp. 664-667 (2008); Beatty, et al., *ChemBioChem*, Vol. 11, pp. 2092-2095 (2010); and Van Geel, et al., *Bioconjug. Chem.* Vol. 26, pp.2233-2242 (2015).

[0219] Antibodies that bind specifically to a cancer or immune cell antigen are available commercially or produced by any method known to one of skill in the art such as, e.g., chemical synthesis or recombinant expression techniques. The nucleotide sequences encoding antibodies that bind specifically to a cancer or immune cell antigen are obtainable, e.g., from the GenBank database or similar database, literature publications, or by routine cloning and sequencing.

[0220] In some embodiments, the antibody can be used for the treatment of a cancer (e.g., an antibody approved by the FDA and/or EMA). Antibodies that bind specifically to a cancer or immune cell antigen are available commercially or produced by any method known to one of skill in the art such as, e.g., recombinant expression techniques. The nucleotide sequences encoding antibodies that bind specifically to a cancer or immune cell antigen are obtainable, e.g., from the GenBank database or similar database, literature publications, or by routine cloning and sequencing.

[0221] In some cases, the antibody has a mutation or post-translational modification which affects non-Fab mediated uptake. Peripheral immune cells, which are highly responsive to TLR7/8 agonists can facilitate strong, systemic responses when activated through non-antigen specific, Fc-mediated uptake of the TLR7/8 antibody drug conjugate which may be harmful or otherwise undesirable. In such cases, the antibody can have an effector function-diminishing

mutation, such as L234A/L235A, D265A/N297A, D270A, K322A, P329A, P329G or a combination thereof, which diminishes non-immune uptake (e.g., FcγR-mediated uptake).

[0222] In some embodiments, an antibody can be configured to bind to a surface antigen of a cell. The antibody, or a complex comprising the antibody, can be configured to internalize within a cell upon binding to the surface antigen. For example, the antibody or an ADC comprising the antibody can be configured to endocytose upon binding to a surface antigen of a cell. In some embodiments, the antibody (or an ADC comprising the antibody) is configured to internalize within a cancer cell. In some embodiments, the antibody (or an ADC comprising the antibody) is configured to internalize within an immune cell. In some embodiments, the immune cell is a tumor associated macrophage. In some embodiments, the surface antigen is a receptor or a receptor complex (e.g., expressed on lymphocytes). In some embodiments, the receptor or receptor complex comprises an immunoglobulin gene superfamily member, a TNF receptor superfamily member, an integrin, a cytokine receptor, a chemokine receptor, a major histocompatibility protein, a lectin, or a complement control protein or other immune cell expressed surface receptor.

[0223] In some embodiments, an antibody is configured to bind specifically to a cancer cell antigen. In some embodiments, an antibody is configured to bind specifically to an immune cell antigen. In some embodiments, the immune cell antigen is a tumor associated macrophage antigen. In some embodiments, an antibody is configured to bind specifically to EphA2. It will be understood that the antibody component in an ADC is an antibody in residue form such that "Ab" in the ADC structures described herein incorporates the structure of the antibody.

[0224] Non-limiting examples of antibodies that can be used for treatment of cancer and antibodies that bind specifically to tumor associated antigens are disclosed in Franke, A. E., Sievers, E. L., and Scheinberg, D. A., "Cell surface receptor-targeted therapy of acute myeloid leukemia: a review" *Cancer Biother Radiopharm*. 2000,15, 459-76; Murray, J. L., "Monoclonal antibody treatment of solid tumors: a coming of age" *Semin Oncol*. 2000, 27, 64-70; Breitling, F., and Dubel, S., *Recombinant Antibodies*, John Wiley, and Sons, New York, 1998, each of which is hereby incorporated by reference in its entirety.

[0225] Non-limiting examples of antigens which antibodies of the present disclosure may target include ADAM12 (e.g., Catalog #14139-1-AP); ADAM9 (e.g., IMGC936); AFP (e.g., ThermoFisher Catalog #PA5-25959); AGR2 (e.g., ThermoFisher Catalog #PA5-34517); AKAP-4 (e.g., Catalog #PA5-52230); ALK (e.g., DLX521); ALPP (e.g., Catalog #MA5-15652); ALPPL2 (e.g., Catalog #PA5-22336); AMHR2 (e.g., ThermoFisher Catalog #PA5-13902); androgen receptor (e.g., ThermoFisher Catalog #MA5-13426); ANTXR1 (e.g., Catalog #MA1-91702); ANXA1 (e.g., Catalog #71-3400); ARTN (e.g., ThermoFisher Catalog #PA5-47063);

ASCT2 (e.g., idactamab); Axl (e.g., BA3011; tilvestamab); B7-DC (e.g., Catalog #PA5-20344); B7-H3 (e.g., enoblituzumab, omburtamab, MGD009, MGC018, DS-7300); B7-H4 (e.g., Catalog #14-5949-82); B7-H6 (e.g., Catalog #12-6526-42); B7-H7; BAFF-R (e.g., Catalog #14-9117-82); BCMA; BCR-ABL; BMPR2; BORIS; C4.4a; CanAg; C5 complement (e.g., BCD-148; CAN106); CA-125; CA19-9 (e.g., AbGn-7; MVT-5873); CA9 (e.g., girentuximab); CALCR (*see,* e.g., International Publication No. WO 2015077826); CAMPATH-1 (e.g., alemtuzumab; ALLO-647; ANT1034); carcinoembryonic antigen (e.g., arcitumomab; cergutuzumab; amunaleukin; labetuzumab); CCNB1; CD112 (*see,* e.g., U.S. Publication No. 20100008928); CD115 (e.g., axatilimab; cabiralizumab; emactuzumab); CD123 (e.g., BAY-943; CSL360); CD137 (e.g., ADG106; CTX-471); CD138; CD142; CD166; CD147 (e.g., gavilimomab; metuzumab); CD155 (e.g., U.S. Publication No. 2018/0251548); CD19 (e.g., ALLO-501); CD20 (e.g., divozilimab; ibritumomab tiuxetan); CD24 (*see,* e.g., U.S. Patent No. 8,614,301); CD244 (e.g., R&D AF1039); CD247 (e.g., AFM15); CD27 (e.g., varlilumab); CD274 (e.g., adebrelimab; atezolizumab; garivulimab); CD3 (e.g., otelixizumab; visilizumab); CD30 (e.g., iratumumab); CD33 (e.g., lintuzumab; BI 836858; AMG 673); CD288; CD352 (e.g., SGN-CD352A); CD37 (e.g., lilotomab; GEN3009); CD38 (e.g., felzartamab; AMG 424); CD3D; CD3E (e.g., foralumab; teplizumab); CD3G; CD45 (e.g., apamistamab); CD47 (e.g., letaplimab; magrolimab); CD48 (e.g., SGN-CD48A); CD5 (e.g., MAT 304; zolimomab aritox); CD56; CD59; CD70 (e.g., cusatuzumab); CD74 (e.g., milatuzumab); CD79A (*see,* e.g., International Publication No. WO 2020252110); CD79b; CD96; CD97; CD-262 (e.g., tigatuzumab); CDCP1 (e.g., RG7287); CDH17 (*see,* e.g., International Publication No. WO 2018115231); CDH3 (e.g., PCA062); CDH6 (e.g., HKT288); CEACAM1; CEACAM5; CEACAM6; CLDN1 (e.g., INSERM anti-Claudin-1); CLDN16; CLDN18.1 (e.g., zolbetuximab); CLDN18.2 (e.g., zolbetuximab); CLDN19; CLDN2 (*see,* e.g., International Publication No. WO 2018123949); CLEC12A (e.g., tepoditamab); CS1; CLPTM1L; CSPG4 (e.g., U.S. Patent No. 10,822,427); CXCR4 (e.g., ulocuplumab); CYP1B1; c-Met; DCLK1 (*see,* e.g., International Publication No. WO 2018222675); DDR1; de2-7 EGFR (e.g., MAb 806); DLL-3; DPEP1; DPEP3; DPP4; DR4 (e.g., mapatumumab); DSG2 (*see,* e.g., U.S. Patent No. 10,836,823); EGF; EGFR; endosialin (e.g., ontuxizumab); ENPP1; EPCAM (e.g., adecatumumab); EPHA receptors; EPHA2; ERBB2 (e.g., trastuzumab); ERBB3; ERVMER34_1; ETV6-AML (e.g., Catalog #PA5-81865); FAS; FasL; Fas-related antigen 1; FBP; FGFR1 (e.g., RG7992); FGFR2 (e.g., aprutumab); FGFR3 (e.g., vofatamab); FGFR4 (e.g., MM-161); FLT3 (e.g., 4G8SDIEM); FN; FN1; FOLR1 (e.g., farletuzumab); FRa; FSHR; FucGM1 (e.g., BMS-986012); FZD5; FZD8; G250; GAGE; GCC; GD2 (e.g., dinutuximab); GD3 (e.g., mitumomab); GITR (e.g., ragifilimab); GloboH; GM2 (e.g., BIW-8962); GM3 (e.g., racotumomab); gp100;

GPA33 (e.g., KRN330); GPC3 (e.g., codrituzumab); gpNMB (e.g., glembatumumab); GPR87; GUCY2C (e.g., indusatumab); HAS3; HAVCR2; HLA-E; HLA-F; HLA-G (e.g., TTX-080); HPV E6 E7; hTERT; ICAM1; IDO1; IFNAR1 (e.g., faralimomab); IFNAR2; IL13Ra2; IL1RAP (e.g., nidanilimab); IL-21R (e.g., PF-05230900); IL-5R (e.g., benralizumab); ITGAV (e.g., abituzumab); ITGB6; ITGB8; KISS1R; L1CAM (e.g., JCAR023); LAG-3 (e.g., encelimab); LAMP1; LCK; legumain; LMP2; LY6G6D (e.g., PA5-23303); LY9 (e.g., PA5-95601); LYPD1 (e.g., ThermoFisher Catalog #PA5-26749); MAD-CT-1; MAD-CT-2; MAGEA1 (e.g., Catalog #MA5-11338); MAGEA3 (e.g., ThermoFisher Catalog #60054-1-IG); MAGEA4 (e.g., Catalog #MA5-26117); MAGEC2 (e.g., ThermoFisher Catalog #PA5-64010); MELTF (e.g., ThermoFisher Catalog #H00004241-M04A); MerTk (e.g., DS5MMER, Catalog #12-5751-82); a metalloproteinase; MFSD13A; MICA (e.g., 1E2C8, Catalog #66384-1-IG); MICB (e.g., Catalog #MA5-29422); Mincle (e.g., OTI2A8, Catalog #TA505101); MLANA (e.g., Catalog #MA5-15237); ML-IAP (e.g., 88C570, ThermoFisher Catalog #40958); MSLN (e.g., 5B2, Catalog #MA5-11918); MUC1 (e.g., MH1 (CT2), ThermoFisher Catalog #MA5-11202); MUC5AC (e.g., 45M1, Catalog #MA5-12178); MYCN (e.g., NCM-II 100, ThermoFisher Catalog #MA1-170); NA17; NCAM1 (e.g., ThermoFisher Catalog #MA5-11563); Nectin-4 (e.g., enfortumab); NOX1 (e.g., Catalog #PA5-103220); NT5E (e.g., 7G2, ThermoFisher Catalog #41-0200); NY-BR-1 (e.g., NY-BR-1 No. 2, Catalog #MA5-12645); NY-ESO-1 (e.g., E978m, Catalog #35-6200); OX40 (e.g., ABM193); OY-TES1; p53; p53mutant; PAP; PAX3 (e.g., GT1210, ThermoFisher Catalog #MA5-31583); PAX5; PDGFR-B (e.g., rinucumab); PDPN (e.g., ThermoFisher Catalog #14-5381-82); PLAVl; PMSA; polysialic acid (*see,* e.g., Watzlawik et al. J Nat Sci. 2015; 1(8):e141); PR1; PROM1 (e.g., Catalog #14-1331-82); PSA (e.g., ThermoFisher Catalog #PA1-38514; Daniels-Wells et al. *BMC Cancer* 2013; 13:195); PSCA (e.g., AGS-1C4D4); PSMA (e.g., BAY 2315497); PTK7 (e.g., cofetuzumab); PVRIG; Ras mutant (e.g., Shin et al. *Sci Adv.* 2020; 6(3):eaay2174); RET (e.g., WO2020210551); RGS5 (e.g., TF-TA503075); RhoC (e.g., ThermoFisher Catalog PA5-77866); ROR1 (e.g., cirmtuzumab); ROR2 (e.g., BA3021); ROS1 (e.g., WO 2019107671); Sarcoma translocation breakpoints; SART3 (e.g., TF 18025-1-AP); Sialyl-Thomsen-nouveau-antigen (e.g., Eavarone et al. *PLoS One.* 2018; 13(7): e0201314); Siglecs 1-16 (*see,* e.g., Angata et al. Trends *Pharmacol Sci.* 2015; 36(10): 645–660); SIRPa (e.g., Catalog #17-1729-42); SIRPg (e.g., PA5-104381); SIT1 (e.g., PA5-53825); SLAMF7 (e.g., elotuzumab); SLC10A2 (e.g., ThermoFisher Catalog #PA5-18990); SLC12A2 (e.g., ThermoFisher Catalog #13884-1-AP); SLC17A2 (e.g., ThermoFisher Catalog #PA5-106752); SLC38A1 (e.g., ThermoFisher Catalog #12039-1-AP); SLC39A5 (e.g., ThermoFisher Catalog #MA5-27260); SLC39A6 (e.g., ladiratuzumab); SLC44A4 (e.g., ASG-5ME); SLC6A15 (e.g.,

ThermoFisher Catalog #PA5-52586); SLC6A6 (e.g., ThermoFisher Catalog #PA5-53431); SLC7A11 (e.g., ThermoFisher Catalog #PA1-16893); SLC7A5; sLe; SLITRK6 (e.g., sirtratumab); Sperm protein 17 (e.g., BS-5754R); SSX2 (e.g., ThermoFisher Catalog #MA5-24971); survivin (e.g., PA1-16836); TACSTD2 (e.g., PA5-47074); TAG-72 (e.g., MA1-25956); tenascin; TF (e.g., tisotumab); Tie3; TLR2/4/1 (e.g., tomaralimab); TM4SF5 (e.g., 18239-1-AP); TMEM132A (e.g., Catalog #PA5-62524); TMEM40 (e.g., PA5-60636); TMPRSS11D (e.g., PA5-30927); Tn; TNFRSF12 (e.g., BAY-356); TRAIL (e.g., Catalog #12-9927-42); TRAIL1; TRP-2 (e.g., PA5-52736); ULBP1/2/3/4/5/6 (e.g., PA5-82302); uPAR (e.g., ATN-658); UPK1B (e.g., ThermoFisher Catalog #PA5-56863); UPK2 (e.g., ThermoFisher Catalog #PA5-60318); UPK3B (e.g., ThermoFisher Catalog #PA5-52696); VEGF (e.g., GNR-011); VEGFR2 (e.g., gentuximab); VSIR (e.g., ThermoFisher Catalog #PA5-52493); WT1 (e.g., ThermoFisher Catalog #MA5-32215); and XAGE1 (e.g., ThermoFisher Catalog #PA5-46413).

[0226] Non-limiting examples of target antigens include Axl (e.g., BA3011; tilvestamab); B7-1 (e.g., galiximab); B7-2 (e.g., Catalog #12-0862-82); B7-DC (e.g., Catalog #PA5-20344); B7-H3 (e.g., enoblituzumab, omburtamab, MGD009, MGC018, DS-7300); B7-H4 (e.g., Catalog #14-5949-82); B7-H6 (e.g., Catalog #12-6526-42); B7-H7; BAFF-R (e.g., Catalog #14-9117-82); BCMA; C5 complement (e.g., BCD-148; CAN106); CCR4 (e.g., AT008; mogamulizumab-kpkc); CCR8 (e.g., JTX-1811); CD112 (*see,* e.g., U.S. Publication No. 20100008928); CD115 (e.g., axatilimab; cabiralizumab; emactuzumab); CD123 (e.g., BAY-943; CSL360); CD137 (e.g., ADG106; CTX-471); CD155 (e.g., U.S. Publication No. 2018/0251548); CD163 (e.g., TBI 304H); CD19 (e.g., ALLO-501); CD2 (e.g., BTI-322; siplizumab); CD20 (e.g., divozilimab; ibritumomab); CD24 (*see,* e.g., U.S. Patent No. 8,614,301); CD244 (e.g., R&D AF1039); CD247 (e.g., AFM15); CD25 (e.g., basiliximab); CD27 (e.g., varlilumab); CD274 (e.g., adebrelimab; atezolizumab; garivulimab); CD278 (e.g., feladilimab; vopratelimab); CD28 (e.g., REGN5668); CD3 (e.g., otelixizumab; visilizumab); CD30 (e.g., iratumumab); CD30L (*see,* e.g., U.S. Patent No. 9,926,373); CD32 (e.g., mAb 2B6); CD33 (e.g., lintuzumab; BI 836858; AMG 673); CD352 (e.g., SGN-CD352A); CD37 (e.g., lilotomab; GEN3009); CD38 (e.g., felzartamab; AMG 424); CD3D; CD3E (e.g., foralumab; teplizumab); CD3G; CD40 (e.g., dacetuzumab; lucatumumab); CD44 (e.g., RG7356); CD45 (e.g., apamistamab); CD47 (e.g., letaplimab; magrolimab); CD48 (e.g., SGN-CD48A); CD5 (e.g., MAT 304; zolimomab aritox); CD51; CD70 (e.g., cusatuzumab); CD74 (e.g., milatuzumab); CD79A (*see,* e.g., International Publication No. WO 2020252110); CD83 (e.g., CBT004); CD97; CD262 (e.g., tigatuzumab); CLEC12A (e.g., tepoditamab); CTLA4 (e.g., ipilimumab); CXCR4 (e.g., ulocuplumab); DCIR; DCSIGN (*see,* e.g., International Publication No. WO 2018134389); Dectin1 (*see,* e.g., U.S. Patent No. 9,045,542); Dectin2 (e.g.,

ThermoFisher Catalog #MA5-16250); DR4 (e.g., mapatumumab); endosialin (e.g., ontuxizumab); FasL; FLT3 (e.g., 4G8SDIEM); GITR (e.g., ragifilimab); HAVCR2; HER2; HER3; HLA-DR; HLA-E; HLA-F; HLA-G (e.g., TTX-080); ICAM1; IDO1; IFNAR1 (e.g., faralimomab); IFNAR2; IGF-1R; IL1RAP (e.g., nidanilimab); IL-21R (e.g., PF-05230900); IL-5R (e.g., benralizumab); Integrin αvβ6; LAG-3 (e.g., encelimab); LAMP1; LAYN; LCK; LILRB2; LILRB4; MerTk (e.g., DS5MMER, Catalog #12-5751-82); Mesothelin; MICA (e.g., 1E2C8, Catalog #66384-1-IG); MICB (e.g., Catalog #MA5-29422); MICA; Mincle (e.g., OTI2A8, Catalog #TA505101); MRC1 (e.g., ThermoFisher Catalog #12-2061-82); MUC1; Muc16; NcaPi2B; Nectin-4; OX40 (e.g., ABM193); PD-1 (e.g., balstilimab; budigalimab; geptanolimab); PD-L1; Prolactin receptor; PTK7; PVRIG; ROR-1; Sialyl-Thomsen-nouveau-antigen (e.g., Eavarone et al. *PLoS One*, 2018; 13(7): e0201314); Siglecs 1-16 (*see,* e.g., Angata et al. Trends Pharmacol Sci. 2015; 36(10): 645–660);); SIRPa (e.g., Catalog #17-1729-42); SIRPg (e.g., PA5-104381); SIT1 (e.g., PA5-53825); SLAMF7 (e.g., elotuzumab); SLTRK6; STEAP1; TIGIT (e.g., etigilimab); TLR2/4/1 (e.g., tomaralimab); Trem2 (e.g., PY314); TROP2; Tyrol; ULBP1/2/3/4/5/6 (e.g., PA5-82302); uPAR (e.g., ATN-658); VSIR (e.g., ThermoFisher Catalog #PA5-52493); ZIP6 (Anti-Integrin αvβ6).

[0227] In some cases, an antibody target is selected from the group consisting of ADAM9, ASCT2, Axl, B7-H3, B7H4, BCMA, BCMA, C4.4a, CanAg, CD123, CD138, CD142, CD166, CD19, CD20, CD228, CD25, CD30, CD33, CD352, CD38, CD48, CD56, CD59, CD70, CD74, CD79b, CDCP1, CEACAM5, Claudin-18.2, c-Met, gpNMB, CS1, DLL-3, DPEP-3, EGFR, EpCAM, EphA2, FGFR2, FRa, GCC, gpA33, GPC3, Integrin αvβ6 , h2A2, H2G12/STn, HER2, HER3, ZIP6, IGF-1R, IL1Rap, ITGav/CD51, Mesothelin, MICA, MUC-1, Muc16, NaPi2B, Nectin-4, PD-L1, Prolactin receptor, PTK7, ROR-1, SLAMF7, SLTRK6, STEAP1, TIGIT, and TROP2.

[0228] In some cases, an antibody of the present disclosure targets an immune checkpoint. Among the diverse mechanisms which can contribute to unchecked cell growth, certain cancers utilize immune checkpoint proteins to generate immunosuppressive environments which limit immune activity proximal to cancer sites. As these cancers often generate high abundances of immune checkpoints, immune checkpoint targeting can be an effective means for localizing ADCs, and thereby TLR7/8 agonist payloads, to cancer sites. In some cases, an antibody of the present disclosure targets an immune checkpoint selected from the group consisting of PDL1, PD1, CTLA-4, B7H4, B7H3, TIGIT, TIM-3, VISTA, GITR/GITRL, CD80/CD86, CD155, PDL1, PDL2, galectin 9, CD40, OX40L, 4-1BB/4-1BBL, ICOS/ICOSL, CD70, and combinations

thereof. In some cases, an antibody of the present disclosure targets an immune checkpoint selected from the group consisting of PDL1, B7H4, B7H3, TIGIT, or a combination thereof.

[0229] **TABLE 1** provides exemplary antibody sequences consistent with the present disclosure. In this table, all targets correspond to human orthologs unless otherwise specified.

TABLE 1

SEQ ID NO	Description	Sequence
1	Anti-PD-L1 HC	QVQLVQSGAEVKKPGSSVKVSCKTSGDTFSTAAISWV RQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMD VWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
2	Anti-PD-L1 HC v2	QVQLVQSGAEVKKPGSSVKVSCKTSGDTFSTAAISWV RQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMD VWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPG
3	Anti-PD-L1 LALA HC	QVQLVQSGAEVKKPGSSVKVSCKTSGDTFSTAAISWV RQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMD VWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK

4	Anti-PD-L1 LALA HC v2	QVQLVQSGAEVKKPGSSVKVSCKTSGDTFSTAAISWV RQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMD VWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPG
5	Anti-PD-L1 LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQ KPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISS LEPEDFAVYYCQQRSNWPTFGQGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC
6	Anti-PD-L1 (engineered cysteines) LALA HC	QVQLVQSGAEVKKPGSSVKVSCKTSGDTFSTAAISWV RQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMD VWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPEAAGGPCVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
7	Anti-PD-L1 (engineered cysteines) LALA HC v2	QVQLVQSGAEVKKPGSSVKVSCKTSGDTFSTAAISWV RQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMD VWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPEAAGGPCVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPG
8	Anti-PD-L1 mIgG2a LALA HC	QVQLVQSGAEVKKPGSSVKVSCKTSGDTFSTAAISWV RQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMD VWGQGTTVTVSSAKTTAPSVYPLAPVCGDTTGSSVTL GCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLY

		TLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPR GPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSP IVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHR EDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLP APIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGS YFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTT KSFSRTPGK
9	Anti-PD-L1 mIgG2a LALA HC v2	QVQLVQSGAEVKKPGSSVKVSCKTSGDTFSTAAISWV RQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMD VWGQGTTVTVSSAKTTAPSVYPLAPVCGDTTGSSVTL GCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLY TLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPR GPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSP IVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHR EDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLP APIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGS YFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTT KSFSRTPG
10	Anti-PD-L1 mK LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQ KPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISS LEPEDFAVYYCQQRSNWPTFGQGTKVEIKRADAAPT VSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDG SERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYER HNSYTCEATHKTSTSPIVKSFNRNEC
11	Anti-PD-L1 mIgG2a (engineered cysteines) LALA HC	QVQLVQSGAEVKKPGSSVKVSCKTSGDTFSTAAISWV RQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMD VWGQGTTVTVSSAKTTAPSVYPLAPVCGDTTGSSVTL GCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLY TLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPR GPTIKPCPPCKCPAPNAAGGPCVFIFPPKIKDVLMISLS PIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHR EDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLP APIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGS YFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTT KSFSRTPGK
12	Anti-PD-L1 mIgG2a (engineered cysteines) LALA HC v2	QVQLVQSGAEVKKPGSSVKVSCKTSGDTFSTAAISWV RQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMD VWGQGTTVTVSSAKTTAPSVYPLAPVCGDTTGSSVTL GCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLY TLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPR GPTIKPCPPCKCPAPNAAGGPCVFIFPPKIKDVLMISLS PIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHR EDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLP APIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC

		MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGS YFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTT KSFSRTPG
13	Anti-PD-L1 CDR-H1	TAAIS
14	Anti-PD-L1 CDR-H2	GIIPIFGKAHYAQKFQG
15	Anti-PD-L1 CDR-H3	KFHFVSGSPFGMDV
16	Anti-PD-L1 CDR-L1	RASQSVSSYLA
17	Anti-PD-L1 CDR-L2	DASNRAT
18	Anti-PD-L1 CDR-L3	QQRSNWPT
19	Anti-PD-L1 VH	QVQLVQSGAEVKKPGSSVKVSCKTSGDTFSTAAISWV RQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMD VWGQGTTVTVSS
20	Anti-PD-L1 VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQ KPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISS LEPEDFAVYYCQQRSNWPTFGQGTKVEIK
21	Anti-EphA2 CDR-H1	HYMMA
22	Anti-EphA2 CDR-H2	RIGPSGGPTHYADSVKG
23	Anti-EphA2 CDR-H3	YDSGYDYVAVAGPAEYFQH
24	Anti-EphA2 CDR-L1	RASQSISTWLA
25	Anti-EphA2 CDR-L2	KASNLHT
26	Anti-EphA2 CDR-L3	QQYNSYSRT
27	Anti-EphA2 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAW VRQAPGKGLEWVSRIGPSGGPTHYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCAGYDSGYDYVAV AGPAEYFQHWGQGTLVTVSS
28	Anti-EphA2 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQ KPGKAPKLLIYKASNLHTGVPSRFSGSGSGTEFSLTISG LQPDDFATYYCQQYNSYSRTFGQGTKVEIK
29	Anti-EphA2 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAW VRQAPGKGLEWVSRIGPSGGPTHYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCAGYDSGYDYVAV AGPAEYFQHWGQGTLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK
30	Anti-EphA2 HC v2	EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAW VRQAPGKGLEWVSRIGPSGGPTHYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCAGYDSGYDYVAV

		AGPAEYFQHWGQGTLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPG
31	Anti-EphA2 LC	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQ KPGKAPKLLIYKASNLHTGVPSRFSGSGSGTEFSLTISG LQPDDFATYYCQQYNSYSRTFGQGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
32	Anti-EphA2 mIgG2a HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAW VRQAPGKGLEWVSRIGPSGGPTHYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCAGYDSGYDYVAV AGPAEYFQHWGQGTLVTVSSAKTTAPSVYPLAPVCG DTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFP AVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTK VDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKD VLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHT AQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCK VNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTK KQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEP VLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGL HNHHTTKSFSRTPGK
33	Anti-EphA2 mIgG2a HC v2	EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAW VRQAPGKGLEWVSRIGPSGGPTHYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCAGYDSGYDYVAV AGPAEYFQHWGQGTLVTVSSAKTTAPSVYPLAPVCG DTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFP AVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTK VDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKD VLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHT AQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCK VNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTK KQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEP VLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGL HNHHTTKSFSRTPG
34	Anti-EphA2 mIgG2a LC	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQ KPGKAPKLLIYKASNLHTGVPSRFSGSGSGTEFSLTISG LQPDDFATYYCQQYNSYSRTFGQGTKVEIKRADAAPT VSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDG SERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYER HNSYTCEATHKTSTSPIVKSFNRNEC

35	Anti-EphA2 mIgG2a LALAPG HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAW VRQAPGKGLEWVSRIGPSGGPTHYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCAGYDSGYDYVAV AGPAEYFQHWGQGTLVTVSSAKTTAPSVYPLAPVCG DTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFP AVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTK VDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIK DVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVH TAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKC KVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEEEMT KKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTE PVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEG LHNHHTTKSFSRTPGK
36	Anti-EphA2 mIgG2a LALAPG HC v2	EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAW VRQAPGKGLEWVSRIGPSGGPTHYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCAGYDSGYDYVAV AGPAEYFQHWGQGTLVTVSSAKTTAPSVYPLAPVCG DTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFP AVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTK VDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIK DVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVH TAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKC KVNNKDLGAPIERTISKPKGSVRAPQVYVLPPPEEEMT KKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTE PVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEG LHNHHTTKSFSRTPG
37	Anti-EphA2 mIgG2a LALAPG LC	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQ KPGKAPKLLIYKASNLHTGVPSRFSGSGSGTEFSLTISG LQPDDFATYYCQQYNSYSRTFGQGTKVEIKRADAAPT VSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDG SERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYER HNSYTCEATHKTSTSPIVKSFNRNEC
38	Anti-CD30 CDR-H1	DYYIT
39	Anti-CD30 CDR-H2	WIYPGSGNTKYNEKFKG
40	Anti-CD30 CDR-H3	YGNYWFAY
41	Anti-CD30 CDR-L1	KASQSVDFDGDSYMN
42	Anti-CD30 CDR-L2	AASNLES
43	Anti-CD30 CDR-L3	QQSNEDPWT
44	Anti-CD30 VH	QIQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWV KQKPGQGLEWIGWIYPGSGNTKYNEKFKGKATLTVD TSSSTAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQ GTQVTVSA
45	Anti-CD30 VL	DIVLTQSPASLAVSLGQRATISCKASQSVDFDGDSYM NWYQQKPGQPPKVLIYAASNLESGIPARFSGSGSGTDF TLNIHPVEEEDAATYYCQQSNEDPWTFGGGTKLEIK
46	Anti-CD30 HC	QIQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWV KQKPGQGLEWIGWIYPGSGNTKYNEKFKGKATLTVD TSSSTAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQ GTQVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLV

		KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
47	Anti-CD30 HC v2	QIQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWV KQKPGQGLEWIGWIYPGSGNTKYNEKFKGKATLTVD TSSSTAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQ GTQVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG
48	Anti-CD30 LC	DIVLTQSPASLAVSLGQRATISCKASQSVDFDGDSYM NWYQQKPGQPPKVLIYAASNLESGIPARFSGSGSGTDF TLNIHPVEEEDAATYYCQQSNEDPWTFGGGTKLEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
49	Anti-CD228 CDR-H1	SGYWN
50	Anti-CD228 CDR-H2	YISDSGITYYNPSLKS
51	Anti-CD228 CDR-H3	RTLATYYAMDY
52	Anti-CD228 CDR-L1	RASQSLVHSDGNTYLH
53	Anti-CD228 CDR-L2	RVSNRFS
54	Anti-CD228 CDR-L3	SQSTHVPPT
55	Anti-CD228 VH	QVQLQESGPGLVKPSETLSLTCTVSGDSITSGYWNWIR QPPGKGLEYIGYISDSGITYYNPSLKSRVTISRDTSKNQ YSLKLSSVTAADTAVYYCARRTLATYYAMDYWGQG TLVTVSS
56	Anti-CD228 VL	DFVMTQSPLSLPVTLGQPASISCRASQSLVHSDGNTYL HWYQQRPGQSPRLLIYRVSNRFSGVPDRFSGSGSGTD FTLKISRVEAEDVGVYYCSQSTHVPPTFGQGTKLEIK
57	Anti-CD228 HC	QVQLQESGPGLVKPSETLSLTCTVSGDSITSGYWNWIR QPPGKGLEYIGYISDSGITYYNPSLKSRVTISRDTSKNQ YSLKLSSVTAADTAVYYCARRTLATYYAMDYWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI

		EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK
58	Anti-CD228 HC v2	QVQLQESGPGLVKPSETLSLTCTVSGDSITSGYWNWIR QPPGKGLEYIGYISDSGITYYNPSLKSRVTISRDTSKNQ YSLKLSSVTAADTAVYYCARRTLATYYAMDYWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG
59	Anti-CD228 LC	DFVMTQSPLSLPVTLGQPASISCRASQSLVHSDGNTYL HWYQQRPGQSPRLLIYRVSNRFSGVPDRFSGSGSGTD FTLKISRVEAEDVGVYYCSQSTHVPPTFGQGTKLEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
60	Anti-CD228 LALAKA HC	QVQLQESGPGLVKPSETLSLTCTVSGDSITSGYWNWIR QPPGKGLEYIGYISDSGITYYNPSLKSRVTISRDTSKNQ YSLKLSSVTAADTAVYYCARRTLATYYAMDYWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK THTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK
61	Anti-CD228 LALAKA HC v2	QVQLQESGPGLVKPSETLSLTCTVSGDSITSGYWNWIR QPPGKGLEYIGYISDSGITYYNPSLKSRVTISRDTSKNQ YSLKLSSVTAADTAVYYCARRTLATYYAMDYWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK THTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG

62	Anti-CD228 LALAKA LC	DFVMTQSPLSLPVTLGQPASISCRASQSLVHSDGNTYL HWYQQRPGQSPRLLIYRVSNRFSGVPDRFSGSGSGTD FTLKISRVEAEDVGVYYCSQSTHVPPTFGQGTKLEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
63	Anti-avB6 HC CDR-H1	DYNVN
64	Anti-AvB6 HC CDR-H2	VINPKYGTTRYNQKFKG
65	Anti-AvB6 HC CDR-H3	GLNAWDY
66	Anti-AvB6 LG CDR-L1	GASENIYGALN
67	Anti-AvB6 LG CDR-L2	GATNLED
68	Anti-AvB6 LG CDR-L3	QNVLTTPYT
69	Anti-AvB6 HC VH	QFQLVQSGAEVKKPGASVKVSCKASGYSFTDYNVNW VRQAPGQGLEWIGVINPKYGTTRYNQKFKGRATLTV DKSTSTAYMELSSLRSEDTAVYYCTRGLNAWDYWG QGTLVTVSS
70	Anti-AvB6 LG VL	DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQ QKPGKAPKLLIYGATNLEDGVPSRFSGSGSGRDYTFTI SSLQPEDIATYYCQNVLTTPYTFGQGTKLEIK
71	Anti-AvB6 HC	QFQLVQSGAEVKKPGASVKVSCKASGYSFTDYNVNW VRQAPGQGLEWIGVINPKYGTTRYNQKFKGRATLTV DKSTSTAYMELSSLRSEDTAVYYCTRGLNAWDYWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
72	Anti-AvB6 HC v2	QFQLVQSGAEVKKPGASVKVSCKASGYSFTDYNVNW VRQAPGQGLEWIGVINPKYGTTRYNQKFKGRATLTV DKSTSTAYMELSSLRSEDTAVYYCTRGLNAWDYWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF

		FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG
73	Anti-AvB6 LG LC	DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQ QKPGKAPKLLIYGATNLEDGVPSRFSGSGSGRDYTFTI SSLQPEDIATYYCQNVLTTPYTFGQGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
74	Anti-AvB6 LALAKA HC	QFQLVQSGAEVKKPGASVKVSCKASGYSFTDYNVNW VRQAPGQGLEWIGVINPKYGTTRYNQKFKGRATLTV DKSTSTAYMELSSLRSEDTAVYYCTRGLNAWDYWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
75	Anti-AvB6 LALAKA HC v2	QFQLVQSGAEVKKPGASVKVSCKASGYSFTDYNVNW VRQAPGQGLEWIGVINPKYGTTRYNQKFKGRATLTV DKSTSTAYMELSSLRSEDTAVYYCTRGLNAWDYWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG
76	Anti-AvB6 LG LALAKA LC	DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQ QKPGKAPKLLIYGATNLEDGVPSRFSGSGSGRDYTFTI SSLQPEDIATYYCQNVLTTPYTFGQGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
77	Anti-B7H4 CDR-H1	SGSYYWG
78	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLRS
79	Anti-B7H4 CDR-H3	EGSYPNQFDP
80	Anti-B7H4 CDR-L1	RASQSVSSNLA
81	Anti-B7H4 CDR-L2	GASTRAT
82	Anti-B7H4 CDR-L3	QQYHSFPFT
83	Anti-B7H4 VH	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSYYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLRSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYPNQFDPWG QGTLVTVSS

84	Anti-B7H4 VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIK
85	Anti-B7H4 HC	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSYYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLRSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYPNQFDPWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
86	Anti-B7H4 HC v2	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSYYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLRSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYPNQFDPWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG
87	Anti-B7H4 LC	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
88	Anti-B7H4 LALAKA HC	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSYYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLRSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYPNQFDPWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
89	Anti-B7H4 LALAKA HC v2	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSYYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLRSRVTISVDT

		SKNQFSLKLSSVTAADTAVYYCAREGSYPNQFDPWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG
90	Anti-B7H4 LALAKA LC	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
91	Anti-B7H4 CDR-H1	GSISSSSYYWG
92	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLKS
93	Anti-B7H4 CDR-H3	AREGSYPNWFDP
94	Anti-B7H4 CDR-L1	RASQSVSSNLA
95	Anti-B7H4 CDR-L2	GASTRAT
96	Anti-B7H4 CDR-L3	QQYHSFPFT
97	Anti-B7H4 VH	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGW IRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDTSK NQFSLKLSSVTAADTAVYYCAREGSYPNWFDPWGQG TLVTVSS
98	Anti-B7H4 VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIK
99	Anti-B7H4 CDR-H1	GSIKSGSHYWG
100	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLRS
101	Anti-B7H4 CDR-H3	AREGSYPNWFDP
102	Anti-B7H4 CDR-L1	RASQSVSSNLA
103	Anti-B7H4 CDR-L2	GASTRAT
104	Anti-B7H4 CDR-L3	QQYHSFPFT
105	Anti-B7H4 VH	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLRSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYPNWFDPWG QGTLVTVSS
106	Anti-B7H4 VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIK
107	Anti-B7H4 CDR-H1	GSIKSGSHYWG
108	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLKS
109	Anti-B7H4 CDR-H3	AREGSYPNWLDP
110	Anti-B7H4 CDR-L1	RASQSVSSNLA
111	Anti-B7H4 CDR-L2	GASTRAT
112	Anti-B7H4 CDR-L3	QQYHSFPFT

113	Anti-B7H4 VH	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYPNWLDPWG QGTLVTVSS
114	Anti-B7H4 VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIK
115	Anti-B7H4 CDR-H1	GSIKSGSYYWG
116	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLKS
117	Anti-B7H4 CDR-H3	AREGSYPNQFDP
118	Anti-B7H4 CDR-L1	RASQSVSSNLA
119	Anti-B7H4 CDR-L2	GASTRAT
120	Anti-B7H4 CDR-L3	QQYHSFPFT
121	Anti-B7H4 VH	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSYYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYPNQFDPWG QGILVTVSS
122	Anti-B7H4 VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIK
123	Anti-B7H4 CDR-H1	GSIKSGSHYWG
124	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLKS
125	Anti-B7H4 CDR-H3	AREGSYPNWFDP
126	Anti-B7H4 CDR-L1	RASQSVSTNLA
127	Anti-B7H4 CDR-L2	DASARVT
128	Anti-B7H4 CDR-L3	QQYHSFPFT
129	Anti-B7H4 VH	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTMSVD TSKNQFSLKLSSVTAADTAVYYCAREGSYPNWFDPW GQGTLVTVSS
130	Anti-B7H4 VL	EIVMTQSPATLSVSPGERATLSCRASQSVSTNLAWYQ QKPGQAPRLLIYDASARVTGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIK
131	Anti-B7H4 CDR-H1	GSISSSSYYWG
132	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLKS
133	Anti-B7H4 CDR-H3	AREGSYTTVLNV
134	Anti-B7H4 CDR-L1	RASQSVSSSYLA
135	Anti-B7H4 CDR-L2	GASSRAT
136	Anti-B7H4 CDR-L3	QQAASYPLT
137	Anti-B7H4 VH	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGW IRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDTSK NQFSLKLSSVTAADTAVYYCAREGSYTTVLNVWGQG TMVTVSS
138	Anti-B7H4 VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQ QKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTIS RLEPEDFAVYYCQQAASYPLTFGGGTKVEIK
139	Anti-B7H4 CDR-H1	GSIGRGSYYWG
140	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLKS
141	Anti-B7H4 CDR-H3	AREGSYTTVLNV

142	Anti-B7H4 CDR-L1	RASQSVASSHLA
143	Anti-B7H4 CDR-L2	DAVSRAT
144	Anti-B7H4 CDR-L3	QQAASYPLT
145	Anti-B7H4 VH	QLQLQESGPGLVKPSETLSLTCTVSGGSIGRGSYYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYTTVLNVWG QGTMVTVSS
146	Anti-B7H4 VL	EIVLTQSPGTLSLSPGERATLSCRASQSVASSHLAWYQ QKPGQAPRLLIYDAVSRATGIPDRFSGSGSGTDFTLTIS RLEPEDFAVYYCQQAASYPLTFGGGTKVEIK
147	Anti-B7H4 CDR-H1	GSISSGGYYWS
148	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLKS
149	Anti-B7H4 CDR-H3	ARESSTISADFDL
150	Anti-B7H4 CDR-L1	RASQGISRWLA
151	Anti-B7H4 CDR-L2	AASSLQS
152	Anti-B7H4 CDR-L3	QQAHTFPYT
153	Anti-B7H4 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWS WIRQHPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARESSTISADFDLWG RGTLVTVSS
154	Anti-B7H4 VL	DIQMTQSPSSVSASVGDRVTITCRASQGISRWLAWYQ QKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQAHTFPYTFGGGTKVEIK
155	Anti-B7H4 CDR-H1	GSISHGGYYWS
156	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLKS
157	Anti-B7H4 CDR-H3	ARESSTISADFDL
158	Anti-B7H4 CDR-L1	RASQGISRWLA
159	Anti-B7H4 CDR-L2	AASSLQS
160	Anti-B7H4 CDR-L3	QQAHTFPYT
161	Anti-B7H4 VH	QLQLQESGPGLVKPSETLSLTCTASGGSISHGGYYWS WIRQHPGKGLEWIGNIYYSGSTYYNPSLKSRVTMSVD TSKNQFSLKLSSVTAADTAVYYCARESSTISADFDLW GRGTLVTVSS
162	Anti-B7H4 VL	DIQMTQSPSSVSASVGDRVTITCRASQGISRWLAWYQ QKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQAHTFPYTFGGGTKVEIK
163	Anti-B7H4 CDR-H1	GSISSGGYYWS
164	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLKS
165	Anti-B7H4 CDR-H3	ARGLSTIDEAFDP
166	Anti-B7H4 CDR-L1	RASQSISSWLA
167	Anti-B7H4 CDR-L2	KASSLES
168	Anti-B7H4 CDR-L3	QQDNSYPYT
169	Anti-B7H4 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWS WIRQHPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARGLSTIDEAFDPWG QGTLVTVSS
170	Anti-B7H4 VL	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQDNSYPYTFGGGTKVEIK

171	Anti-B7H4 CDR-H1	GSISDGSYYWS
172	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLRS
173	Anti-B7H4 CDR-H3	ARGLSTIDEAFDP
174	Anti-B7H4 CDR-L1	RASQSISSWLA
175	Anti-B7H4 CDR-L2	KASSLES
176	Anti-B7H4 CDR-L3	QQDNSYPYT
177	Anti-B7H4 VH	QLQLQESGPGLVKPSETLSLTCTVSGGSISDGSYYWS WIRQHPGKGLEWIGNIYYSGSTYYNPSLRSRVTMSVD TSKNQFSLKLSSVTAADTAVYYCARGLSTIDEAFDPW GQGTLVTVSS
178	Anti-B7H4 VL	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQDNSYPYTFGGGTKVEIK
179	Anti-B7H4 CDR-H1	GSISDGSYYWS
180	Anti-B7H4 CDR-H2	NIYYSGSTYYNPSLRS
181	Anti-B7H4 CDR-H3	ARGLSTIDEAFDP
182	Anti-B7H4 CDR-L1	RASKSISSWLA
183	Anti-B7H4 CDR-L2	EASSLHS
184	Anti-B7H4 CDR-L3	QQDNSYPYT
185	Anti-B7H4 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISDGSYYWS WIRQHPGKGLEWIGNIYYSGSTYYNPSLRSRVTMSVD TSKNQFSLKLSSVTAADTAVYYCARGLSTIDEAFDPW GQGTLVTVSS
186	Anti-B7H4 VL	DIQMTQSPSTLSASVGDRVTITCRASKSISSWLAWYQQ KPGKAPKLLIYEASSLHSGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQDNSYPYTFGGGTKVEIK
187	Anti-B7H4 CDR-H1	GSISSYYWS
188	Anti-B7H4 CDR-H2	YIYSSGSTNYNPSLKS
189	Anti-B7H4 CDR-H3	ARGSGQYAAPDYGMD
190	Anti-B7H4 CDR-L1	RASQSISSWLA
191	Anti-B7H4 CDR-L2	KASSLES
192	Anti-B7H4 CDR-L3	QQDNSFPFT
193	Anti-B7H4 VH	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIR QPPGKGLEWIGYIYSSGSTNYNPSLKSRVTISVDTSKN QFSLKLSSVTAADTAVYYCARGSGQYAAPDYGMDV WGQGTTVTVSS
194	Anti-B7H4 VL	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQDNSFPFTFGGGTKVEIK
195	Anti-B7H4 CDR-H1	GSIISYYWG
196	Anti-B7H4 CDR-H2	YIYSSGSTSYNPSLKS
197	Anti-B7H4 CDR-H3	ARGSGLYAAPDYGLDV
198	Anti-B7H4 CDR-L1	RASQSISSWLA
199	Anti-B7H4 CDR-L2	KASSLES
200	Anti-B7H4 CDR-L3	QQDNSFPFT
201	Anti-B7H4 VH	QVQLQESGPGLVKPSETLSLTCTVSGGSIISYYWGWIR QPPGKGLEWIGYIYSSGSTSYNPSLKSRVTISVDTSKN QFSLKLSSVTAADTAVYYCARGSGLYAAPDYGLDVW GQGTTVTVSS

202	Anti-B7H4 VL	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQDNSFPFTFGGGTKVEIK
203	Anti-B7H4 CDR-H1	FTFSSYAMS
204	Anti-B7H4 CDR-H2	TISGSGGSTYYADSVKG
205	Anti-B7H4 CDR-H3	ARGAGHYDLVGRY
206	Anti-B7H4 CDR-L1	RASQSISSYLN
207	Anti-B7H4 CDR-L2	AASSLQS
208	Anti-B7H4 CDR-L3	QQLYSLPPT
209	Anti-B7H4 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSTISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGAGHYDLVGRY WGQGTLVTVSS
210	Anti-B7H4 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQLYSLPPTFGGGTKVEIK
211	Anti-B7H4 CDR-H1	FTFSSYAMS
212	Anti-B7H4 CDR-H2	AISGSGGSTYYADSVKG
213	Anti-B7H4 CDR-H3	ARVGFRALNY
214	Anti-B7H4 CDR-L1	RASQDISSWLA
215	Anti-B7H4 CDR-L2	AASSLQS
216	Anti-B7H4 CDR-L3	QQATSYPPWT
217	Anti-B7H4 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARVGFRALNYWGQ GTTVTVSS
218	Anti-B7H4 VL	DIQLTQSPSSVSASVGDRVTITCRASQDISSWLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQATSYPPWTFGGGTKVEIK
219	Anti-B7H4 CDR-H1	GTFSSYAIS
220	Anti-B7H4 CDR-H2	GIIPIFGTASYAQKFQG
221	Anti-B7H4 CDR-H3	ARQQYDGRRYFGL
222	Anti-B7H4 CDR-L1	RASQSVSSNLA
223	Anti-B7H4 CDR-L2	SASTRAT
224	Anti-B7H4 CDR-L3	QQVNVWPPT
225	Anti-B7H4 VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTASYAQKFQGRVTITADES TSTAYMELSSLRSEDTAVYYCARQQYDGRRYFGLWG RGTLVTVSS
226	Anti-B7H4 VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYSASTRATGIPARFSGSGSGTEFTLTISS LQSEDFAVYYCQQVNVWPPTFGGGTKVEIK
227	Anti-B7H4 CDR-H1	GTFSSYAIS
228	Anti-B7H4 CDR-H2	GIIPIFGTANYAQKFQG
229	Anti-B7H4 CDR-H3	ARGGPWFDP
230	Anti-B7H4 CDR-L1	RASQSISSWLA
231	Anti-B7H4 CDR-L2	KASSLES
232	Anti-B7H4 CDR-L3	QQYNSYPPFT

233	Anti-B7H4 VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARGGPWFDPWGQGT LVTVSS
234	Anti-B7H4 VL	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQYNSYPPFTFGGGTKVEIK
235	Anti-B7H4 CDR-H1	FTFSSYAMS
236	Anti-B7H4 CDR-H2	AISGSGGSTSYADSVKG
237	Anti-B7H4 CDR-H3	AKPSLATMLAFDI
238	Anti-B7H4 CDR-L1	RASQSISSWLA
239	Anti-B7H4 CDR-L2	DASSLES
240	Anti-B7H4 CDR-L3	QQSKSYPRT
241	Anti-B7H4 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSAISGSGGSTSYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKPSLATMLAFDIW GQGTMVTVSS
242	Anti-B7H4 VL	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYDASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQSKSYPRTFGGGTKVEIK
243	Anti-B7H4 CDR-H1	GSISSSVYYWS
244	Anti-B7H4 CDR-H2	SILVSGSTYYNPSLKS
245	Anti-B7H4 CDR-H3	ARAVSFLDV
246	Anti-B7H4 CDR-L1	RASQSISSYLN
247	Anti-B7H4 CDR-L2	GASSLQS
248	Anti-B7H4 CDR-L3	QQSYDPPWT
249	Anti-B7H4 VH	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSVYYWSW IRQPPGKGLEWIGSILVSGSTYYNPSLKSRVTISVDTSK NQFSLKLSSVTAADTAVYYCARAVSFLDVWGQGTM VIVSS
250	Anti-B7H4 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQ KPGKAPKLLIYGASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQSYDPPWTFGGGTKVEIK
251	Anti-B7H4 HC	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGW IRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDTSK NQFSLKLSSVTAADTAVYYCAREGSYPNWFDPWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK
252	Anti-B7H4 LC	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV

		DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
253	Anti-B7H4 HC	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLRSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYPNWFDPWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
254	Anti-B7H4 LC	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
255	Anti-B7H4 HC	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYPNWLDPWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
256	Anti-B7H4 LC	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
257	Anti-B7H4 HC	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSYYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYPNQFDPWG QGILVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC

		LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
258	Anti-B7H4 LC	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
259	Anti-B7H4 HC	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTMSVD TSKNQFSLKLSSVTAADTAVYYCAREGSYPNWFDPW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
260	Anti-B7H4 LC	EIVMTQSPATLSVSPGERATLSCRASQSVSTNLAWYQ QKPGQAPRLLIYDASARVTGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYHSFPFTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
261	Anti-B7H4 HC	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGW IRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDTSK NQFSLKLSSVTAADTAVYYCAREGSYTTVLNVWGQG TMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
262	Anti-B7H4 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQ QKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTIS RLEPEDFAVYYCQQAASYPLTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
263	Anti-B7H4 HC	QLQLQESGPGLVKPSETLSLTCTVSGGSIGRGSYYWG WIRQPPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREGSYTTVLNVWG

		QGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
264	Anti-B7H4 LC	EIVLTQSPGTLSLSPGERATLSCRASQSVASSHLAWYQ QKPGQAPRLLIYDAVSRATGIPDRFSGSGSGTDFTLTIS RLEPEDFAVYYCQQAASYPLTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
265	Anti-B7H4 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWS WIRQHPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARESSTISADFDLWG RGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
266	Anti-B7H4 LC	DIQMTQSPSSVSASVGDRVTITCRASQGISRWLAWYQ QKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQAHTFPYTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
267	Anti-B7H4 HC	QLQLQESGPGLVKPSETLSLTCTASGGSISHGGYYWS WIRQHPGKGLEWIGNIYYSGSTYYNPSLKSRVTMSVD TSKNQFSLKLSSVTAADTAVYYCARESSTISADFDLW GRGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
268	Anti-B7H4 LC	DIQMTQSPSSVSASVGDRVTITCRASQGISRWLAWYQ QKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS

		SLQPEDFATYYCQQAHTFPYTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
269	Anti-B7H4 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWS WIRQHPGKGLEWIGNIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARGLSTIDEAFDPWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
270	Anti-B7H4 LC	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQDNSYPYTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
271	Anti-B7H4 HC	QLQLQESGPGLVKPSETLSLTCTVSGGSISDGSYYWS WIRQHPGKGLEWIGNIYYSGSTYYNPSLRSRVTMSVD TSKNQFSLKLSSVTAADTAVYYCARGLSTIDEAFDPW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
272	Anti-B7H4 LC	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQDNSYPYTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
273	Anti-B7H4 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISDGSYYWS WIRQHPGKGLEWIGNIYYSGSTYYNPSLRSRVTMSVD TSKNQFSLKLSSVTAADTAVYYCARGLSTIDEAFDPW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE

		EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
274	Anti-B7H4 LC	DIQMTQSPSTLSASVGDRVTITCRASKSISSWLAWYQQ KPGKAPKLLIYEASSLHSGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQDNSYPYTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
275	Anti-B7H4 HC	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIR QPPGKGLEWIGYIYSSGSTNYNPSLKSRVTISVDTSKN QFSLKLSSVTAADTAVYYCARGSGQYAAPDYGMDV WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK
276	Anti-B7H4 LC	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQDNSFPFTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
277	Anti-B7H4 HC	QVQLQESGPGLVKPSETLSLTCTVSGGSIISYYWGWIR QPPGKGLEWIGYIYSSGSTSYNPSLKSRVTISVDTSKN QFSLKLSSVTAADTAVYYCARGSGLYAAPDYGLDVW GQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
278	Anti-B7H4 LC	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQDNSFPFTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC

279	Anti-B7H4 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSTISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGAGHYDLVGRY WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK
280	Anti-B7H4 LC	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQLYSLPPTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
281	Anti-B7H4 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARVGFRALNYWGQ GTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
282	Anti-B7H4 LC	DIQLTQSPSSVSASVGDRVTITCRASQDISSWLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQATSYPPWTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
283	Anti-B7H4 HC	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTASYAQKFQGRVTITADES TSTAYMELSSLRSEDTAVYYCARQQYDGRRYFGLWG RGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF

		FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
284	Anti-B7H4 LC	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLLIYSASTRATGIPARFSGSGSGTEFTLTISS LQSEDFAVYYCQQVNVWPPTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
285	Anti-B7H4 HC	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARGGPWFDPWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
286	Anti-B7H4 LC	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQYNSYPPFTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
287	Anti-B7H4 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSAISGSGGSTSYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKPSLATMLAFDIW GQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
288	Anti-B7H4 LC	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQ KPGKAPKLLIYDASSLESGVPSRFSGSGSGTEFTLTISS LQPDDFATYYCQQSKSYPRTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
289	Anti-B7H4 HC	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSVYYWSW IRQPPGKGLEWIGSILVSGSTYYNPSLKSRVTISVDTSK NQFSLKLSSVTAADTAVYYCARAVSFLDVWGQGTM VIVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT

		VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
290	Anti-B7H4 LC	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQ KPGKAPKLLIYGASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQSYDPPWTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
291	Anti-CD70 CDR-H1	NYGMN
292	Anti-CD70CDR-H2	WINTYTGEPTYADAFKG
293	Anti-CD70 CDR-H3	DYGDYGMDY
294	Anti-CD70 CDR-L1	RASKSVSTSGYSFMH
295	Anti-CD70 CDR-L2	LASNLES
296	Anti-CD70 CDR-L3	QHSREVPWT
297	Anti-CD70 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMN WVRQAPGQGLKWMGWINTYTGEPTYADAFKGRVT MTRDTSISTAYMELSRLRSDDTAVYYCARDYGDYGM DYWGQGTTVTVSS
298	Anti-CD70 VL	DIVMTQSPDSLAVSLGERATINCRASKSVSTSGYSFMH WYQQKPGQPPKLLIYLASNLESGVPDRFSGSGSGTDF TLTISSLQAEDVAVYYCQHSREVPWTFGQGTKVEIK
299	Anti-CD70 HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMN WVRQAPGQGLKWMGWINTYTGEPTYADAFKGRVT MTRDTSISTAYMELSRLRSDDTAVYYCARDYGDYGM DYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK
300	Anti-CD70 LC	DIVMTQSPDSLAVSLGERATINCRASKSVSTSGYSFMH WYQQKPGQPPKLLIYLASNLESGVPDRFSGSGSGTDF TLTISSLQAEDVAVYYCQHSREVPWTFGQGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
301	Anti-TROP2 CDR-H1	NYGMN
302	Anti-TROP2 CDR-H2	WINTYTGEPTYTDDFKG
303	Anti-TROP2 CDR-H3	GGFGSSYWYFDV
304	Anti-TROP2 CDR-L1	KASQDVSIAVA
305	Anti-TROP2 CDR-L2	SASYRYT

306	Anti-TROP2 CDR-L3	QQHYITPLT
307	Anti-TROP2 VH	QVQLQQSGSELKKPGASVKVSCKASGYTFTNYGMN WVKQAPGQGLKWMGWINTYTGEPTYTDDFKGRFAF SLDTSVSTAYLQISSLKADDTAVYFCARGGFGSSYWY FDVWGQGSLVTVSS
308	Anti-TROP2 VL	DIQLTQSPSSLSASVGDRVSITCKASQDVSIAVAWYQQ KPGKAPKLLIYSASYRYTGVPDRFSGSGSGTDFTLTISS LQPEDFAVYYCQQHYITPLTFGAGTKVEIK
309	Anti-TROP2 CDR-H1	TAGMQ
310	Anti-TROP2 CDR-H2	WINTHSGVPKYAEDFKG
311	Anti-TROP2 CDR-H3	SGFGSSYWYFDV
312	Anti-TROP2 CDR-L1	KASQDVSTAVA
313	Anti-TROP2 CDR-L2	SASYRYT
314	Anti-TROP2 CDR-L3	QQHYITPLT
315	Anti-TROP2 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTTAGMQ WVRQAPGQGLEWMGWINTHSGVPKYAEDFKGRVTIS ADTSTSTAYLQLSSLKSEDTAVYYCARSGFGSSYWYF DVWGQGTLVTVSS
316	Anti-TROP2 VL	DIQMTQSPSSLSASVGDRVTITCKASQDVSTAVAWYQ QKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLTIS SLQPEDFAVYYCQQHYITPLTFGQGTKLEIK
317	MICA CDR-H1	SQNIY
318	MICA CDR-H2	YIEPYNVVPMYNPKFKG
319	MICA CDR-H3	SGSSNFDY
320	MICA CDR-L1	SASSSISSHYLH
321	MICA CDR-L2	RTSNLAS
322	MICA CDR-L3	QQGSSLPLT
323	Anti-MICA VH	EIQLVQSGAEVKKPGASVKVSCKASGYAFTSQNIYWV RQAPGQGLEWIGYIEPYNVVPMYNPKFKGRATLTVD KSTSTAYLELSSLRSEDTAVYYCARSGSSNFDYWGQG TLVTVSS
324	Anti-MICA VL	DIQLTQSPSSLSASVGDRVTITCSASSSISSHYLHWYQQ KPGKSPKLLIYRTSNLASGVPSRFSGSGSGTDYTLTISS LQPEDFATYYCQQGSSLPLTFGQGTKVEIK
325	Anti-MICA CDR-H1	NYAMH
326	Anti-MICA CDR-H2	LIWYDGSNKFYGDSVKG
327	Anti-MICA CDR-H3	EGSGHY
328	Anti-MICA CDR-L1	RASQGISSALA
329	Anti-MICA CDR-L2	DASSLES
330	Anti-MICA CDR-L3	QQFNSYPIT
331	Anti-MICA VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYAMHW VRQAPGEGLEWVALIWYDGSNKFYGDSVKGRFTISR DNSKNTLYLQMNSLSAEDTAVYYCAREGSGHYWGQ GTLVTVSS
332	Anti-MICA VL	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQ KPGKVPKSLIYDASSLESGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQFNSYPITFGQGTRLEIK
333	Anti-MICA CDR-H1	NYAMS
334	Anti-MICA CDR-H2	YISPGGDYIYYADSVKG

335	Anti-MICA CDR-H3	DRRHYGSYAMDY
336	Anti-MICA CDR-L1	RSSKSLLHSNLNTYLY
337	Anti-MICA CDR-L2	RMSNLAS
338	Anti-MICA CDR-L3	MQHLEYPFT
339	Anti-MICA VH	QVQLVESGGGLVKPGGSLRLSCAASGFTFSNYAMSWI RQAPGKGLEWVSYISPGGDYIYYADSVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCTTDRRHYGSYAMD YWGQGTLVTVSS
340	Anti-MICA VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLLHSNLNTYLY WFLQKPGQSPQILIYRMSNLASGVPDRFSGSGSGTAFT LKISRVEAEDVGVYYCMQHLEYPFTFGPGTKLEIK
341	Anti-MICA CDR-H1	TYAFH
342	Anti-MICA CDR-H2	GIVPIFGTLKYAQKFQD
343	Anti-MICA CDR-H3	AIQLEGRPFDH
344	Anti-MICA CDR-L1	RASQGITSYLA
345	Anti-MICA CDR-L2	AASALQS
346	Anti-MICA CDR-L3	QQVNRGAAIT
347	Anti-MICA VH	QVQLVQSGAEVKKPGSSVRVSCRASGGSSTTYAFHW VRQAPGQGLEWMGGIVPIFGTLKYAQKFQDRVTLTA DKSTGTAYMELNSLRLDDTAVYYCARAIQLEGRPFD HWGQGTQVTVSA
348	Anti-MICA VL	DIQLTQSPSFLSASVGDRVTITCRASQGITSYLAWYQQ KPGKAPKLLIYAASALQSGVPSRFSGRGSGTEFTLTISS LQPEDFATYYCQQVNRGAAITFGHGTRLDIK
349	Anti-ITGav/CD51 CDR-H1	RYTMH
350	Anti-ITGav/CD51 CDR-H2	VISFDGSNKYYVDSVKG
351	Anti-ITGav/CD51 CDR-H3	EARGSYAFDI
352	Anti-ITGav/CD51 CDR-L1	RASQSVSSYLA
353	Anti-ITGav/CD51 CDR-L2	DASNRAT
354	Anti-ITGav/CD51 CDR-L3	QQRSNWPPFT
355	Anti-ITGav/CD51 VH	QVQLVESGGGVVQPGRSRRLSCAASGFTFSRYTMHW VRQAPGKGLEWVAVISFDGSNKYYVDSVKGRFTISRD NSENTLYLQVNILRAEDTAVYYCAREARGSYAFDIWG QGTMVTVSS
356	Anti-ITGav/CD51 VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQ KPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISS LEPEDFAVYYCQQRSNWPPFTFGPGTKVDIK
357	Anti-ITGav CDR-H1	SFWMH
358	Anti-ITGav CDR-H2	YINPRSGYTEYNEIFRD
359	Anti-ITGav CDR-H3	FLGRGAMDY
360	Anti-ITGav CDR-L1	RASQDISNYLA
361	Anti-ITGav CDR-L2	YTSKIHS
362	Anti-ITGav CDR-L3	QQGNTFPYT

363	Anti-ITGav VH	QVQLQQSGGELAKPGASVKVSCKASGYTFSSFWMH WVRQAPGQGLEWIGYINPRSGYTEYNEIFRDKATMTT DTSTSTAYMELSSLRSEDTAVYYCASFLGRGAMDYW GQGTTVTVSS
364	Anti-ITGav VL	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQ QKPGKAPKLLIYYTSKIHSGVPSRFSGSGSGTDYTFTIS SLQPEDIATYYCQQGNTFPYTFGQGTKVEIK
365	Anti-gpA33 CDR-H1	TSSYYWG
366	Anti-gpA33 CDR-H2	TIYYNGSTYYSPSLKS
367	Anti-gpA33 CDR-H3	QGYDIKINIDV
368	Anti-gpA33 CDR-L1	RASQSVSSYLA
369	Anti-gpA33 CDR-L2	VASNRAT
370	Anti-gpA33 CDR-L3	QQRSNWPLT
371	Anti-gpA33 VH	QLQLQESGPGLVKPSETLSLTCTVSGGSISTSSYYWGW IRQPPGKGLEWIGTIYYNGSTYYSPSLKSRVSISVDTSK NQFSLKLSSVTAADTSVYYCARQGYDIKINIDVWGQG TTVTVSS
372	Anti-gpA33 VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQ KPGQAPRLLIYVASNRATGIPARFSGSGSGTDFTLTISS LEPEDFAVYYCQQRSNWPLTFGGGTKVEIK
373	Anti-IL1Rap CDR-H1	SSWMN
374	Anti-IL1Rap CDR-H2	RIYPGDGNTHYAQKFQG
375	Anti-IL1Rap CDR-H3	GYLDPMDY
376	Anti-IL1Rap CDR-L1	QASQGINNYLN
377	Anti-IL1Rap CDR-L2	YTSGLHA
378	Anti-IL1Rap CDR-L3	QQYSILPWT
379	Anti-IL1Rap VH	QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSSWMN WVRQAPGQGLEWMGRIYPGDGNTHYAQKFQGRVTL TADKSTSTAYMELSSLRSEDTAVYYCGEGYLDPMDY WGQGTLVTVSS
380	Anti-IL1Rap VL	DIQMTQSPSSLSASVGDRVTITCQASQGINNYLNWYQ QKPGKAPKLLIHYTSGLHAGVPSRFSGSGSGTDYTLTI SSLEPEDVATYYCQQYSILPWTFGGGTKVEIK
381	Anti-EpCAM CDR-H1	SYGMH
382	Anti-EpCAM CDR-H2	VISYDGSNKYYADSVKG
383	Anti-EpCAM CDR-H3	DMGWGSGWRPYYYYGMDV
384	Anti-EpCAM CDR-L1	RTSQSISSYLN
385	Anti-EpCAM CDR-L2	WASTRES
386	Anti-EpCAM CDR-L3	QQSYDIPYT
387	Anti-EpCAM VH	EVQLLESGGGVVQPGRSLRLSCAASGFTFSSYGMHW VRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYCAKDMGWGSGW RPYYYYGMDVWGQGTTVTVSS
388	Anti-EpCAM VL	ELQMTQSPSSLSASVGDRVTITCRTSQSISSYLNWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISS LQPEDSATYYCQQSYDIPYTFGQGTKLEIK
389	Anti-EpCAM CDR-H1	NYWMS
390	Anti-EpCAM CDR-H2	NIKQDGSEKFYADSVKG
391	Anti-EpCAM CDR-H3	VGPSWEQDY

392	Anti-EpCAM CDR-L1	TGSSSNIGSYYGVH
393	Anti-EpCAM CDR-L2	SDTNRPS
394	Anti-EpCAM CDR-L3	QSYDKGFGHRV
395	Anti-EpCAM VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMSW VRQAPGKGLEWVANIKQDGSEKFYADSVKGRFTISRD NAKNSLYLQMNSLRAEDTAVYYCARVGPSWEQDYW GQGTLVTVSA
396	Anti-EpCAM VL	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGSYYGVHWY QQLPGTAPKLLIYSDTNRPSGVPDRFSGSKSGTSASLAI TGLQAEDEADYYCQSYDKGFGHRVFGGGTKLTVL
397	Anti-EpCAM CDR-H1	SYAIS
398	Anti-EpCAM CDR-H2	GIIPIFGTANYAQKFQG
399	Anti-EpCAM CDR-H3	GLLWNY
400	Anti-EpCAM CDR-L1	RASQSVSSNLA
401	Anti-EpCAM CDR-L2	GASTTAS
402	Anti-EpCAM CDR-L3	QQYNNWPPAYT
403	Anti-EpCAM VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARGLLWNYWGQGTL VTVSS
404	Anti-EpCAM VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQ QKPGQAPRLIIYGASTTASGIPARFSASGSGTDFTLTISS LQSEDFAVYYCQQYNNWPPAYTFGQGTKLEIK
405	Anti-EpCAM CDR-H1	NYGMN
406	Anti-EpCAM CDR-H2	WINTYTGEPTYGEDFKG
407	Anti-EpCAM CDR-H3	FGNYVDY
408	Anti-EpCAM CDR-L1	RSSKNLLHSNGITYLY
409	Anti-EpCAM CDR-L2	QMSNLAS
410	Anti-EpCAM CDR-L3	AQNLEIPRT
411	Anti-EpCAM VH	QVQLVQSGPEVKKPGASVKVSCKASGYTFTNYGMN WVRQAPGQGLEWMGWINTYTGEPTYGEDFKGRFAFS LDTSASTAYMELSSLRSEDTAVYFCARFGNYVDYWG QGSLVTVSS
412	Anti-EpCAM VL	DIVMTQSPLSLPVTPGEPASISCRSSKNLLHSNGITYLY WYLQKPGQSPQLLIYQMSNLASGVPDRFSSSGSGTDF TLKISRVEAEDVGVYYCAQNLEIPRTFGQGTKVEIK
413	Anti-EpCAM CDR-H1	KYGMN
414	Anti-EpCAM CDR-H2	WINTYTEEPTYGDDFKG
415	Anti-EpCAM CDR-H3	FGSAVDY
416	Anti-EpCAM CDR-L1	RSSKSLLHSNGITYLY
417	Anti-EpCAM CDR-L2	QMSNRAS
418	Anti-EpCAM CDR-L3	AQNLELPRT
419	Anti-EpCAM VH	QIQLVQSGPEVKKPGESVKISCKASGYTFTKYGMNWV KQAPGQGLKWMGWINTYTEEPTYGDDFKGRFTFTLD TSTSTAYLEISSLRSEDTATYFCARFGSAVDYWGQGTL VTVSS
420	Anti-EpCAM VL	DIVMTQSALSNPVTLGESGSISCRSSKSLLHSNGITYLY WYLQKPGQSPQLLIYQMSNRASGVPDRFSSSGSGTDF TLKISRVEAEDVGVYYCAQNLELPRTFGQGTKLEMKR

421	Anti-EpCAM CDR-H1	DYSMH
422	Anti-EpCAM CDR-H2	WINTETGEPTYADDFKG
423	Anti-EpCAM CDR-H3	TAVY
424	Anti-EpCAM CDR-L1	RASQEISVSLS
425	Anti-EpCAM CDR-L2	ATSTLDS
426	Anti-EpCAM CDR-L3	LQYASYPWT
427	Anti-EpCAM VH	QVKLQESGPELKKPGETVKISCKASGYTFTDYSMHW VKQAPGKGLKWMGWINTETGEPTYADDFKGRFAFSL ETSASTAYLQINNLKNEDTATYFCARTAVYWGQGTT VTVSS
428	Anti-EpCAM VL	DIQMTQSPSSLSASLGERVSLTCRASQEISVSLSWLQQ EPDGTIKRLIYATSTLDSGVPKRFSGSRSGSDYSLTISSL ESEDFVDYYCLQYASYPWTFGGGTKLEIKR
429	Anti-CD352 CDR-H1	NYGMN
430	Anti-CD352 CDR-H2	WINTYSGEPRYADDFKG
431	Anti-CD352 CDR-H3	DYGRWYFDV
432	Anti-CD352 CDR-L1	RASSSVSHMH
433	Anti-CD352 CDR-L2	ATSNLAS
434	Anti-CD352 CDR-L3	QQWSSTPRT
435	Anti-CD352 VH	QIQLVQSGSELKKPGASVKVSCKASGYTFTNYGMNW VRQAPGQDLKWMGWINTYSGEPRYADDFKGRFVFSL DKSVNTAYLQISSLKAEDTAVYYCARDYGRWYFDV WGQGTTVTVSS
436	Anti-CD352 VL	QIVLSQSPATLSLSPGERATMSCRASSSVSHMHWYQQ KPGQAPRPWIYATSNLASGVPARFSGSGSGTDYTLTIS SLEPEDFAVYYCQQWSSTPRTFGGGTKVEIKR
437	Anti-CS1 CDR-H1	RYWMS
438	Anti-CS1 CDR-H2	EINPDSSTINYAPSLKD
439	Anti-CS1 CDR-H3	PDGNYWYFDV
440	Anti-CS1 CDR-L1	KASQDVGIAVA
441	Anti-CS1 CDR-L2	WASTRHT
442	Anti-CS1 CDR-L3	QQYSSYPYT
443	Anti-CS1 VH	EVQLVESGGGLVQPGGSLRLSCAASGFDFSRYWMSW VRQAPGKGLEWIGEINPDSSTINYAPSLKDKFIISRDNA KNSLYLQMNSLRAEDTAVYYCARPDGNYWYFDVWG QGTLVTVSS
444	Anti-CS1 VL	DIQMTQSPSSLSASVGDRVTITCKASQDVGIAVAWYQ QKPGKVPKLLIYWASTRHTGVPDRFSGSGSGTDFTLTI SSLQPEDVATYYCQQYSSYPYTFGQGTKVEIKR
445	Anti-CD38 CDR-H1	SFAMS
446	Anti-CD38 CDR-H2	AISGSGGGTYYADSVKG
447	Anti-CD38 CDR-H3	DKILWFGEPVFDY
448	Anti-CD38 CDR-L1	RASQSVSSYLA
449	Anti-CD38 CDR-L2	DASNRAT
450	Anti-CD38 CDR-L3	QQRSNWPPT
451	Anti-CD38 VH	EVQLLESGGGLVQPGGSLRLSCAVSGFTFNSFAMSWV RQAPGKGLEWVSAISGSGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYFCAKDKILWFGEPVFD YWGQGTLVTVSS

452	Anti-CD38 VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQ KPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISS LEPEDFAVYYCQQRSNWPPTFGQGTKVEIKR
453	Anti-CD25 CDR-H1	SYRMH
454	Anti-CD25 CDR-H2	YINPSTGYTEYNQKFKD
455	Anti-CD25 CDR-H3	GGGVFDY
456	Anti-CD25 CDR-L1	SASSSISYMH
457	Anti-CD25 CDR-L2	TTSNLAS
458	Anti-CD25 CDR-L3	HQRSTYPLT
459	Anti-CD25 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYRMHW VRQAPGQGLEWIGYINPSTGYTEYNQKFKDKATITAD ESTNTAYMELSSLRSEDTAVYYCARGGGVFDYWGQG TLVTVSS
460	Anti-CD25 VL	DIQMTQSPSTLSASVGDRVTITCSASSSISYMHWYQQK PGKAPKLLIYTTSNLASGVPARFSGSGSGTEFTLTISSL QPDDFATYYCHQRSTYPLTFGQGTKVEVK
461	Anti-ADAM9 CDR-H1	SYWMH
462	Anti-ADAM9 CDR-H2	EIIPINGHTNYNEKFKS
463	Anti-ADAM9 CDR-H3	GGYYYYGSRDYFDY
464	Anti-ADAM9 CDR-L1	KASQSVDYDGDSYMN
465	Anti-ADAM9 CDR-L2	AASDLES
466	Anti-ADAM9 CDR-L3	QQSHEDPFT
467	Anti-ADAM9 VH	QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMH WVKQRPGQGLEWIGEIIPINGHTNYNEKFKSKATLTL DKSSSTAYMQLSSLASEDSAVYYCARGGYYYYGSRD YFDYWGQGTTLTVSS
468	Anti-ADAM9 VL	DIVLTQSPASLAVSLGQRATISCKASQSVDYDGDSYM NWYQQIPGQPPKLLIYAASDLESGIPARFSGSGSGTDF TLNIHPVEEEDAATYYCQQSHEDPFTFGGGTKLEIK
469	Anti-ADAM9 CDR-H1	SYWMH
470	Anti-ADAM9 CDR-H2	EIIPIFGHTNYNEKFKS
471	Anti-ADAM9 CDR-H3	GGYYYYPRQGFLDY
472	Anti-ADAM9 CDR-L1	KASQSVDYSGDSYMN
473	Anti-ADAM9 CDR-L2	AASDLES
474	Anti-ADAM9 CDR-L3	QQSHEDPFT
475	Anti-ADAM9 VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYWMHW VRQAPGKGLEWVGEIIPIFGHTNYNEKFKSRFTISLDN SKNTLYLQMGSLRAEDTAVYYCARGGYYYYPRQGFL DYWGQGTTVTVSS
476	Anti-ADAM9 VL	DIVMTQSPDSLAVSLGERATISCKASQSVDYSGDSYM NWYQQKPGQPPKLLIYAASDLESGIPARFSGSGSGTDF TLTISSLEPEDFATYYCQQSHEDPFTFGQGTKLEIK
477	Anti-CD59 CDR-H1	SYGMN
478	Anti-CD59 CDR-H2	YISSSSSTIYYADSVKG
479	Anti-CD59 CDR-H3	GPGMDV
480	Anti-CD59 CDR-L1	KSSQSVLYSSNNKNYLA
481	Anti-CD59 CDR-L2	WASTRES
482	Anti-CD59 CDR-L3	QQYYSTPQLT

483	Anti-CD59 VH	QVQLQQSGGGVVQPGRSLGLSCAASGFTFSSYGMNW VRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGPGMDVWGQGT TVTVS
484	Anti-CD59 VL	DIVLTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNY LAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGT DFTPAISSLQAEDVAVYYCQQYYSTPQLTFGGGTKVD IK
485	Anti-CD19 (hBU12) CDR-H1	TSGMGVG
486	Anti-CD19 (hBU12) CDR-H2	HIWWDDDKRYNPALKS
487	Anti-CD19 (hBU12) CDR-H3	MELWSYYFDY
488	Anti-CD19 (hBU12) CDR-L1	SASSSVSYMH
489	Anti-CD19 (hBU12) CDR-L2	DTSKLAS
490	Anti-CD19 (hBU12) CDR-L3	FQGSVYPFT
491	Anti-CD19 (hBU12) VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISTSGMGVG WIRQHPGKGLEWIGHIWWDDDKRYNPALKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARMELWSYYFDY WGQGTLVTVSS
492	Anti-CD19 (hBU12) VL	EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQK PGQAPRLLIYDTSKLASGIPARFSGSGSGTDFTLTISSLE PEDVAVYYCFQGSVYPFTFGQGTKLEIKR
493	Anti-CD19 (hBU12) HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISTSGMGVG WIRQHPGKGLEWIGHIWWDDDKRYNPALKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARMELWSYYFDY WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK
494	Anti-CD19 (hBU12) LC	EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQK PGQAPRLLIYDTSKLASGIPARFSGSGSGTDFTLTISSLE PEDVAVYYCFQGSVYPFTFGQGTKLEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC
495	Anti-CD138 CDR-H1	NYWIE
496	Anti-CD138 CDR-H2	EILPGTGRTIYNEKFKG
497	Anti-CD138 CDR-H3	RDYYGNFYYAMDY
498	Anti-CD138 CDR-L1	SASQGINNYLN

499	Anti-CD138 CDR-L2	YTSTLQS
500	Anti-CD138 CDR-L3	QQYSKLPRT
501	Anti-CD138 VH	QVQLQQSGSELMMPGASVKISCKATGYTFSNYWIEW VKQRPGHGLEWIGEILPGTGRTIYNEKFKGKATFTADI SSNTVQMQLSSLTSEDSAVYYCARRDYYGNFYYAMD YWGQGTSVTVSS
502	Anti-CD138 VL	DIQMTQSTSSLSASLGDRVTISCSASQGINNYLNWYQQ KPDGTVELLIYYTSTLQSGVPSRFSGSGSGTDYSLTISN LEPEDIGTYYCQQYSKLPRTFGGGTKLEIK
503	Anti-CD166 CDR-H1	TYGMGVG
504	Anti-CD166 CDR-H2	NIWWSEDKHYSPSLKS
505	Anti-CD166 CDR-H3	IDYGNDYAFTY
506	Anti-CD166 CDR-L1	RSSKSLLHSNGITYLY
507	Anti-CD166 CDR-L2	QMSNLAS
508	Anti-CD166 CDR-L3	AQNLELPYT
509	Anti-CD166 VH	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTYGMGVGW IRQPPGKALEWLANIWWSEDKHYSPSLKSRLTITKDTS KNQVVLTITNVDPVDTATYYCVQIDYGNDYAFTYWG QGTLVTVSS
510	Anti-CD166 VL	DIVMTQSPLSLPVTPGEPASISCRSSKSLLHSNGITYLY WYLQKPGQSPQLLIYQMSNLASGVPDRFSGSGSGTDF TLKISRVEAEDVGVYYCAQNLELPYTFGQGTKLEIK
511	Anti-CD56 CDR-H1	SFGMH
512	Anti-CD56 CDR-H2	YISSGSFTIYYADSVKG
513	Anti-CD56 CDR-H3	MRKGYAMDY
514	Anti-CD56 CDR-L1	RSSQIIIHSDGNTYLE
515	Anti-CD56 CDR-L2	KVSNRFS
516	Anti-CD56 CDR-L3	FQGSHVPHT
517	Anti-CD56 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFGMHW VRQAPGKGLEWVAYISSGSFTIYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARMRKGYAMDYW GQGTLVTVSS
518	Anti-CD56 VL	DVVMTQSPLSLPVTLGQPASISCRSSQIIIHSDGNTYLE WFQQRPGQSPRRLIYKVSNRFSGVPDRFSGSGSGTDFT LKISRVEAEDVGVYYCFQGSHVPHTFGQGTKVEIK
519	Anti-CD74 CDR-H1	NYGVN
520	Anti-CD74 CDR-H2	WINPNTGEPTFDDDFKG
521	Anti-CD74 CDR-H3	SRGKNEAWFAY
522	Anti-CD74 CDR-L1	RSSQSLVHRNGNTYLH
523	Anti-CD74 CDR-L2	TVSNRFS
524	Anti-CD74 CDR-L3	SQSSHVPPT
525	Anti-CD74 VH	QVQLQQSGSELKKPGASVKVSCKASGYTFTNYGVNW IKQAPGQGLQWMGWINPNTGEPTFDDDFKGRFAFSL DTSVSTAYLQISSLKADDTAVYFCSRSRGKNEAWFAY WGQGTLVTVSS
526	Anti-CD74 VL	DIQLTQSPLSLPVTLGQPASISCRSSQSLVHRNGNTYLH WFQQRPGQSPRLLIYTVSNRFSGVPDRFSGSGSGTDFT LKISRVEAEDVGVYFCSQSSHVPPTFGAGTRLEIK

527	Anti-CEACAM5 CDR-H1	TYWMS
528	Anti-CEACAM5 CDR-H2	EIHPDSSTINYAPSLKD
529	Anti-CEACAM5 CDR-H3	LYFGFPWFAY
530	Anti-CEACAM5 CDR-L1	KASQDVGTSVA
531	Anti-CEACAM5 CDR-L2	WTSTRHT
532	Anti-CEACAM5 CDR-L3	QQYSLYRS
533	Anti-CEACAM5 VH	EVQLVESGGGVVQPGRSLRLSCSASGFDFTTYWMSW VRQAPGKGLEWIGEIHPDSSTINYAPSLKDRFTISRDN AKNTLFLQMDSLRPEDTGVYFCASLYFGFPWFAYWG QGTPVTVSS
534	Anti-CEACAM5 VL	DIQLTQSPSSLSASVGDRVTITCKASQDVGTSVAWYQ QKPGKAPKLLIYWTSTRHTGVPSRFSGSGSGTDFTFTI SSLQPEDIATYYCQQYSLYRSFGQGTKVEIK
535	Anti-CanAg CDR-H1	YYGMN
536	Anti-CanAg CDR-H2	WIDTTTGEPTYAQKFQG
537	Anti-CanAg CDR-H3	RGPYNWYFDV
538	Anti-CanAg CDR-L1	RSSKSLLHSNGNTYLY
539	Anti-CanAg CDR-L2	RMSNLVS
540	Anti-CanAg CDR-L3	LQHLEYPFT
541	Anti-CanAg VH	QVQLVQSGAEVKKPGETVKISCKASDYTFTYYGMNW VKQAPGQGLKWMGWIDTTTGEPTYAQKFQGRIAFSL ETSASTAYLQIKSLKSEDTATYFCARRGPYNWYFDVW GQGTTVTVSS
542	Anti-CanAg VL	DIVMTQSPLSVPVTPGEPVSISCRSSKSLLHSNGNTYLY WFLQRPGQSPQLLIYRMSNLVSGVPDRFSGSGSGTAF TLRISRVEAEDVGVYYCLQHLEYPFTFGPGTKLELK
543	Anti-DLL-3 CDR-H1	NYGMN
544	Anti-DLL-3 CDR-H2	WINTYTGEPTYADDFKG
545	Anti-DLL-3 CDR-H3	IGDSSPSDY
546	Anti-DLL-3 CDR-L1	KASQSVSNDVV
547	Anti-DLL-3 CDR-L2	YASNRYT
548	Anti-DLL-3 CDR-L3	QQDYTSPWT
549	Anti-DLL-3 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMN WVRQAPGQGLEWMGWINTYTGEPTYADDFKGRVTM TTDTSTSTAYMELRSLRSDDTAVYYCARIGDSSPSDY WGQGTLVTVSS
550	Anti-DLL-3 VL	EIVMTQSPATLSVSPGERATLSCKASQSVSNDVVWYQ QKPGQAPRLLIYYASNRYTGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQDYTSPWTFGQGTKLEIK
551	Anti-DPEP-3 CDR-H1	SYWIE
552	Anti-DPEP-3 CDR-H2	EILPGSGNTYYNERFKD
553	Anti-DPEP-3 CDR-H3	RAAAYYSNPEWFAY
554	Anti-DPEP-3 CDR-L1	TASSSVNSFYLH

555	Anti-DPEP-3 CDR-L2	STSNLAS
556	Anti-DPEP-3 CDR-L3	HQYHRSPYT
557	Anti-DPEP-3 VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYWIEW VRQAPGQGLEWMGEILPGSGNTYYNERFKDRVTITA DESTSTAYMELSSLRSEDTAVYYCARRAAAYYSNPE WFAYWGQGTLVTVSS
558	Anti-DPEP-3 VL	EIVLTQSPATLSLSPGERATLSCTASSSVNSFYLHWYQ QKPGLAPRLLIYSTSNLASGIPDRFSGSGSGTDFTLTISR LEPEDFAVYYCHQYHRSPYTFGQGTKLEIK
559	Anti-EGFR CDR-H1	SYWMQ
560	Anti-EGFR CDR-H2	TIYPGDGDTTYTQKFQG
561	Anti-EGFR CDR-H3	YDAPGYAMDY
562	Anti-EGFR CDR-L1	RASQDINNYLA
563	Anti-EGFR CDR-L2	YTSTLHP
564	Anti-EGFR CDR-L3	LQYDNLLYT
565	Anti-EGFR VH	QVQLVQSGAEVAKPGASVKLSCKASGYTFTSYWMQ WVKQRPGQGLECIGTIYPGDGDTTYTQKFQGKATLTA DKSSSTAYMQLSSLRSEDSAVYYCARYDAPGYAMDY WGQGTLVTVSS
566	Anti-EGFR VL	DIQMTQSPSSLSASVGDRVTITCRASQDINNYLAWYQ HKPGKGPKLLIHYTSTLHPGIPSRFSGSGSGRDYSFSISS LEPEDIATYYCLQYDNLLYTFGQGTKLEIK
567	Anti-EGFR CDR-H1	RDFAWN
568	Anti-EGFR CDR-H2	YISYNGNTRYQPSLKS
569	Anti-EGFR CDR-H3	ASRGFPY
570	Anti-EGFR CDR-L1	HSSQDINSNIG
571	Anti-EGFR CDR-L2	HGTNLDD
572	Anti-EGFR CDR-L3	VQYAQFPWT
573	Anti-EGFR VH	EVQLQESGPGLVKPSQTLSLTCTVSGYSISRDFAWNWI RQPPGKGLEWMGYISYNGNTRYQPSLKSRITISRDTSK NQFFLKLNSVTAADTATYYCVTASRGFPYWGQGTLV TVSS
574	Anti-EGFR VL	DIQMTQSPSSMSVSVGDRVTITCHSSQDINSNIGWLQQ KPGKSFKGLIYHGTNLDDGVPSRFSGSGSGTDYTLTIS SLQPEDFATYYCVQYAQFPWTFGGGTKLEIK
575	Anti-EGFR CDR-H1	NYGVH
576	Anti-EGFR CDR-H2	VIWSGGNTDYNTPFTS
577	Anti-EGFR CDR-H3	ALTYYDYEFAY
578	Anti-EGFR CDR-L1	RASQSIGTNIH
579	Anti-EGFR CDR-L2	YASESIS
580	Anti-EGFR CDR-L3	QQNNNWPTT
581	Anti-EGFR VH	QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWV RQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNS KSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWG QGTLVTVSA
582	Anti-EGFR VL	DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQR TNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSINSVES EDIADYYCQQNNNWPTTFGAGTKLELK
583	Anti-FRa CDR-H1	GYFMN

584	Anti-FRa CDR-H2	RIHPYDGDTFYNQKFQG
585	Anti-FRa CDR-H3	YDGSRAMDY
586	Anti-FRa CDR-L1	KASQSVSFAGTSLMH
587	Anti-FRa CDR-L2	RASNLEA
588	Anti-FRa CDR-L3	QQSREYPYT
589	Anti-FRa VH	QVQLVQSGAEVVKPGASVKISCKASGYTFTGYFMNW VKQSPGQSLEWIGRIHPYDGDTFYNQKFQGKATLTVD KSSNTAHMELLSLTSEDFAVYYCTRYDGSRAMDYWG QGTTVTVSS
590	Anti-FRa VL	DIVLTQSPLSLAVSLGQPAIISCKASQSVSFAGTSLMH WYHQKPGQQPRLLIYRASNLEAGVPDRFSGSGSKTDF TLTISPVEAEDAATYYCQQSREYPYTFGGGTKLEIK
591	Anti-FRa CDR-H1	GYGLS
592	Anti-FRa CDR-H2	MISSGGSYTYYADSVKG
593	Anti-FRa CDR-H3	HGDDPAWFAY
594	Anti-FRa CDR-L1	SVSSSISSNNLH
595	Anti-FRa CDR-L2	GTSNLAS
596	Anti-FRa CDR-L3	QQWSSYPYMYT
597	Anti-FRa VH	EVQLVESGGGVVQPGRSLRLSCSASGFTFSGYGLSWV RQAPGKGLEWVAMISSGGSYTYYADSVKGRFAISRD NAKNTLFLQMDSLRPEDTGVYFCARHGDDPAWFAY WGQGTPVTVSS
598	Anti-FRa VL	DIQLTQSPSSLSASVGDRVTITCSVSSSISSNNLHWYQQ KPGKAPKPWIYGTSNLASGVPSRFSGSGSGTDYTFTIS SLQPEDIATYYCQQWSSYPYMYTFGQGTKVEIK
599	Anti-MUC-1 CDR-H1	NYWMN
600	Anti-MUC-1 CDR-H2	EIRLKSNNYTTHYAESVKG
601	Anti-MUC-1 CDR-H3	HYYFDY
602	Anti-MUC-1 CDR-L1	RSSKSLLHSNGITYFF
603	Anti-MUC-1 CDR-L2	QMSNLAS
604	Anti-MUC-1 CDR-L3	AQNLELPPT
605	Anti-MUC-1 VH	EVQLVESGGGLVQPGGSMRLSCVASGFPFSNYWMN WVRQAPGKGLEWVGEIRLKSNNYTTHYAESVKGRFT ISRDDSKNSLYLQMNSLKTEDTAVYYCTRHYYFDYW GQGTLVTVSS
606	Anti-MUC-1 VL	DIVMTQSPLSNPVTPGEPASISCRSSKSLLHSNGITYFF WYLQKPGQSPQLLIYQMSNLASGVPDRFSGSGSGTDF TLRISRVEAEDVGVYYCAQNLELPPTFGQGTKVEIK
607	Anti-Mesothelin CDR-H1	SYWIG
608	Anti-Mesothelin CDR-H2	IIDPGDSRTRYSPSFQG
609	Anti-Mesothelin CDR-H3	GQLYGGTYMDG
610	Anti-Mesothelin CDR-L1	TGTSSDIGGYNSVS
611	Anti-Mesothelin CDR-L2	GVNNRPS

612	Anti-Mesothelin CDR-L3	SSYDIESATPV
613	Anti-Mesothelin VH	QVELVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWV RQAPGKGLEWMGIIDPGDSRTRYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARGQLYGGTYMDGW GQGTLVTVSS
614	Anti-Mesothelin VL	DIALTQPASVSGSPGQSITISCTGTSSDIGGYNSVSWYQ QHPGKAPKLMIYGVNNRPSGVSNRFSGSKSGNTASLT ISGLQAEDEADYYCSSYDIESATPVFGGGTKLTVL
615	Anti-ROR-1 CDR-H1	AYNIH
616	Anti-ROR-1 CDR-H2	SFDPYDGGSSYNQKFKD
617	Anti-ROR-1 CDR-H3	GWYYFDY
618	Anti-ROR-1 CDR-L1	RASKSISKYLA
619	Anti-ROR-1 CDR-L2	SGSTLQS
620	Anti-ROR-1 CDR-L3	QQHDESPYT
621	Anti-ROR-1 VH	QVQLQESGPGLVKPSQTLSLTCTVSGYAFTAYNIHWV RQAPGQGLEWMGSFDPYDGGSSYNQKFKDRLTISKD TSKNQVVLTMTNMDPVDTATYYCARGWYYFDYWG HGTLVTVSS
622	Anti-ROR-1 VL	DIVMTQTPLSLPVTPGEPASISCRASKSISKYLAWYQQ KPGQAPRLLIYSGSTLQSGIPPRFSGSGYGTDFTLTINNI ESEDAAYYFCQQHDESPYTFGEGTKVEIK
623	Anti-B7-H3 CDR-H1	SFGMH
624	Anti-B7-H3 CDR-H2	YISSDSSAIYYADTVKG
625	Anti-B7-H3 CDR-H3	GRENIYYGSRLDY
626	Anti-B7-H3 CDR-L1	KASQNVDTNVA
627	Anti-B7-H3 CDR-L2	SASYRYS
628	Anti-B7-H3 CDR-L3	QQYNNYPFT
629	Anti-B7-H3 VH	DVQLVESGGGLVQPGGSRKLSCAASGFTFSSFGMHW VRQAPEKGLEWVAYISSDSSAIYYADTVKGRFTISRD NPKNTLFLQMTSLRSEDTAMYYCGRGRENIYYGSRLD YWGQGTTLTVSS
630	Anti-B7-H3 VL	DIAMTQSQKFMSTSVGDRVSVTCKASQNVDTNVAW YQQKPGQSPKALIYSASYRYSGVPDRFTGSGSGTDFTL TINNVQSEDLAEYFCQQYNNYPFTFGSGTKLEIK
631	Anti-B7-H3 CDR-H1	SYGMS
632	Anti-B7-H3 CDR-H2	TINSGGSNTYYPDSLKG
633	Anti-B7-H3 CDR-H3	HDGGAMDY
634	Anti-B7-H3 CDR-L1	RASESIYSYLA
635	Anti-B7-H3 CDR-L2	NTKTLPE
636	Anti-B7-H3 CDR-L3	QHHYGTPPWT
637	Anti-B7-H3 VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYGMSWV RQAPGKGLEWVATINSGGSNTYYPDSLKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCARHDGGAMDYWG QGTTVTVSS
638	Anti-B7-H3 VL	DIQMTQSPSSLSASVGDRVTITCRASESIYSYLAWYQQ KPGKAPKLLVYNTKTLPEGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQHHYGTPPWTFGQGTRLEIK
639	Anti-B7-H3 CDR-H1	SFGMH

640	Anti-B7-H3 CDR-H2	YISSGSGTIYYADTVKG
641	Anti-B7-H3 CDR-H3	HGYRYEGFDY
642	Anti-B7-H3 CDR-L1	KASQNVDTNVA
643	Anti-B7-H3 CDR-L2	SASYRYS
644	Anti-B7-H3 CDR-L3	QQYNNYPFT
645	Anti-B7-H3 VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGMHWV RQAPGKGLEWVAYISSGSGTIYYADTVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCARHGYRYEGFDYW GQGTTVTVSS
646	Anti-B7-H3 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDTNVAWYQ QKPGKAPKALIYSASYRYSGVPSRFSGSGSGTDFTLTIS SLQPEDFAEYFCQQYNNYPFTFGQGTKLEIK
647	Anti-B7-H3 CDR-H1	NYVMH
648	Anti-B7-H3 CDR-H2	YINPYNDDVKYNEKFKG
649	Anti-B7-H3 CDR-H3	WGYYGSPLYYFDY
650	Anti-B7-H3 CDR-L1	RASSRLIYMH
651	Anti-B7-H3 CDR-L2	ATSNLAS
652	Anti-B7-H3 CDR-L3	QQWNSNPPT
653	Anti-B7-H3 VH	EVQLQQSGPELVKPGASVKMSCKASGYTFTNYVMH WVKQKPGQGLEWIGYINPYNDDVKYNEKFKGKATQ TSDKSSSTAYMELSSLTSEDSAVYYCARWGYYGSPLY YFDYWGQGTTLTVSS
654	Anti-B7-H3 VL	QIVLSQSPTILSASPGEKVTMTCRASSRLIYMHWYQQK PGSSPKPWIYATSNLASGVPARFSGSGSGTSYSLTISRV EAEDAATYYCQQWNSNPPTFGTGTKLELK
655	Anti-B7-H3 CDR-H1	NYVMH
656	Anti-B7-H3 CDR-H2	YINPYNDDVKYNEKFKG
657	Anti-B7-H3 CDR-H3	WGYYGSPLYYFDY
658	Anti-B7-H3 CDR-L1	RASSRLIYMH
659	Anti-B7-H3 CDR-L2	ATSNLAS
660	Anti-B7-H3 CDR-L3	QQWNSNPPT
661	Anti-B7-H3 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTNYVMH WVRQAPGQGLEWMGYINPYNDDVKYNEKFKGRVTI TADESTSTAYMELSSLRSEDTAVYYCARWGYYGSPL YYFDYWGQGTLVTVSS
662	Anti-B7-H3 VL	EIVLTQSPATLSLSPGERATLSCRASSRLIYMHWYQQK PGQAPRPLIYATSNLASGIPARFSGSGSGTDFTLTISSLE PEDFAVYYCQQWNSNPPTFGQGTKVEIK
663	Anti-B7-H3 CDR-H1	SYTIH
664	Anti-B7-H3 CDR-H2	YINPNSRNTDYAQKFQG
665	Anti-B7-H3 CDR-H3	YSGSTPYWYFDV
666	Anti-B7-H3 CDR-L1	RASSSVSYMN
667	Anti-B7-H3 CDR-L2	ATSNLAS
668	Anti-B7-H3 CDR-L3	QQWSSNPLT
669	Anti-B7-H3 VH	EVQLVQSGAEVKKPGSSVKVSCKASGYSFTSYTIHWV RQAPGQGLEWMGYINPNSRNTDYAQKFQGRVTLTAD KSTSTAYMELSSLRSEDTAVYYCARYSGSTPYWYFDV WGQGTTVTVSS

670	Anti-B7-H3 VL	DIQLTQSPSFLSASVGDRVTITCRASSSVSYMNWYQQ KPGKSPKPWIYATSNLASGVPSRFSVSVSGTEHTLTISS LQPEDFATYYCQQWSSNPLTFGQGTKLEIK
671	Anti-B7-H3 CDR-H1	SYWMH
672	Anti-B7-H3 CDR-H2	LIHPDSGSTNYNEMFKN
673	Anti-B7-H3 CDR-H3	GGRLYFDY
674	Anti-B7-H3 CDR-L1	RSSQSLVHSNGDTYLR
675	Anti-B7-H3 CDR-L2	KVSNRFS
676	Anti-B7-H3 CDR-L3	SQSTHVPYT
677	Anti-B7-H3 VH	EVQLVQSGAEVKKPGSSVKVSCKASGYTFSSYWMH WVRQAPGQGLEWIGLIHPDSGSTNYNEMFKNRATLT VDRSTSTAYVELSSLRSEDTAVYFCAGGGRLYFDYW GQGTTVTVSS
678	Anti-B7-H3 VL	DVVMTQSPLSLPVTPGEPASISCRSSQSLVHSNGDTYL RWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTD FTLKISRVEAEDVGVYYCSQSTHVPYTFGGGTKVEIK
679	Anti-B7-H3 CDR-H1	SYWMH
680	Anti-B7-H3 CDR-H2	LIHPESGSTNYNEMFKN
681	Anti-B7-H3 CDR-H3	GGRLYFDY
682	Anti-B7-H3 CDR-L1	RSSQSLVHSNQDTYLR
683	Anti-B7-H3 CDR-L2	KVSNRFS
684	Anti-B7-H3 CDR-L3	SQSTHVPYT
685	Anti-B7-H3 VH	EVQLVQSGAEVKKPGSSVKVSCKASGYTFSSYWMH WVRQAPGQGLEWIGLIHPESGSTNYNEMFKNRATLT VDRSTSTAYMELSSLRSEDTAVYYCAGGGRLYFDYW GQGTTVTVSS
686	Anti-B7-H3 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLVHSNQDTYLR WYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDF TLKISRVEAEDVGVYYCSQSTHVPYTFGGGTKVEIK
687	Anti-B7-H3 CDR-H1	SGYSWH
688	Anti-B7-H3 CDR-H2	YIHSSGSTNYNPSLKS
689	Anti-B7-H3 CDR-H3	YDDYFEY
690	Anti-B7-H3 CDR-L1	KASQNVGFNVAW
691	Anti-B7-H3 CDR-L2	SASYRYS
692	Anti-B7-H3 CDR-L3	QQYNWYPFT
693	Anti-B7-H3 VH	EVQLQESGPGLVKPSETLSLTCAVTGYSITSGYSWHWI RQFPGNGLEWMGYIHSSGSTNYNPSLKSRISISRDTSK NQFFLKLSSVTAADTAVYYCAGYDDYFEYWGQGTTV TVSS
694	Anti-B7-H3 VL	DIQMTQSPSSLSASVGDRVTITCKASQNVGFNVAWYQ QKPGKSPKALIYSASYRYSGVPSRFSGSGSGTDFTLTIS SLQPEDFAEYFCQQYNWYPFTFGQGTKLEIK
695	Anti-B7-H3 CDR-H1	NYDIN
696	Anti-B7-H3 CDR-H2	WIFPGDDSTQYNEKFKG
697	Anti-B7-H3 CDR-H3	QTTGTWFAY
698	Anti-B7-H3 CDR-L1	RASQSISDYLY
699	Anti-B7-H3 CDR-L2	YASQSIS
700	Anti-B7-H3 CDR-L3	QNGHSFPLT

701	Anti-B7-H3 VH	QVQLVQSGAEVVKPGASVKLSCKTSGYTFTNYDINW VRQRPGQGLEWIGWIFPGDDSTQYNEKFKGKATLTTD TSTSTAYMELSSLRSEDTAVYFCARQTTGTWFAYWG QGTLVTVSS
702	Anti-B7-H3 VL	EIVMTQSPATLSVSPGERVTLSCRASQSISDYLYWYQQ KSHESPRLLIKYASQSISGIPARFSGSGSGSEFTLTINSV EPEDVGVYYCQNGHSFPLTFGQGTKLELK
703	Anti-B7-H3 VH	QVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPILGIANYAQKFQGRVTITADES TSTAYMELSSLRSEDTAVYYCARGGSGSYHMDVWG KGTTVTVSS
704	Anti-B7-H3 VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQ KPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISS LEPEDFAVYYCQQRSNWPPRITFGQGTRLEIK
705	Anti-B7-H3 CDR-H1	IYNVH
706	Anti-B7-H3 CDR-H2	TIFPGNGDTSYNQKFKD
707	Anti-B7-H3 CDR-H3	WDDGNVGFAH
708	Anti-B7-H3 CDR-L1	RASENINNYLT
709	Anti-B7-H3 CDR-L2	HAKTLAE
710	Anti-B7-H3 CDR-L3	QHHYGTPPT
711	Anti-B7-H3 VH	QVQLQQPGAELVKPGASVKMSCKASGYTFTIYNVHW IKQTPGQGLEWMGTIFPGNGDTSYNQKFKDKATLTTD KSSKTAYMQLNSLTSEDSAVYYCARWDDGNVGFAH WGQGTLVTVSA
712	Anti-B7-H3 VL	DIQMTQSPASLSASVGETVTITCRASENINNYLTWFQQ KQGKSPQLLVYHAKTLAEGVPSRFSGSGSGTQFSLKIN SLQPEDFGSYYCQHHYGTPPTFGGGTKLEIK
713	Anti-B7-H3 VH	EVQLVQSGAEVKKPGASVKVSCKASGYTFTIYNVHW VRQAPGQGLEWMGTIFPGNGDTSYNQKFKDKVTMTT DTSTSTAYMELSSLRSEDTAVYYCARWDDGNVGFAH WGQGTLVTVSS
714	Anti-B7-H3 VL	DIQMTQSPSSLSASVGDRVTITCRASENINNYLTWFQQ KQGKSPQLLIYHAKTLAEGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQHHYGTPPTFGGGTKVEIK
715	Anti-B7-H3 VH	EVQLVQSGAEVKKPGASVKVSCKASGYTFTIYNVHWI RQAPGQGLEWMGTIFPGNGDTSYNQKFKDRATLTTD KSTKTAYMELRSLRSDDTAVYYCARWDDGNVGFAH WGQGTLVTVSS
716	Anti-B7-H3 VL	DIQMTQSPSSLSASVGDRVTITCRASENINNYLTWFQQ KPGKAPKLLVYHAKTLAEGVPSRFSGSGSGTQFTLTIS SLQPEDFATYYCQHHYGTPPTFGQGTKLEIK
717	Anti-HER3 H	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSW IRQPPGKGLEWIGEINHSGSTNYNPSLKSRVTISVETSK NQFSLKLSSVTAADTAVYYCARDKWTWYFDLWGRG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI

		EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
718	Anti-HER3 L	DIEMTQSPDSLAVSLGERATINCRSSQSVLYSSSNRNY LAWYQQNPGQPPKLLIYWASTRESGVPDRFSGSGSGT DFTLTISSLQAEDVAVYYCQQYYSTPRTFGQGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
719	Anti-HER3 H	EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYVMAW VRQAPGKGLEWVSSISSSGGWTLYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCTRGLKMATIFDYW GQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKC CVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEK TISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
720	Anti-HER3 L	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNVVSWY QQHPGKAPKLIIYEVSQRPSGVSNRFSGSKSGNTASLTI SGLQTEDEADYYCCSYAGSSIFVIFGGGTKVTVLGQP KAAPSVTLFPPSSEELQANKATLVCLVSDFYPGAVTV AWKADGSPVKVGVETTKPSKQSNNKYAASSYLSLTP EQWKSHRSYSCRVTHEGSTVEKTVAPAECS
721	Anti-HER3 H	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSAINSQGKSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARWGDEGFDIWGQ GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
722	Anti-HER3 L	DIQMTQSPSSLSASVGDRVTITCRASQGISNWLAWYQ QKPGKAPKLLIYGASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQYSSFPTTFGQGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
723	Anti-HER3 H	QVQLVQSGAEVKKPGASVKVSCKASGYTFRSSYISW VRQAPGQGLEWMGWIYAGTGSPSYNQKLQGRVTMT

		TDTSTSTAYMELRSLRSDDTAVYYCARHRDYYSNSLT YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPG
724	Anti-HER3 L	DIVMTQSPDSLAVSLGERATINCKSSQSVLNSGNQKN YLTWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSG TDFTLTISSLQAEDVAVYYCQSDYSYPYTFGQGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
725	Anti-PTK7 CDR-H1	TSNMGVG
726	Anti-PTK7 CDR-H2	HIWWDDDKYYSPSLKS
727	Anti-PTK7 CDR-H3	SNYGYAWFAY
728	Anti-PTK7 CDR-L1	KASQDIYPYLN
729	Anti-PTK7 CDR-L2	RTNRLLD
730	Anti-PTK7 CDR-L3	LQYDEFPLT
731	Anti-PTK7 VH	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSNMGVGW IRQPPGKALEWLAHIWWDDDKYYSPSLKSRLTITKDT SKNQVVLTMTNMDPVDTATYYCVRSNYGYAWFAY WGQGTLVTVSS
732	Anti-PTK7 VL	DIQMTQSPSSLSASVGDRVTITCKASQDIYPYLNWFQQ KPGKAPKTLIYRTNRLLDGVPSRFSGSGSGTDFTFTISS LQPEDIATYYCLQYDEFPLTFGAGTKLEIK
733	Anti-PTK7 CDR-H1	DYAVH
734	Anti-PTK7 CDR-H2	VISTYNDYTYNNQDFKG
735	Anti-PTK7 CDR-H3	GNSYFYALDY
736	Anti-PTK7 CDR-L1	RASESVDSYGKSFMH
737	Anti-PTK7 CDR-L2	RASNLES
738	Anti-PTK7 CDR-L3	QQSNEDPWT
739	Anti-PTK7 VH	QVQLVQSGPEVKKPGASVKVSCKASGYTFTDYAVHW VRQAPGKRLEWIGVISTYNDYTYNNQDFKGRVTMTR DTSASTAYMELSRLRSEDTAVYYCARGNSYFYALDY WGQGTSVTVSS
740	Anti-PTK7 VL	EIVLTQSPATLSLSPGERATLSCRASESVDSYGKSFMH WYQQKPGQAPRLLIYRASNLESGIPARFSGSGSGTDFT LTISSLEPEDFAVYYCQQSNEDPWTFGGGTKLEIK
741	Anti-PTK7 CDR-H1	RYWMS
742	Anti-PTK7 CDR-H2	DLNPDSSAINYVDSVKG
743	Anti-PTK7 CDR-H3	ITTLVPYTMDF
744	Anti-PTK7 CDR-L1	ITNTDIDDDMN
745	Anti-PTK7 CDR-L2	EGNGLRP
746	Anti-PTK7 CDR-L3	LQSDNLPLT

747	Anti-PTK7 VH	EVQLVESGGGLVQPGGSLRLSCAASGFDFSRYWMSW VRQAPGKGLEWIGDLNPDSSAINYVDSVKGRFTISRD NAKNSLYLQMNSLRAEDTAVYYCTLITTLVPYTMDF WGQGTSVTVSS
748	Anti-PTK7 VL	ETTLTQSPAFMSATPGDKVNISCITNTDIDDDMNWYQ QKPGEAAILLISEGNGLRPGIPPRFSGSGYGTDFTLTIN NIESEDAAYYFCLQSDNLPLTFGSGTKLEIK
749	Anti-ZIP6 CDR-H1	DYYMH
750	Anti-ZIP6 CDR-H2	WIDPENGDTEYGPKFQG
751	Anti-ZIP6 CDR-H3	HNAHYGTWFAY
752	Anti-ZIP6 CDR-L1	RSSQSLLHSSGNTYLE
753	Anti-ZIP6 CDR-L2	KISTRFS
754	Anti-ZIP6 CDR-L3	FQGSHVPYT
755	Anti-ZIP6 VH	QVQLVQSGAEVKKPGASVKVSCKASGLTIEDYYMHW VRQAPGQGLEWMGWIDPENGDTEYGPKFQGRVTMT RDTSINTAYMELSRLRSDDTAVYYCAVHNAHYGTWF AYWGQGTLVTVSS
756	Anti-ZIP6 VL	DVVMTQSPLSLPVTLGQPASISCRSSQSLLHSSGNTYL EWYQQRPGQSPRPLIYKISTRFSGVPDRFSGSGSGTDF TLKISRVEAEDVGVYYCFQGSHVPYTFGGGTKVEIK
757	Anti-ZIP6 HC	QVQLVQSGAEVKKPGASVKVSCKASGLTIEDYYMHW VRQAPGQGLEWMGWIDPENGDTEYGPKFQGRVTMT RDTSINTAYMELSRLRSDDTAVYYCAVHNAHYGTWF AYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPG
758	Anti-ZIP6 LC	DVVMTQSPLSLPVTLGQPASISCRSSQSLLHSSGNTYL EWYQQRPGQSPRPLIYKISTRFSGVPDRFSGSGSGTDF TLKISRVEAEDVGVYYCFQGSHVPYTFGGGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
759	Anti-Integrin αvβ6 CDR-H1	GYFMN
760	Anti-Integrin αvβ6 CDR-H2	LINPYNGDSFYNQKFKG
761	Anti-Integrin αvβ6 CDR-H3	GLRRDFDY
762	Anti-Integrin αvβ6 CDR-L1	KSSQSLLDSDGKTYLN
763	Anti-Integrin αvβ6 CDR-L2	LVSELDS

764	Anti-Integrin αvβ6 CDR-L3	WQGTHFPRT
765	Anti-Integrin αvβ6 VH	QVQLVQSGAEVKKPGASVKVSCKASGYSFSGYFMN WVRQAPGQGLEWMGLINPYNGDSFYNQKFKGRVTM TRQTSTSTVYMELSSLRSEDTAVYYCVRGLRRDFDY WGQGTLVTVSS
766	Anti-Integrin αvβ6 VL	DVVMTQSPLSLPVTLGQPASISCKSSQSLLDSDGKTYL NWLFQRPGQSPRRLIYLVSELDSGVPDRFSGSGSGTDF TLKISRVEAEDVGVYYCWQGTHFPRTFGGGTKLEIK
767	Anti-CD48 CDR-H1	DFGMN
768	Anti-CD48 CDR-H2	WINTFTGEPSYGNVFKG
769	Anti-CD48 CDR-H3	RHGNGNVFDS
770	Anti-CD48 CDR-L1	RASQSIGSNIH
771	Anti-CD48 CDR-L2	YTSESIS
772	Anti-CD48 CDR-L3	QQSNSWPLT
773	Anti-CD48 VH	QVQLVQSGSELKKPGASVKVSCKASGYTFTDFGMNW VRQAPGQGLEWMGWINTFTGEPSYGNVFKGRFVFSL DTSVSTAYLQISSLKAEDTAVYYCARRHGNGNVFDS WGQGTLVTVSS
774	Anti-CD48 VL	EIVLTQSPDFQSVTPKEKVTITCRASQSIGSNIHWYQQ KPDQSPKLLIKYTSESISGVPSRFSGSGSGTDFTLTINSL EAEDAATYYCQQSNSWPLTFGGGTKVEIKR
775	Anti-IGF-1R CDR-H1	SYAIS
776	Anti-IGF-1R CDR-H2	GIIPIFGTANYAQKFQG
777	Anti-IGF-1R CDR-H3	APLRFLEWSTQDHYYYYYMDV
778	Anti-IGF-1R CDR-L1	QGDSLRSYYAT
779	Anti-IGF-1R CDR-L2	GENKRPS
780	Anti-IGF-1R CDR-L3	KSRDGSGQHLV
781	Anti-IGF-1R VH	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADK STSTAYMELSSLRSEDTAVYYCARAPLRFLEWSTQDH YYYYYMDVWGKGTTVTVSS
782	Anti-IGF-1R VL	SSELTQDPAVSVALGQTVRITCQGDSLRSYYATWYQQ KPGQAPILVIYGENKRPSGIPDRFSGSSSGNTASLTITG AQAEDEADYYCKSRDGSGQHLVFGGGTKLTVL
783	Anti-Claudin-18.2 CDR-H1	SYWIN
784	Anti-Claudin-18.2 CDR-H2	NIYPSDSYTNYNQKFKD
785	Anti-Claudin-18.2 CDR-H3	SWRGNSFDY
786	Anti-Claudin-18.2 CDR-L1	KSSQSLLNSGNQKNYLT
787	Anti-Claudin-18.2 CDR-L2	WASTRES
788	Anti-Claudin-18.2 CDR-L3	QNDYSYPFT
789	Anti-Claudin-18.2 VH	QVQLQQPGAELVRPGASVKLSCKASGYTFTSYWINW VKQRPGQGLEWIGNIYPSDSYTNYNQKFKDKATLTV

		DKSSSTAYMQLSSPTSEDSAVYYCTRSWRGNSFDYW GQGTTLTVSS
790	Anti-Claudin-18.2 VL	DIVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKN YLTWYQQKPGQPPKLLIYWASTRESGVPDRFTGSGSG TDFTLTISSVQAEDLAVYYCQNDYSYPFTFGSGTKLEI K
791	Anti-Claudin-18.2 CDR-H1	NYGMN
792	Anti-Claudin-18.2 CDR-H2	WINTNTGEPTYAEEFKG
793	Anti-Claudin-18.2 CDR-H3	LGFGNAMDY
794	Anti-Claudin-18.2 CDR-L1	KSSQSLLNSGNQKNYLT
795	Anti-Claudin-18.2 CDR-L2	WASTRES
796	Anti-Claudin-18.2 CDR-L3	QNDYSYPLT
797	Anti-Claudin-18.2 VH	QIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNWV KQAPGKGLKWMGWINTNTGEPTYAEEFKGRFAFSLE TSASTAYLQINNLKNEDTATYFCARLGFGNAMDYWG QGTSVTVSS
798	Anti-Claudin-18.2 VL	DIVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKN YLTWYQQKPGQPPKLLIYWASTRESGVPDRFTGSGSG TDFTLTISSVQAEDLAVYYCQNDYSYPLTFGAGTKLE LK
799	Anti-Nectin-4 CDR-H1	SYNMN
800	Anti-Nectin-4 CDR-H2	YISSSSSTIYYADSVKG
801	Anti-Nectin-4 CDR-H3	AYYYGMDV
802	Anti-Nectin-4 CDR-L1	RASQGISGWLA
803	Anti-Nectin-4 CDR-L2	AASTLQS
804	Anti-Nectin-4 CDR-L3	QQANSFPPT
805	Anti-Nectin-4 VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYNMNW VRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRDN AKNSLSLQMNSLRDEDTAVYYCARAYYYGMDVWG QGTTVTVSS
806	Anti-Nectin-4 VL	DIQMTQSPSSVSASVGDRVTITCRASQGISGWLAWYQ QKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPPTFGGGTKVEIK
807	Anti-SLTRK6 CDR-H1	SYGMH
808	Anti-SLTRK6 CDR-H2	VIWYDGSNQYYADSVKG
809	Anti-SLTRK6 CDR-H3	GLTSGRYGMDV
810	Anti-SLTRK6 CDR-L1	RSSQSLLLSHGFNYLD
811	Anti-SLTRK6 CDR-L2	LGSSRAS
812	Anti-SLTRK6 CDR-L3	MQPLQIPWT

813	Anti-SLTRK6 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHW VRQAPGKGLEWVAVIWYDGSNQYYADSVKGRFTISR DNSKNTLFLQMHSLRAEDTAVYYCARGLTSGRYGMD VWGQGTTVTVSS
814	Anti-SLTRK6 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLLSHGFNYLD WYLQKPGQSPQLLIYLGSSRASGVPDRFSGSGSGTDFT LKISRVEAEDVGLYYCMQPLQIPWTFGQGTKVEIK
815	Anti-CD142 (TF) CDR-H1	NYAMS
816	Anti-CD142 (TF) CDR-H2	SISGSGDYTYYTDSVKG
817	Anti-CD142 (TF) CDR-H3	SPWGYYLDS
818	Anti-CD142 (TF) CDR-L1	RASQGISSRLA
819	Anti-CD142 (TF) CDR-L2	AASSLQS
820	Anti-CD142 (TF) CDR-L3	QQYNSYPYT
821	Anti-CD142 (TF) VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSW VRQAPGKGLEWVSSISGSGDYTYYTDSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCARSPWGYYLDSW GQGTLVTVSS
822	Anti-CD142 (TF) VL	DIQMTQSPPSLSASAGDRVTITCRASQGISSRLAWYQQ KPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQYNSYPYTFGQGTKLEIK
823	Anti-h2G12/STn CDR-H1	DHAIH
824	Anti-STn CDR-H2	YFSPGNDDIKYNEKFRG
825	Anti-STn CDR-H3	SLSTPY
826	Anti-STn CDR-L1	KSSQSLLNRGNHKNYLT
827	Anti-STn CDR-L2	WASTRES
828	Anti-STn CDR-L3	QNDYTYPYT
829	Anti-STn VH	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDHAIHW VRQAPGQGLEWMGYFSPGNDDIKYNEKFRGRVTMT ADKSSSTAYMELRSLRSDDTAVYFCKRSLSTPYWGQ GTLVTVSS
830	Anti-STn VL	DIVMTQSPDSLAVSLGERATINCKSSQSLLNRGNHKN YLTWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSG TDFTLTISSLQAEDVAVYYCQNDYTYPYTFGQGTKVE IK
831	Anti-CD20 CDR-H1	SYNMH
832	Anti-CD20 CDR-H2	AIYPGNGDTSYNQKFKG
833	Anti-CD20 CDR-H3	STYYGGDWYFNV
834	Anti-CD20 CDR-L1	RASSSVSYIH
835	Anti-CD20 CDR-L2	ATSNLAS
836	Anti-CD20 CDR-L3	QQWTSNPPT
837	Anti-CD20 VH	QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMH WVKQTPGRGLEWIGAIYPGNGDTSYNQKFKGKATLT

		ADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWY FNVWGAGTTVTVSA
838	Anti-CD20 VL	QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQK PGSSPKPWIYATSNLASGVPVRFSGSGSGTSYSLTISRV EAEDAATYYCQQWTSNPPTFGGGTKLEIK
839	Anti-HER2 CDR-H1	DTYIH
840	Anti-HER2 CDR-H2	RIYPTNGYTRYADSVKG
841	Anti-HER2 CDR-H3	WGGDGFYAMDY
842	Anti-HER2 CDR-L1	RASQDVNTAVA
843	Anti-HER2 CDR-L2	SASFLYS
844	Anti-HER2 CDR-L3	QQHYTTPPT
845	Anti-HER2 VH	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWV RQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDY WGQGTLVTVSS
846	Anti-HER2 VL	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQ QKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTIS SLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
847	Anti-CD79b CDR-H1	SYWIE
848	Anti-CD79b CDR-H2	EILPGGGDTNYNEIFKG
849	Anti-CD79b CDR-H3	RVPIRLDY
850	Anti-CD79b CDR-L1	KASQSVDYEGDSFLN
851	Anti-CD79b CDR-L2	AASNLES
852	Anti-CD79b CDR-L3	QQSNEDPLT
853	Anti-CD79b VH	EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWV RQAPGKGLEWIGEILPGGGDTNYNEIFKGRATFSADTS KNTAYLQMNSLRAEDTAVYYCTRRVPIRLDYWGQGT LVTVSS
854	Anti-CD79b VL	DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLN WYQQKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQSNEDPLTFGQGTKVEIK
855	Anti-NaPi2B CDR-H1	DFAMS
856	Anti-NaPi2B CDR-H2	TIGRVAFHTYYPDSMKG
857	Anti-NaPi2B CDR-H3	HRGFDVGHFDF
858	Anti-NaPi2B CDR-L1	RSSETLVHSSGNTYLE
859	Anti-NaPi2B CDR-L2	RVSNRFS
860	Anti-NaPi2B CDR-L3	FQGSFNPLT
861	Anti-NaPi2B VH	EVQLVESGGGLVQPGGSLRLSCAASGFSFSDFAMSWV RQAPGKGLEWVATIGRVAFHTYYPDSMKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARHRGFDVGHFDF WGQGTLVTVSS
862	Anti-NaPi2B VL	DIQMTQSPSSLSASVGDRVTITCRSSETLVHSSGNTYL EWYQQKPGKAPKLLIYRVSNRFSGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCFQGSFNPLTFGQGTKVEIK
863	Anti-Muc16 CDR-H1	NDYAWN
864	Anti-Muc16 CDR-H2	YISYSGYTTYNPSLKS
865	Anti-Muc16 CDR-H3	WTSGLDY
866	Anti-Muc16 CDR-L1	KASDLIHNWLA
867	Anti-Muc16 CDR-L2	GATSLET

868	Anti-Muc16 CDR-L3	QQYWTTPFT
869	Anti-Muc16 VH	EVQLVESGGGLVQPGGSLRLSCAASGYSITNDYAWN WVRQAPGKGLEWVGYISYSGYTTYNPSLKSRFTISRD TSKNTLYLQMNSLRAEDTAVYYCARWTSGLDYWGQ GTLVTVSS
870	Anti-Muc16 VL	DIQMTQSPSSLSASVGDRVTITCKASDLIHNWLAWYQ QKPGKAPKLLIYGATSLETGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQYWTTPFTFGQGTKVEIK
871	Anti-STEAP1 CDR-H1	SDYAWN
872	Anti-STEAP1 CDR-H2	YISNSGSTSYNPSLKS
873	Anti-STEAP1 CDR-H3	ERNYDYDDYYYAMDY
874	Anti-STEAP1 CDR-L1	KSSQSLLYRSNQKNYLA
875	Anti-STEAP1 CDR-L2	WASTRES
876	Anti-STEAP1 CDR-L3	QQYYNYPRT
877	Anti-STEAP1 VH	EVQLVESGGGLVQPGGSLRLSCAVSGYSITSDYAWN WVRQAPGKGLEWVGYISNSGSTSYNPSLKSRFTISRD TSKNTLYLQMNSLRAEDTAVYYCARERNYDYDDYY YAMDYWGQGTLVTVSS
878	Anti-STEAP1 VL	DIQMTQSPSSLSASVGDRVTITCKSSQSLLYRSNQKNY LAWYQQKPGKAPKLLIYWASTRESGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQYYNYPRTFGQGTKVEIK
879	Anti-BCMA CDR-H1	NYWMH
880	Anti-BCMA CDR-H2	ATYRGHSDTYYNQKFKG
881	Anti-BCMA CDR-H3	GAIYDGYDVLDN
882	Anti-BCMA CDR-L1	SASQDISNYLN
883	Anti-BCMA CDR-L2	YTSNLHS
884	Anti-BCMA CDR-L3	QQYRKLPWT
885	Anti-BCMA VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSNYWMH WVRQAPGQGLEWMGATYRGHSDTYYNQKFKGRVTI TADKSTSTAYMELSSLRSEDTAVYYCARGAIYDGYD VLDNWGQGTLVTVSS
886	Anti-BCMA VL	DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQ KPGKAPKLLIYYTSNLHSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQYRKLPWTFGQGTKLEIK
887	Anti-c-Met CDR-H1	AYTMH
888	Anti-c-Met CDR-H2	WIKPNNGLANYAQKFQG
889	Anti-c-Met CDR-H3	SEITTEFDY
890	Anti-c-Met CDR-L1	KSSESVDSYANSFLH
891	Anti-c-Met CDR-L2	RASTRES
892	Anti-c-Met CDR-L3	QQSKEDPLT
893	Anti-c-Met VH	QVQLVQSGAEVKKPGASVKVSCKASGYIFTAYTMHW VRQAPGQGLEWMGWIKPNNGLANYAQKFQGRVTMT RDTSISTAYMELSRLRSDDTAVYYCARSEITTEFDYW GQGTLVTVSS
894	Anti-c-Met VL	DIVMTQSPDSLAVSLGERATINCKSSESVDSYANSFLH WYQQKPGQPPKLLIYRASTRESGVPDRFSGSGSGTDF TLTISSLQAEDVAVYYCQQSKEDPLTFGGGTKVEIK
895	Anti-EGFR CDR-H1	SDFAWN
896	Anti-EGFR CDR-H2	YISYSGNTRYQPSLKS

897	Anti-EGFR CDR-H3	AGRGFPY
898	Anti-EGFR CDR-L1	HSSQDINSNIG
899	Anti-EGFR CDR-L2	HGTNLDD
900	Anti-EGFR CDR-L3	VQYAQFPWT
901	Anti-EGFR VH	QVQLQESGPGLVKPSQTLSLTCTVSGYSISSDFAWNWI RQPPGKGLEWMGYISYSGNTRYQPSLKSRITISRDTSK NQFFLKLNSVTAADTATYYCVTAGRGFPYWGQGTLV TVSS
902	Anti-EGFR VL	DIQMTQSPSSMSVSVGDRVTITCHSSQDINSNIGWLQQ KPGKSFKGLIYHGTNLDDGVPSRFSGSGSGTDYTLTIS SLQPEDFATYYCVQYAQFPWTFGGGTKLEIK
903	Anti-SLAMF7 CDR-H1	DYYMA
904	Anti-SLAMF7 CDR-H2	SINYDGSSTYYVDSVKG
905	Anti-SLAMF7 CDR-H3	DRGYYFDY
906	Anti-SLAMF7 CDR-L1	RSSQSLVHSNGNTYLH
907	Anti-SLAMF7 CDR-L2	KVSNRFS
908	Anti-SLAMF7 CDR-L3	SQSTHVPPFT
909	Anti-SLAMF7 VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMAW VRQAPGKGLEWVASINYDGSSTYYVDSVKGRFTISRD NAKNSLYLQMNSLRAEDTAVYYCARDRGYYFDYWG QGTTVTVSS
910	Anti-SLAMF7 VL	DVVMTQTPLSLSVTPGQPASISCRSSQSLVHSNGNTYL HWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTD FTLKISRVEAEDVGVYFCSQSTHVPPFTFGGGTKVEIK
911	Anti-C4.4a CDR-H1	NAWMS
912	Anti-C4.4a CDR-H2	YISSSGSTIYYADSVKG
913	Anti-C4.4a CDR-H3	EGLWAFDY
914	Anti-C4.4a CDR-L1	TGSSSNIGAGYVVH
915	Anti-C4.4a CDR-L2	DNNKRPS
916	Anti-C4.4a CDR-L3	AAWDDRLNGPV
917	Anti-C4.4a VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSW VRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAREGLWAFDYWGQ GTLVTVSS
918	Anti-C4.4a VL	ESVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYVVHWY QQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLA ISGLRSEDEADYYCAAWDDRLNGPVFGGGTKLTVL
919	Anti-GCC CDR-H1	GYYWS
920	Anti-GCC CDR-H2	EINHRGNTNDNPSLKS
921	Anti-GCC CDR-H3	ERGYTYGNFDH
922	Anti-GCC CDR-L1	RASQSVSRNLA
923	Anti-GCC CDR-L2	GASTRAT
924	Anti-GCC CDR-L3	QQYKTWPRT

925	Anti-GCC VH	QVQLQQWGAGLLKPSETLSLTCAVFGGSFSGYYWSW IRQPPGKGLEWIGEINHRGNTNDNPSLKSRVTISVDTS KNQFALKLSSVTAADTAVYYCARERGYTYGNFDHW GQGTLVTVSS
926	Anti-GCC VL	EIVMTQSPATLSVSPGERATLSCRASQSVSRNLAWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIG SLQSEDFAVYYCQQYKTWPRTFGQGTNVEIK
927	Anti-Axl CDR-H1	SYAMN
928	Anti-Axl CDR-H2	TTSGSGASTYYADSVKG
929	Anti-Axl CDR-H3	IWIAFDI
930	Anti-Axl CDR-L1	RASQSVSSSYLA
931	Anti-Axl CDR-L2	GASSRAT
932	Anti-Axl CDR-L3	QQYGSSPYT
933	Anti-Axl VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNW VRQAPGKGLEWVSTTSGSGASTYYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCAKIWIAFDIWGQG TMVTVSS
934	Anti-Axl VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQ QKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTIS RLEPEDFAVYYCQQYGSSPYTFGQGTKLEIK
935	Anti-gpNMB CDR-H1	SFNYYWS
936	Anti-gpNMB CDR-H2	YIYYSGSTYSNPSLKS
937	Anti-gpNMB CDR-H3	GYNWNYFDY
938	Anti-gpNMB CDR-L1	RASQSVDNNLV
939	Anti-gpNMB CDR-L2	GASTRAT
940	Anti-gpNMB CDR-L3	QQYNNWPPWT
941	Anti-gpNMB VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSFNYYWS WIRHHPGKGLEWIGYIYYSGSTYSNPSLKSRVTISVDT SKNQFSLTLSSVTAADTAVYYCARGYNWNYFDYWG QGTLVTVSS
942	Anti-gpNMB VL	EIVMTQSPATLSVSPGERATLSCRASQSVDNNLVWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYNNWPPWTFGQGTKVEIK
943	Anti-gpNMB HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSFNYYWS WIRHHPGKGLEWIGYIYYSGSTYSNPSLKSRVTISVDT SKNQFSLTLSSVTAADTAVYYCARGYNWNYFDYWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
944	Anti-gpNMB LC	EIVMTQSPATLSVSPGERATLSCRASQSVDNNLVWYQ QKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIS SLQSEDFAVYYCQQYNNWPPWTFGQGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW

		KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC
945	Anti-Prolactin receptor CDR-H1	TYWMH
946	Anti-Prolactin receptor CDR-H2	EIDPSDSYSNYNQKFKD
947	Anti-Prolactin receptor CDR-H3	NGGLGPAWFSY
948	Anti-Prolactin receptor CDR-L1	KASQYVGTAVA
949	Anti-Prolactin receptor CDR-L2	SASNRYT
950	Anti-Prolactin receptor CDR-L3	QQYSSYPWT
951	Anti-Prolactin receptor VH	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTTYWMH WVRQAPGQGLEWIGEIDPSDSYSNYNQKFKDRATLT VDKSTSTAYMELSSLRSEDTAVYYCARNGGLGPAWF SYWGQGTLVTVSS
952	Anti-Prolactin receptor VL	DIQMTQSPSSVSASVGDRVTITCKASQYVGTAVAWY QQKPGKSPKLLIYSASNRYTGVPSRFSDSGSGTDFTLTI SSLQPEDFATYFCQQYSSYPWTFGGGTKVEIK
953	Anti-FGFR2 CDR-H1	SYAMS
954	Anti-FGFR2 CDR-H2	AISGSGTSTYYADSVKG
955	Anti-FGFR2 CDR-H3	VRYNWNHGDWFDP
956	Anti-FGFR2 CDR-L1	SGSSSNIGNNYVS
957	Anti-FGFR2 CDR-L2	ENYNRPA
958	Anti-FGFR2 CDR-L3	SSWDDSLNYWV
959	Anti-FGFR2 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSAISGSGTSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARVRYNWNHGDWF DPWGQGTLVTVSS
960	Anti-FGFR2 VL	QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNYVSWYQ QLPGTAPKLLIYENYNRPAGVPDRFSGSKSGTSASLAI SGLRSEDEADYYCSSWDDSLNYWVFGGGTKLTVL
961	Anti-CDCP1 CDR-H1	SYGMS
962	Anti-CDCP1 CDR-H2	TISSGGSYKYYVDSVKG
963	Anti-CDCP1 CDR-H3	HPDYDGVWFAY
964	Anti-CDCP1 CDR-L1	SVSSSVFYVH
965	Anti-CDCP1 CDR-L2	DTSKLAS
966	Anti-CDCP1 CDR-L3	QQWNSNPPT
967	Anti-CDCP1 VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFNSYGMSW VRQAPGKGLEWVATISSGGSYKYYVDSVKGRFTISRD NAKNSLYLQMNSLRAEDTAVYYCARHPDYDGVWFA YWGQGTLVTVSS
968	Anti-CDCP1 VL	DIQMTQSPSSLSASVGDRVTITCSVSSSVFYVHWYQQ KPGKAPKLLIYDTSKLASGVPSRFSGSGSGTDFTFTISS LQPEDIATYYCQQWNSNPPTFGGGTKVEIK
969	Anti-CDCP1 CDR-H1	SYGMS
970	Anti-CDCP1 CDR-H2	TISSGGSYTYYPDSVKG

971	Anti-CDCP1 CDR-H3	HPDYDGVWFAY
972	Anti-CDCP1 CDR-L1	SVSSSVFYVH
973	Anti-CDCP1 CDR-L2	DTSKLAS
974	Anti-CDCP1 CDR-L3	QQWNSNPPT
975	Anti-CDCP1 VH	EVQLVESGGDLVKPGGSLKLSCAASGFTFNSYGMSW VRQTPDKRLEWVATISSGGSYTYYPDSVKGRFTISRD NAKNTLYLQMSSLKSEDTAMYYCARHPDYDGVWFA YWGQGTLVTVSA
976	Anti-CDCP1 VL	QIVLTQSPAIMSASPGEKVTMTCSVSSSVFYVHWYQQ KSGTSPKRWIYDTSKLASGVPARFSGSGSGTSYSLTISS MEAEDAATYYCQQWNSNPPTFGGGTKLEIK
977	Anti-CDCP1 CDR-H1	SYYMH
978	Anti-CDCP1 CDR-H2	IINPSGGSTSYAQKFQG
979	Anti-CDCP1 CDR-H3	DGVLRYFDWLLDYYYYMDV
980	Anti-CDCP1 CDR-L1	RASQSVGSYLA
981	Anti-CDCP1 CDR-L2	DASNRAT
982	Anti-CDCP1 CDR-L3	QQRANVFT
983	Anti-CDCP1 VH	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMH WVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARDGVLRYFDW LLDYYYYMDVWGKGTTVTVSS
984	Anti-CDCP1 VL	EIVLTQSPATLSLSPGERATLSCRASQSVGSYLAWYQQ RPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISS LEPEDFAVYYCQQRANVFTFGQGTKVEIK
985	Anti-CDCP1 CDR-H1	SYYMH
986	Anti-CDCP1 CDR-H2	IINPSGGSTSYAQKFQG
987	Anti-CDCP1 CDR-H3	DAELRHFDHLLDYHYYMDV
988	Anti-CDCP1 CDR-L1	RASQSVGSYLA
989	Anti-CDCP1 CDR-L2	DASNRAT
990	Anti-CDCP1 CDR-L3	QQRAQEFT
991	Anti-CDCP1 VH	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMH WVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARDAELRHFDHL LDYHYYMDVWGQGTTVTVSS
992	Anti-CDCP1 VL	EIVMTQSPATLSLSPGERATLSCRASQSVGSYLAWYQ QKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTIS SLQPEDFAVYYCQQRAQEFTFGQGTKVEIK
993	Anti-ASCT2 VH	QVQLVQSGSELKKPGAPVKVSCKASGYTFSTFGMSW VRQAPGQGLKWMGWIHTYAGVPIYGDDFKGRFVFSL DTSVSTAYLQISSLKAEDTAVYFCARRSDNYRYFFDY WGQGTTVTVSS
994	Anti-ASCT2 VL	DIQMTQSPSSLSASLGDRVTITCRASQDIRNYLNWYQ QKPGKAPKLLIYYTSRLHSGVPSRFSGSGSGTDYTLTIS SLQPEDFATYFCQQGHTLPPTFGQGTKLEIK
995	Anti-ASCT2 VH	QIQLVQSGPELKKPGAPVKISCKASGYTFTTFGMSWV KQAPGQGLKWMGWIHTYAGVPIYGDDFKGRFVFSLD TSVSTAYLQISSVKAEDTATYFCARRSDNYRYFFDYW GQGTTLTVSS

996	Anti-ASCT2 VL	DIQMTQSPSSLSASLGDRVTITCRASQDIRNYLNWYQ QKPGKAPKLLIYYTSRLHSGVPSRFSGSGSGTDYTLTIS SLQPEDFATYFCQQGHTLPPTFGQGTKLEIK
997	Anti-ASCT2 CDR-H1	NYYMA
998	Anti-ASCT2 CDR-H2	SITKGGGNTYYRDSVKG
999	Anti-ASCT2 CDR-H3	QVTIAAVSTSYFDS
1000	Anti-ASCT2 CDR-L1	KTNQKVDYYGNSYVY
1001	Anti-ASCT2 CDR-L2	LASNLAS
1002	Anti-ASCT2 CDR-L3	QQSRNLPYT
1003	Anti-ASCT2 VH	EVQLVESGGGLVQSGRSIRLSCAASGFSFSNYYMAWV RQAPSKGLEWVASITKGGGNTYYRDSVKGRFTFSRD NAKSTLYLQMDSLRSEDTATYYCARQVTIAAVSTSYF DSWGQGVMVTVSS
1004	Anti-ASCT2 VL	DIVLTQSPALAVSLGQRATISCKTNQKVDYYGNSYVY WYQQKPGQQPKLLIYLASNLASGIPARFSGRGSGTDF TLTIDPVEADDTATYYCQQSRNLPYTFGAGTKLELK
1005	Anti-CD123 CDR-H1	DYYMK
1006	Anti-CD123 CDR-H2	DIIPSNGATFYNQKFKG
1007	Anti-CD123 CDR-H3	SHLLRASWFAY
1008	Anti-CD123 CDR-L1	KSSQSLLNSGNQKNYLT
1009	Anti-CD123 CDR-L2	WASTRES
1010	Anti-CD123 CDR-L3	QNDYSYPYT
1011	Anti-CD123 VH	QVQLVQSGAEVKKPGASVKMSCKASGYTFTDYYMK WVKQAPGQGLEWIGDIIPSNGATFYNQKFKGKATLTV DRSISTAYMHLNRLRSDDTAVYYCTRSHLLRASWFA YWGQGTLVTVSS
1012	Anti-CD123 VL	DFVMTQSPDSLAVSLGERATINCKSSQSLLNSGNQKN YLTWYLQKPGQPPKLLIYWASTRESGVPDRFSGSGSG TDFTLTISSLQAEDVAVYYCQNDYSYPYTFGQGTKLEI K
1013	Anti-GPC3 CDR-H1	DYEMH
1014	Anti-GPC3 CDR-H2	GIDPETGGTAYNQKFKG
1015	Anti-GPC3 CDR-H3	YYSFAY
1016	Anti-GPC3 CDR-L1	RSSQSIVHSNANTYLQ
1017	Anti-GPC3 CDR-L2	KVSNRFS
1018	Anti-GPC3 CDR-L3	FQVSHVPYT
1019	Anti-GPC3 VH	EVQLVQSGAEVKKPGATVKISCKVSGYTFTDYEMHW VQQAPGKGLEWMGGIDPETGGTAYNQKFKGRVTLTA DKSTDTAYMELSSLRSEDTAVYYCGRYYSFAYWGQG TLVTVSS
1020	Anti-GPC3 VL	DVVMTQSPLSLPVTLGQPASISCRSSQSIVHSNANTYL QWFQQRPGQSPRLLIYKVSNRFSGVPDRFSGSGSGTDF TLKISRVEAEDVGVYYCFQVSHVPYTFGQGTKLEIK
1021	Anti-TIGIT CDR-H1	SYAIS
1022	Anti-TIGIT CDR-H2	SIIPIFGTANYAQKFQG
1023	Anti-TIGIT CDR-H3	GPSEVGAILGYVWFDP
1024	Anti-TIGIT CDR-L1	RSSQSLLHSNGYNYLD
1025	Anti-TIGIT CDR-L2	LGSNRAS
1026	Anti-TIGIT CDR-L3	MQARRIPIT

1027	Anti-TIGIT VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGSIIPIFGTANYAQKFQGRVTITADES TSTAYMELSSLRSEDTAVYYCARGPSEVGAILGYVWF DPWGQGTLVTVSS
1028	Anti-TIGIT VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLD WYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDF TLKISRVEAEDVGVYYCMQARRIPITFGGGTKVEIK
1029	Anti-CD33 CDR-H1	NYDIN
1030	Anti-CD33 CDR-H2	WIYPGDGSTKYNEKFKA
1031	Anti-CD33 CDR-H3	GYEDAMDY
1032	Anti-CD33 CDR-L1	KASQDINSYLS
1033	Anti-CD33 CDR-L2	RANRLVD
1034	Anti-CD33 CDR-L3	LQYDEFPLT
1035	Anti-CD33 VH	QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYDINWVRQA PGQGLEWIGW IYPGDGSTKY NEKFKAKATL TADTSTSTAY MELRSLRSDD TAVYYCASGY EDAMDYWGQG TTVTVSS
1036	Anti-CD33 VL	DIQMTQSPSSLSASVGDRVTINCKASQDINSYLSWFQQ KPGKAPKTLIYRANRVDGVPSRFSGSGSGQDYTLT ISSLQPEDFATYYCLQYDEFPLTFGGGTKVEIK
1037	Anti-BCMA CDR-H1	DYYIH
1038	Anti-BCMA CDR-H2	YINPNSGYTNYAQKFQG
1039	Anti-BCMA CDR-H3	YMWERVTGFFDF
1040	Anti-BCMA CDR-L1	LASEDISDDLA
1041	Anti-BCMA CDR-L2	TTSSLQS
1042	Anti-BCMA CDR-L3	QQTYKFPPT
1043	Anti-BCMA VH	QVQLVQSGAEVKKPGASVKLSCKASGYTFTDYYIHW VRQAPGQGLEWIGYINPNSGYTNYAQKFQGRATMTA DKSINTAYVELSRLRSDDTAVYFCTRYMWERVTGFFD FWGQGTMVTVSS
1044	Anti-BCMA VL	DIQMTQSPSSVSASVGDRVTITCLASEDISDDLAWYQQ KPGKAPKVLVYTTSSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYFCQQTYKFPPTFGGGTKVEIK

(i) Heavy Chain and Light Chain Variable Regions

[0230] In some cases, an antibody of the present disclosure comprises a heavy chain variable region having at least 80% sequence identity to a first sequence and a light chain variable region having at least 80% sequence identity to a second sequence, and wherein: the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20; the first sequence is SEQ ID NO: 44 and the second sequence is SEQ ID NO: 45; the first sequence is SEQ ID NO: 55 and the second sequence is SEQ ID NO: 56; the first sequence is SEQ ID NO: 69 and the second sequence is SEQ ID NO: 70; the first sequence is SEQ ID NO: 83 and the second sequence is SEQ ID NO: 84; the first sequence is SEQ ID NO: 97 and the second sequence is SEQ ID NO: 98; the first sequence is SEQ ID NO: 105 and the second sequence is SEQ ID NO: 106; the first sequence is SEQ ID

NO:113 and the second sequence is SEQ ID NO: 114; the first sequence is SEQ ID NO: 121 and the second sequence is SEQ ID NO: 122; the first sequence is SEQ ID NO: 129 and the second sequence is SEQ ID NO: 130; the first sequence is SEQ ID NO: 137 and the second sequence is SEQ ID NO: 138; the first sequence is SEQ ID NO: 153 and the second sequence is SEQ ID NO: 154; the first sequence is SEQ ID NO: 161 and the second sequence is SEQ ID NO: 162; the first sequence is SEQ ID NO: 169 and the second sequence is SEQ ID NO: 170; the first sequence is SEQ ID NO: 177 and the second sequence is SEQ ID NO: 178; the first sequence is SEQ ID NO: 185 and the second sequence is SEQ ID NO: 186; the first sequence is SEQ ID NO: 193 and the second sequence is SEQ ID NO: 194; the first sequence is SEQ ID NO: 201 and the second sequence is SEQ ID NO: 202; the first sequence is SEQ ID NO: 209 and the second sequence is SEQ ID NO: 210; the first sequence is SEQ ID NO: 217 and the second sequence is SEQ ID NO: 218; the first sequence is SEQ ID NO: 225 and the second sequence is SEQ ID NO: 226; the first sequence is SEQ ID NO: 233 and the second sequence is SEQ ID NO: 234; the first sequence is SEQ ID NO: 241 and the second sequence is SEQ ID NO: 242; the first sequence is SEQ ID NO: 249 and the second sequence is SEQ ID NO: 250; the first sequence is SEQ ID NO: 297 and the second sequence is SEQ ID NO: 298; the first sequence is SEQ ID NO: 307 and the second sequence is SEQ ID NO: 308; the first sequence is SEQ ID NO: 315 and the second sequence is SEQ ID NO: 316; the first sequence is SEQ ID NO: 323 and the second sequence is SEQ ID NO: 324; the first sequence is SEQ ID NO: 331 and the second sequence is SEQ ID NO: 332; the first sequence is SEQ ID NO: 339 and the second sequence is SEQ ID NO: 340; the first sequence is SEQ ID NO: 347 and the second sequence is SEQ ID NO: 348; the first sequence is SEQ ID NO: 355 and the second sequence is SEQ ID NO: 356; the first sequence is SEQ ID NO: 363 and the second sequence is SEQ ID NO: 364; the first sequence is SEQ ID NO: 371 and the second sequence is SEQ ID NO: 372; the first sequence is SEQ ID NO: 379 and the second sequence is SEQ ID NO: 380; the first sequence is SEQ ID NO: 387 and the second sequence is SEQ ID NO: 388; the first sequence is SEQ ID NO: 395 and the second sequence is SEQ ID NO: 396; the first sequence is SEQ ID NO: 403 and the second sequence is SEQ ID NO: 404; the first sequence is SEQ ID NO: 411 and the second sequence is SEQ ID NO: 412; the first sequence is SEQ ID NO: 419 and the second sequence is SEQ ID NO: 420; the first sequence is SEQ ID NO: 427 and the second sequence is SEQ ID NO: 428; the first sequence is SEQ ID NO: 435 and the second sequence is SEQ ID NO: 436; the first sequence is SEQ ID NO: 443 and the second sequence is SEQ ID NO: 444; the first sequence is SEQ ID NO: 451 and the second sequence is SEQ ID NO: 452; the first sequence is SEQ ID NO: 459 and the second sequence is SEQ ID NO: 460; the first sequence is SEQ ID NO: 467 and the second sequence is SEQ ID NO: 468; the first sequence is

SEQ ID NO: 475 and the second sequence is SEQ ID NO: 476; the first sequence is SEQ ID NO: 483 and the second sequence is SEQ ID NO: 484; the first sequence is SEQ ID NO: 491 and the second sequence is SEQ ID NO: 492; the first sequence is SEQ ID NO: 501 and the second sequence is SEQ ID NO: 502; the first sequence is SEQ ID NO: 509 and the second sequence is SEQ ID NO: 510; the first sequence is SEQ ID NO: 517 and the second sequence is SEQ ID NO: 518; the first sequence is SEQ ID NO: 525 and the second sequence is SEQ ID NO: 526; the first sequence is SEQ ID NO: 533 and the second sequence is SEQ ID NO: 534; the first sequence is SEQ ID NO: 541 and the second sequence is SEQ ID NO: 542; the first sequence is SEQ ID NO: 549 and the second sequence is SEQ ID NO: 550; the first sequence is SEQ ID NO: 557 and the second sequence is SEQ ID NO: 558; the first sequence is SEQ ID NO: 565 and the second sequence is SEQ ID NO: 566; the first sequence is SEQ ID NO: 574 and the second sequence is SEQ ID NO: 574; the first sequence is SEQ ID NO: 581 and the second sequence is SEQ ID NO: 582; the first sequence is SEQ ID NO: 589 and the second sequence is SEQ ID NO: 590; the first sequence is SEQ ID NO: 597 and the second sequence is SEQ ID NO: 598; the first sequence is SEQ ID NO: 605 and the second sequence is SEQ ID NO: 606; the first sequence is SEQ ID NO: 613 and the second sequence is SEQ ID NO: 614; the first sequence is SEQ ID NO: 621 and the second sequence is SEQ ID NO: 622; the first sequence is SEQ ID NO: 629 and the second sequence is SEQ ID NO: 630; the first sequence is SEQ ID NO: 637 and the second sequence is SEQ ID NO: 638; the first sequence is SEQ ID NO: 645 and the second sequence is SEQ ID NO: 646; the first sequence is SEQ ID NO: 653 and the second sequence is SEQ ID NO: 654; the first sequence is SEQ ID NO: 661 and the second sequence is SEQ ID NO: 662; the first sequence is SEQ ID NO: 669 and the second sequence is SEQ ID NO: 670; the first sequence is SEQ ID NO: 677 and the second sequence is SEQ ID NO: 678; the first sequence is SEQ ID NO: 685 and the second sequence is SEQ ID NO: 686; the first sequence is SEQ ID NO: 693 and the second sequence is SEQ ID NO: 694; the first sequence is SEQ ID NO: 701 and the second sequence is SEQ ID NO: 702; the first sequence is SEQ ID NO: 703 and the second sequence is SEQ ID NO: 704; the first sequence is SEQ ID NO: 711 and the second sequence is SEQ ID NO: 712; the first sequence is SEQ ID NO: 713 and the second sequence is SEQ ID NO: 714; the first sequence is SEQ ID NO: 715 and the second sequence is SEQ ID NO: 716; the first sequence is SEQ ID NO: 731 and the second sequence is SEQ ID NO: 732; the first sequence is SEQ ID NO: 739 and the second sequence is SEQ ID NO: 740; the first sequence is SEQ ID NO: 747 and the second sequence is SEQ ID NO: 748; the first sequence is SEQ ID NO: 755 and the second sequence is SEQ ID NO: 756; the first sequence is SEQ ID NO: 765 and the second sequence is SEQ ID NO: 766; the first sequence is SEQ ID NO: 773 and the second sequence is SEQ ID NO: 774; the first

sequence is SEQ ID NO: 781 and the second sequence is SEQ ID NO: 782; the first sequence is SEQ ID NO: 789 and the second sequence is SEQ ID NO: 790; the first sequence is SEQ ID NO: 797 and the second sequence is SEQ ID NO: 798; the first sequence is SEQ ID NO: 805 and the second sequence is SEQ ID NO: 806; the first sequence is SEQ ID NO: 813 and the second sequence is SEQ ID NO: 814; the first sequence is SEQ ID NO: 821 and the second sequence is SEQ ID NO: 822; the first sequence is SEQ ID NO: 829 and the second sequence is SEQ ID NO: 830; the first sequence is SEQ ID NO: 837 and the second sequence is SEQ ID NO: 838; the first sequence is SEQ ID NO: 845 and the second sequence is SEQ ID NO: 846; the first sequence is SEQ ID NO: 853 and the second sequence is SEQ ID NO: 854; the first sequence is SEQ ID NO: 861 and the second sequence is SEQ ID NO: 862; the first sequence is SEQ ID NO: 869 and the second sequence is SEQ ID NO: 870; the first sequence is SEQ ID NO: 877 and the second sequence is SEQ ID NO: 878; the first sequence is SEQ ID NO: 885 and the second sequence is SEQ ID NO: 886; the first sequence is SEQ ID NO: 893 and the second sequence is SEQ ID NO: 894; the first sequence is SEQ ID NO: 900 and the second sequence is SEQ ID NO: 901; the first sequence is SEQ ID NO: 909 and the second sequence is SEQ ID NO: 910; the first sequence is SEQ ID NO: 917 and the second sequence is SEQ ID NO: 918; the first sequence is SEQ ID NO: 925 and the second sequence is SEQ ID NO: 926; the first sequence is SEQ ID NO: 933 and the second sequence is SEQ ID NO: 934; the first sequence is SEQ ID NO: 941 and the second sequence is SEQ ID NO: 942; the first sequence is SEQ ID NO: 943 and the second sequence is SEQ ID NO: 944; the first sequence is SEQ ID NO: 951 and the second sequence is SEQ ID NO: 952; the first sequence is SEQ ID NO: 959 and the second sequence is SEQ ID NO: 960; the first sequence is SEQ ID NO: 967 and the second sequence is SEQ ID NO: 968; the first sequence is SEQ ID NO: 975 and the second sequence is SEQ ID NO: 976; the first sequence is SEQ ID NO: 983 and the second sequence is SEQ ID NO: 984; the first sequence is SEQ ID NO: 991 and the second sequence is SEQ ID NO: 992; the first sequence is SEQ ID NO: 993 and the second sequence is SEQ ID NO: 994; the first sequence is SEQ ID NO: 995 and the second sequence is SEQ ID NO: 996; the first sequence is SEQ ID NO: 1003 and the second sequence is SEQ ID NO: 1004; the first sequence is SEQ ID NO: 1011 and the second sequence is SEQ ID NO: 1012; the first sequence is SEQ ID NO: 1019 and the second sequence is SEQ ID NO: 1020; the first sequence is SEQ ID NO: 1027 and the second sequence is SEQ ID NO: 1028; the first sequence is SEQ ID NO: 1035 and 1036; or the first sequence is SEQ ID NO: 1043 and the second sequence is SEQ ID NO: 1044.

[0231] In some cases, an antibody of the present disclosure targets an immune checkpoint selected from the group consisting of PDL1, B7H4, B7H3, and TIGIT. For example, in some

cases, the antibody comprises a heavy chain variable region having at least 80% sequence identity to a first sequence and a light chain variable region having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20; the first sequence is SEQ ID NO: 83 and the second sequence is SEQ ID NO: 84; the first sequence is SEQ ID NO: 97 and the second sequence is SEQ ID NO: 98; the first sequence is SEQ ID NO: 105 and the second sequence is SEQ ID NO: 106; the first sequence is SEQ ID NO:113 and the second sequence is SEQ ID NO: 114; the first sequence is SEQ ID NO: 121 and the second sequence is SEQ ID NO: 122; the first sequence is SEQ ID NO: 129 and the second sequence is SEQ ID NO: 130; the first sequence is SEQ ID NO: 137 and the second sequence is SEQ ID NO: 138; the first sequence is SEQ ID NO: 153 and the second sequence is SEQ ID NO: 154; the first sequence is SEQ ID NO: 161 and the second sequence is SEQ ID NO: 162; the first sequence is SEQ ID NO: 169 and the second sequence is SEQ ID NO: 170; the first sequence is SEQ ID NO: 177 and the second sequence is SEQ ID NO: 178; the first sequence is SEQ ID NO: 185 and the second sequence is SEQ ID NO: 186; the first sequence is SEQ ID NO: 193 and the second sequence is SEQ ID NO: 194; the first sequence is SEQ ID NO: 201 and the second sequence is SEQ ID NO: 202; the first sequence is SEQ ID NO: 209 and the second sequence is SEQ ID NO: 210; the first sequence is SEQ ID NO: 217 and the second sequence is SEQ ID NO: 218; the first sequence is SEQ ID NO: 225 and the second sequence is SEQ ID NO: 226; the first sequence is SEQ ID NO: 233 and the second sequence is SEQ ID NO: 234; the first sequence is SEQ ID NO: 241 and the second sequence is SEQ ID NO: 242; the first sequence is SEQ ID NO: 249 and the second sequence is SEQ ID NO: 250; the first sequence is SEQ ID NO: 629 and the second sequence is SEQ ID NO: 630; the first sequence is SEQ ID NO: 637 and the second sequence is SEQ ID NO: 638; the first sequence is SEQ ID NO: 645 and the second sequence is SEQ ID NO: 646; the first sequence is SEQ ID NO: 653 and the second sequence is SEQ ID NO: 654; the first sequence is SEQ ID NO: 661 and the second sequence is SEQ ID NO: 662; the first sequence is SEQ ID NO: 669 and the second sequence is SEQ ID NO: 670; the first sequence is SEQ ID NO: 677 and the second sequence is SEQ ID NO: 678; the first sequence is SEQ ID NO: 685 and the second sequence is SEQ ID NO: 686; the first sequence is SEQ ID NO: 693 and the second sequence is SEQ ID NO: 694; the first sequence is SEQ ID NO: 701 and the second sequence is SEQ ID NO: 702; the first sequence is SEQ ID NO: 703 and the second sequence is SEQ ID NO: 704; the first sequence is SEQ ID NO: 711 and the second sequence is SEQ ID NO: 712; the first sequence is SEQ ID NO: 713 and the second sequence is SEQ ID NO: 714; the first sequence is SEQ ID NO: 715 and the second sequence is SEQ ID NO: 716; or the first sequence is SEQ ID NO: 1027 and the second sequence is SEQ ID NO: 1028.

[0232] In some cases, an antibody of the present disclosure comprises a heavy chain variable region having at least 80% sequence identity to a first sequence and a light chain variable region having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20; the first sequence is SEQ ID NO: 83 and the second sequence is SEQ ID NO: 84; the first sequence is SEQ ID NO: 97 and the second sequence is SEQ ID NO: 98; the first sequence is SEQ ID NO: 105 and the second sequence is SEQ ID NO: 106; the first sequence is SEQ ID NO: 113 and the second sequence is SEQ ID NO: 114; the first sequence is SEQ ID NO: 121 and the second sequence is SEQ ID NO: 122; the first sequence is SEQ ID NO: 129 and the second sequence is SEQ ID NO: 130; the first sequence is SEQ ID NO: 137 and the second sequence is SEQ ID NO: 138; the first sequence is SEQ ID NO: 153 and the second sequence is SEQ ID NO: 154; the first sequence is SEQ ID NO: 161 and the second sequence is SEQ ID NO: 162; the first sequence is SEQ ID NO: 169 and the second sequence is SEQ ID NO: 170; the first sequence is SEQ ID NO: 177 and the second sequence is SEQ ID NO: 178; the first sequence is SEQ ID NO: 185 and the second sequence is SEQ ID NO: 186; the first sequence is SEQ ID NO: 193 and the second sequence is SEQ ID NO: 194; the first sequence is SEQ ID NO: 201 and the second sequence is SEQ ID NO: 202; the first sequence is SEQ ID NO: 209 and the second sequence is SEQ ID NO: 210; the first sequence is SEQ ID NO: 217 and the second sequence is SEQ ID NO: 218; the first sequence is SEQ ID NO: 225 and the second sequence is SEQ ID NO: 226; the first sequence is SEQ ID NO: 233 and the second sequence is SEQ ID NO: 234; the first sequence is SEQ ID NO: 241 and the second sequence is SEQ ID NO: 242; the first sequence is SEQ ID NO: 249 and the second sequence is SEQ ID NO: 250; or the first sequence is SEQ ID NO: 1027 and the second sequence is SEQ ID NO: 1028. In some cases, the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20.

[0233] In some cases, the heavy chain variable region has at least 85% sequence identity to the first sequence and the light chain variable region has at least 85% sequence identity to the second sequence. In some cases, the heavy chain variable region has at least 90% sequence identity to the first sequence and the light chain variable region has at least 90% sequence identity to the second sequence. In some cases, the heavy chain variable region has at least 95% sequence identity to the first sequence and the light chain variable region has at least 95% sequence identity to the second sequence. In some cases, the heavy chain variable region has at least 98% sequence identity to the first sequence and the light chain variable region has at least 98% sequence identity to the second sequence. In some cases, the heavy chain variable region has at least 99% sequence identity to the first sequence and the light chain variable region has at least 99% sequence identity to the

second sequence. In some cases, the heavy chain variable region comprises the first sequence and the light chain variable region comprises the second sequence.

(ii) Heavy and Light Chains

[0234] In some cases, an antibody of the present disclosure comprises a heavy chain having at least 80% sequence identity to a first sequence and a light chain having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 1 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 2 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 4 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 6 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 7 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 8 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 9 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 46 and the second sequence is SEQ ID NO: 48; the first sequence is SEQ ID NO: 47 and the second sequence is SEQ ID NO: 48; the first sequence is SEQ ID NO: 57 and the second sequence is SEQ ID NO: 59; the first sequence is SEQ ID NO: 58 and the second sequence is SEQ ID NO: 59; the first sequence is SEQ ID NO: 60 and the second sequence is SEQ ID NO: 62; the first sequence is SEQ ID NO: 61 and the second sequence is SEQ ID NO: 62; the first sequence is SEQ ID NO: 71 and the second sequence is SEQ ID NO: 73; the first sequence is SEQ ID NO: 72 and the second sequence is SEQ ID NO: 73; the first sequence is SEQ ID NO: 74 and the second sequence is SEQ ID NO: 76; the first sequence is SEQ ID NO: 75 and the second sequence is SEQ ID NO: 76; the first sequence is SEQ ID NO: 85 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 86 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 88 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 89 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 251 and the second sequence is SEQ ID NO: 252; the first sequence is SEQ ID NO: 253 and the second sequence is SEQ ID NO: 254; the first sequence is SEQ ID NO: 255 and the second sequence is SEQ ID NO: 256; the first sequence is SEQ ID NO: 257 and the second sequence is SEQ ID NO: 258; the first sequence is SEQ ID NO: 259 and the second sequence is SEQ ID NO: 260; the first sequence is SEQ ID NO: 261 and the second sequence is SEQ ID NO: 262; the first sequence is SEQ ID NO: 263 and the second sequence is SEQ ID NO: 264; the first sequence is SEQ ID NO: 265 and the second sequence is SEQ ID NO: 266; the first sequence is SEQ ID NO: 267 and the second sequence is SEQ ID NO: 268; the first sequence is SEQ ID NO: 269 and the second sequence is SEQ ID NO: 270; the first sequence is SEQ ID NO: 271 and the second sequence is SEQ ID NO: 272; the first sequence is SEQ ID NO: 273 and the

second sequence is SEQ ID NO: 274; the first sequence is SEQ ID NO: 275 and the second sequence is SEQ ID NO: 276; the first sequence is SEQ ID NO: 277 and the second sequence is SEQ ID NO: 278; the first sequence is SEQ ID NO: 279 and the second sequence is SEQ ID NO: 280; the first sequence is SEQ ID NO: 281 and the second sequence is SEQ ID NO: 282; the first sequence is SEQ ID NO: 283 and the second sequence is SEQ ID NO: 284; the first sequence is SEQ ID NO: 285 and the second sequence is SEQ ID NO: 286; the first sequence is SEQ ID NO: 287 and the second sequence is SEQ ID NO: 288; the first sequence is SEQ ID NO: 289 and the second sequence is SEQ ID NO: 290; the first sequence is SEQ ID NO: 299 and the second sequence is SEQ ID NO: 300; the first sequence is SEQ ID NO: 493 and the second sequence is SEQ ID NO: 494; the first sequence is SEQ ID NO: 717 and the second sequence is SEQ ID NO: 718; the first sequence is SEQ ID NO: 719 and the second sequence is SEQ ID NO: 720; the first sequence is SEQ ID NO: 721 and the second sequence is SEQ ID NO: 722; the first sequence is SEQ ID NO: 723 and the second sequence is SEQ ID NO: 724; or the first sequence is SEQ ID NO: 757 and the second sequence is SEQ ID NO: 758.

[0235] In some cases, an antibody of the present disclosure comprises a heavy chain having at least 80% sequence identity to a first sequence and a light chain having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 1 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 2 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 4 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 6 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 7 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 8 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 9 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 85 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 86 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 88 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 89 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 251 and the second sequence is SEQ ID NO: 252; the first sequence is SEQ ID NO: 253 and the second sequence is SEQ ID NO: 254; the first sequence is SEQ ID NO: 255 and the second sequence is SEQ ID NO: 256; the first sequence is SEQ ID NO: 257 and the second sequence is SEQ ID NO: 258; the first sequence is SEQ ID NO: 259 and the second sequence is SEQ ID NO: 260; the first sequence is SEQ ID NO: 261 and the second sequence is SEQ ID NO: 262; the first sequence is SEQ ID NO: 263 and the second sequence is SEQ ID NO: 264; the first sequence is SEQ ID NO: 265 and the second sequence is SEQ ID NO: 266; the first sequence is SEQ ID NO: 267 and the second

sequence is SEQ ID NO: 268; the first sequence is SEQ ID NO: 269 and the second sequence is SEQ ID NO: 270; the first sequence is SEQ ID NO: 271 and the second sequence is SEQ ID NO: 272; the first sequence is SEQ ID NO: 273 and the second sequence is SEQ ID NO: 274; the first sequence is SEQ ID NO: 275 and the second sequence is SEQ ID NO: 276; the first sequence is SEQ ID NO: 277 and the second sequence is SEQ ID NO: 278; the first sequence is SEQ ID NO: 279 and the second sequence is SEQ ID NO: 280; the first sequence is SEQ ID NO: 281 and the second sequence is SEQ ID NO: 282; the first sequence is SEQ ID NO: 283 and the second sequence is SEQ ID NO: 284; the first sequence is SEQ ID NO: 285 and the second sequence is SEQ ID NO: 286; the first sequence is SEQ ID NO: 287 and the second sequence is SEQ ID NO: 288; the first sequence is SEQ ID NO: 289 and the second sequence is SEQ ID NO: 290; the first sequence is SEQ ID NO: 717 and the second sequence is SEQ ID NO: 718; the first sequence is SEQ ID NO: 719 and the second sequence is SEQ ID NO: 720; the first sequence is SEQ ID NO: 721 and the second sequence is SEQ ID NO: 722; or the first sequence is SEQ ID NO: 723 and the second sequence is SEQ ID NO: 724.

[0236] In some cases, an antibody of the present disclosure comprises a heavy chain having at least 80% sequence identity to a first sequence and a light chain having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 1 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 2 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 4 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 6 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 7 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 8 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 9 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 85 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 86 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 88 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 89 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 251 and the second sequence is SEQ ID NO: 252; the first sequence is SEQ ID NO: 253 and the second sequence is SEQ ID NO: 254; the first sequence is SEQ ID NO: 255 and the second sequence is SEQ ID NO: 256; the first sequence is SEQ ID NO: 257 and the second sequence is SEQ ID NO: 258; the first sequence is SEQ ID NO: 259 and the second sequence is SEQ ID NO: 260; the first sequence is SEQ ID NO: 261 and the second sequence is SEQ ID NO: 262; the first sequence is SEQ ID NO: 263 and the second sequence is SEQ ID NO: 264; the first sequence is SEQ ID NO: 265 and the second sequence is SEQ ID NO: 266; the first sequence is SEQ ID NO: 267 and the second

sequence is SEQ ID NO: 268; the first sequence is SEQ ID NO: 269 and the second sequence is SEQ ID NO: 270; the first sequence is SEQ ID NO: 271 and the second sequence is SEQ ID NO: 272; the first sequence is SEQ ID NO: 273 and the second sequence is SEQ ID NO: 274; the first sequence is SEQ ID NO: 275 and the second sequence is SEQ ID NO: 276; the first sequence is SEQ ID NO: 277 and the second sequence is SEQ ID NO: 278; the first sequence is SEQ ID NO: 279 and the second sequence is SEQ ID NO: 280; the first sequence is SEQ ID NO: 281 and the second sequence is SEQ ID NO: 282; the first sequence is SEQ ID NO: 283 and the second sequence is SEQ ID NO: 284; the first sequence is SEQ ID NO: 285 and the second sequence is SEQ ID NO: 286; the first sequence is SEQ ID NO: 287 and the second sequence is SEQ ID NO: 288; or the first sequence is SEQ ID NO: 289 and the second sequence is SEQ ID NO: 290.

[0237] In some cases, an antibody of the present disclosure comprises a heavy chain having at least 80% sequence identity to a first sequence and a light chain having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 1 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 2 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 4 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 6 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 7 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 8 and the second sequence is SEQ ID NO: 10; or the first sequence is SEQ ID NO: 9 and the second sequence is SEQ ID NO: 10.

[0238] In some cases, an antibody of the present disclosure comprises a heavy chain having at least 80% sequence identity to a first sequence and a light chain having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 3 or SEQ ID NO: 4 and the second sequence is SEQ ID NO: 5.

[0239] In some cases, the heavy chain has at least 85% sequence identity to the first sequence and the light chain has at least 85% sequence identity to the second sequence. In some cases, the heavy chain has at least 90% sequence identity to the first sequence and the light chain has at least 90% sequence identity to the second sequence. In some cases, the heavy chain has at least 95% sequence identity to the first sequence and the light chain has at least 95% sequence identity to the second sequence. In some cases, the heavy chain has at least 98% sequence identity to the first sequence and the light chain has at least 98% sequence identity to the second sequence. In some cases, the heavy chain has at least 99% sequence identity to the first sequence and the light chain has at least 99% sequence identity to the second sequence. In some cases, the heavy chain comprises the first sequence and the light chain comprises the second sequence.

(iii) Complementarity-Determining Regions

[0240] In some cases, the antibody comprises a CDR-H1 comprising at least 80% sequence identity to a first sequence, a CDR-H2 comprising at least 80% sequence identity to a second sequence, a CDR-H3 comprising at least 80% sequence identity to a third sequence, a CDR-L1 comprising at least 80% sequence identity to a fourth sequence, a CDR-L2 comprising at least 80% sequence identity to a fifth sequence, and a CDR-L3 comprising at least 80% sequence identity to a sixth sequence, wherein the first, second, third, fourth, fifth, and sixth sequences are: SEQ ID NO: 13, 14, 15, 16, 17, and 18, respectively; SEQ ID NO: 21, 22, 23, 24, 25, and 26, respectively; SEQ ID NO: 38, 39, 40, 41, 42, and 43, respectively; SEQ ID NO: 49, 50, 51, 52, 53, and 54, respectively; SEQ ID NO: 63, 64, 65, 66, 67, and 68, respectively; SEQ ID NO: 77, 78, 79, 80, 81, and 82, , respectively; SEQ ID NO: 91, 92, 93, 94, 95, and 96, respectively; SEQ ID NO: 99, 100, 101, 102, 103, and 104, respectively; SEQ ID NO: 107, 108, 109, 110, 111, and 112, respectively; SEQ ID NO: 115, 116, 117, 118, 119, and 120, respectively; SEQ ID NO: 123, 124, 125, 126, 127, and 128, respectively; SEQ ID NO: 131, 132, 133, 134, 135, and 136, respectively; SEQ ID NO: 139, 140, 141, 142, 143, and 144, respectively; SEQ ID NO: 147, 148, 149, 150, 151, and 152, respectively; SEQ ID NO: 155, 156, 157, 158, 159, and 160, respectively; SEQ ID NO: 163, 164, 165, 166, 167, and 168, respectively; SEQ ID NO: 171, 172, 173, 174, 175, and 176, respectively; SEQ ID NO: 179, 180, 181, 182, 183, and 184, respectively; SEQ ID NO: 187, 188, 189, 190, 191, and 192, respectively; SEQ ID NO: 195, 196, 197, 198, 199, and 200, respectively; SEQ ID NO: 203, 204, 205, 206, 207 and 208, respectively; SEQ ID NO: 211, 212, 213, 214, 215, and 216, respectively; SEQ ID NO: 219, 220, 221, 222, 223, and 224, respectively; SEQ ID NO: 227, 228, 229, 230, 231, and 232, respectively; SEQ ID NO: 235, 236, 237, 238, 239, and 240, respectively; SEQ ID NO: 243, 244, 245, 246, 247, and 248, respectively; SEQ ID NO: 291, 292, 293, 294, 295, and 296, respectively; SEQ ID NO: 301, 302, 303, 304, 305, and 306, respectively; SEQ ID NO: 309, 310, 311, 312, 313, and 314, respectively; SEQ ID NO: 317, 318, 319, 320, 321, and 322, respectively; SEQ ID NO: 325, 326, 327, 328, 329, and 330, respectively; SEQ ID NO: 333, 334, 335, 336, 337, and 338, respectively; SEQ ID NO: 341, 342, 343, 344, 345, and 346, respectively; SEQ ID NO: 349, 350, 351, 352, 353, and 354, respectively; SEQ ID NO: 357, 358, 359, 360, 361, and 362, respectively; SEQ ID NO: 365, 366, 367, 368, 369, and 370, respectively; SEQ ID NO: 373, 374, 375, 376, 377, and 378, respectively; SEQ ID NO: 381, 382, 383, 384, 385, and 386, respectively; SEQ ID NO: 389, 390, 391, 392, 393, and 394, respectively; SEQ ID NO: 397, 398, 399, 400, 401, and 402, respectively; SEQ ID NO: 405, 406, 407, 408, 409, and 410, respectively; SEQ ID NO: 413, 414, 415, 416, 417, and 418, respectively; SEQ ID NO: 421, 422, 423, 424, 425, and 426, respectively; SEQ ID NO: 429,

430, 431, 432, 433, and 434, respectively; SEQ ID NO: 437, 438, 439, 440, 441, and 442, respectively; SEQ ID NO: 445, 446, 447, 448, 449, and 450, respectively; SEQ ID NO: 453, 454, 455, 456, 457, and 458, respectively; SEQ ID NO: 461, 462, 463, 464, 465, and 466, respectively; SEQ ID NO: 469, 470, 471, 472, 473, and 474, respectively; SEQ ID NO: 477, 478, 479, 480, 481, and 482, respectively; SEQ ID NO: 485, 486, 487, 488, 489, and 490, respectively; SEQ ID NO: 495, 496, 497, 498, 499, and 500, respectively; SEQ ID NO: 503, 504, 505, 506, 507, and 508, respectively; SEQ ID NO: 511, 512, 513, 514, 515, and 516, respectively; SEQ ID NO: 519, 520, 521, 522, 523, and 524, respectively; SEQ ID NO: 527, 528, 529, 530, 531, and 532, respectively; SEQ ID NO: 535, 536, 537, 538, 539, and 540, respectively; SEQ ID NO: 543, 544, 545, 546, 547, and 548, respectively; SEQ ID NO: 551, 552, 553, 554, 555, and 556, respectively; SEQ ID NO: 559, 560, 561, 562, 563, and 564, respectively; SEQ ID NO: 567, 568, 569, 570, 571, and 572, respectively; SEQ ID NO: 575, 576, 577, 578, 579, and 580, respectively; SEQ ID NO: 583, 584, 585, 586, 587, and 588, respectively; SEQ ID NO: 591, 592, 593, 594, 595, and 596, respectively; SEQ ID NO: 599, 600, 601, 602, 603, and 604, respectively; SEQ ID NO: 607, 608, 609, 610, 611, and 612, respectively; SEQ ID NO: 615, 616, 617, 618, 619, and 620, respectively; SEQ ID NO: 623, 624, 625, 626, 627, and 628, respectively; SEQ ID NO: 631, 632, 633, 634, 635, and 636, respectively; SEQ ID NO: 639, 640, 641, 642, 643, and 644, respectively; SEQ ID NO: 647, 648, 649, 650, 651, and 652, respectively; SEQ ID NO: 655, 656, 657, 658, 659, and 660, respectively; SEQ ID NO: 663, 664, 665, 666, 667, and 668, respectively; SEQ ID NO: 671, 672, 673, 674, 675, and 676, respectively; SEQ ID NO: 679, 680, 681, 682, 683, and 684, respectively; SEQ ID NO: 687, 688, 689, 690, 691, and 692, respectively; SEQ ID NO: 695, 696, 697, 698, 699, and 700, respectively; SEQ ID NO: 705, 706, 707, 708, 709, and 710, respectively; SEQ ID NO: 725, 726, 727, 728, 729, and 730, respectively; SEQ ID NO: 733, 734, 735, 736, 737, and 738, respectively; SEQ ID NO: 741, 742, 743, 744, 745, and 746, respectively; SEQ ID NO: 749, 750, 751, 752, 753, and 754, respectively; SEQ ID NO: 759, 760, 761, 762, 763, and 764, respectively; SEQ ID NO: 767, 768, 769, 770, 771, and 772, respectively; SEQ ID NO: 775, 776, 777, 778, 779, and 780, respectively; SEQ ID NO: 783, 784, 785, 786, 787, and 788, respectively; SEQ ID NO: 791, 792, 793, 794, 795, and 796, respectively; SEQ ID NO: 799, 800, 801, 802, 803, and 804, respectively; SEQ ID NO: 807, 808, 809, 810, 811, and 812, respectively; SEQ ID NO: 815, 816, 817, 818, 819, and 820, respectively; SEQ ID NO: 823, 824, 825, 826, 827, and 828, respectively; SEQ ID NO: 831, 832, 833, 834, 835, and 836, respectively; SEQ ID NO: 839, 840, 841, 842, 843, and 844, respectively; SEQ ID NO: 847, 848, 849, 850, 851, and 852, respectively; SEQ ID NO: 855, 856, 857, 858, 859, and 860, respectively; SEQ ID NO: 863, 864, 865, 866, 867, and 868, respectively; SEQ ID NO: 871, 872, 873, 874, 875, and

876, respectively; SEQ ID NO: 879, 880, 881, 882, 883, and 884, respectively; SEQ ID NO: 887, 888, 889, 890, 891, and 892, respectively; SEQ ID NO: 895, 896, 897, 898, 899, and 900, respectively; SEQ ID NO: 903, 904, 905, 906, 907, and 908, respectively; SEQ ID NO: 911, 912, 913, 914, 915, and 916, respectively; SEQ ID NO: 919, 920, 921, 922, 923, and 924, respectively; SEQ ID NO: 927, 928, 929, 930, 931, and 932, respectively; SEQ ID NO: 935, 936, 937, 938, 939, and 940, respectively; SEQ ID NO: 945, 946, 947, 948, 949, and 950, respectively; SEQ ID NO: 953, 954, 955, 956, 957, and 958, respectively; SEQ ID NO: 961, 962, 963, 964, 965, and 966, respectively; SEQ ID NO: 969, 970, 971, 972, 973, and 974, respectively; SEQ ID NO: 977, 978, 979, 980, 981, and 982, respectively; SEQ ID NO: 985, 986, 987, 988, 989, and 990, respectively; SEQ ID NO: 997, 998, 999, 1000, 1001, and 1002, respectively; SEQ ID NO: 1005, 1006, 1007, 1008, 1009, and 1010, respectively; SEQ ID NO: 1013, 1014, 1015, 1016, 1017, and 1018, respectively; SEQ ID NO: 1021, 1022, 1023, 1024, 1025, and 1026, respectively; SEQ ID NO: 1029, 1030, 1031, 1032, 1033, and 1034, respectively; or SEQ ID NO: 1037, 1038, 1039, 1040, 1041, and 1042, respectively.

[0241] In some cases, an antibody of the present disclosure targets an immune checkpoint selected from the group consisting of PDL1, B7H4, B7H3, and TIGIT. For example, in some cases, the antibody comprises a CDR-H1 comprising at least 80% sequence identity to a first sequence, a CDR-H2 comprising at least 80% sequence identity to a second sequence, a CDR-H3 comprising at least 80% sequence identity to a third sequence, a CDR-L1 comprising at least 80% sequence identity to a fourth sequence, a CDR-L2 comprising at least 80% sequence identity to a fifth sequence, and a CDR-L3 comprising at least 80% sequence identity to a sixth sequence, wherein the first, second, third, fourth, fifth, and sixth sequences are: SEQ ID NO: 13, 14, 15, 16, 17, and 18, respectively; SEQ ID NO: 77, 78, 79, 80, 81, and 82, , respectively; SEQ ID NO: 91, 92, 93, 94, 95, and 96, respectively; SEQ ID NO: 99, 100, 101, 102, 103, and 104, respectively; SEQ ID NO: 107, 108, 109, 110, 111, and 112, respectively; SEQ ID NO: 115, 116, 117, 118, 119, and 120, respectively; SEQ ID NO: 123, 124, 125, 126, 127, and 128, respectively; SEQ ID NO: 131, 132, 133, 134, 135, and 136, respectively; SEQ ID NO: 139, 140, 141, 142, 143, and 144, respectively; SEQ ID NO: 147, 148, 149, 150, 151, and 152, respectively; SEQ ID NO: 155, 156, 157, 158, 159, and 160, respectively; SEQ ID NO: 163, 164, 165, 166, 167, and 168, respectively; SEQ ID NO: 171, 172, 173, 174, 175, and 176, respectively; SEQ ID NO: 179, 180, 181, 182, 183, and 184, respectively; SEQ ID NO: 187, 188, 189, 190, 191, and 192, respectively; SEQ ID NO: 195, 196, 197, 198, 199, and 200, respectively; SEQ ID NO: 203, 204, 205, 206, 207 and 208, respectively; SEQ ID NO: 211, 212, 213, 214, 215, and 216, respectively; SEQ ID NO: 219, 220, 221, 222, 223, and 224, respectively; SEQ ID NO: 227, 228, 229, 230, 231, and 232,

respectively; SEQ ID NO: 235, 236, 237, 238, 239, and 240, respectively; SEQ ID NO: 243, 244, 245, 246, 247, and 248, respectively; SEQ ID NO: 623, 624, 625, 626, 627, and 628, respectively; SEQ ID NO: 631, 632, 633, 634, 635, and 636, respectively; SEQ ID NO: 639, 640, 641, 642, 643, and 644, respectively; SEQ ID NO: 647, 648, 649, 650, 651, and 652, respectively; SEQ ID NO: 655, 656, 657, 658, 659, and 660, respectively; SEQ ID NO: 663, 664, 665, 666, 667, and 668, respectively; SEQ ID NO: 671, 672, 673, 674, 675, and 676, respectively; SEQ ID NO: 679, 680, 681, 682, 683, and 684, respectively; SEQ ID NO: 687, 688, 689, 690, 691, and 692, respectively; SEQ ID NO: 695, 696, 697, 698, 699, and 700, respectively; SEQ ID NO: 705, 706, 707, 708, 709, and 710, respectively; or SEQ ID NO: 1021, 1022, 1023, 1024, 1025, and 1026, respectively.

[0242] In some cases, the antibody comprises a CDR-H1 comprising at least 85% sequence identity to the first sequence, a CDR-H2 comprising at least 85% sequence identity to the second sequence, a CDR-H3 comprising at least 85% sequence identity to the third sequence, a CDR-L1 comprising at least 85% sequence identity to the fourth sequence, a CDR-L2 comprising at least 85% sequence identity to the fifth sequence, and a CDR-L3 comprising at least 85% sequence identity to the sixth sequence. In some cases, the antibody comprises a CDR-H1 comprising at least 90% sequence identity to the first sequence, a CDR-H2 comprising at least 90% sequence identity to the second sequence, a CDR-H3 comprising at least 90% sequence identity to the third sequence, a CDR-L1 comprising at least 90% sequence identity to the fourth sequence, a CDR-L2 comprising at least 90% sequence identity to the fifth sequence, and a CDR-L3 comprising at least 90% sequence identity to the sixth sequence. In some cases, the CDR-H1 comprises at most one mutation relative to the first sequence, the CDR-H2 comprises at most one mutation relative to the second sequence, the CDR-H3 comprises at most one mutation relative to the third sequence, the CDR-L1 comprises at most one mutation relative to the fourth sequence, the CDR-L2 comprises at most one mutation relative to the fifth sequence, and the CDR-L3 comprises at most one mutation relative to the sixth sequence.

(iv) Exemplary Antibodies

[0243] In some cases, an antibody provided herein binds to PDL1. PDL1 is expressed in a broad range of cancers, as well as certain immune cells, and often serves as a primary mechanism for immune suppression in tumor microenvironments. The PDL1 agonism of PD-1 can act as an immune checkpoint, diminishing lymphocyte tumor infiltration, and T-cell receptor mediated proliferation and signaling. While PDL1 antagonism can reverse immune suppression, PDL1 targeting can also localize treatments to the sites of cancers, allowing drugs to selectively target cancer cells or stimulate immune responses in the presence of tumors.

[0244] In some cases, an anti-PDL1 antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, at least 95%, at least 98%, or at least 99% sequence identity to the amino acid sequences of SEQ ID NOs: 13, 14, 15, 16, 17, and 18 respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 13, 14, 15, 16, 17, and 18, respectively.

[0245] In some embodiments, the antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of any one of SEQ ID NO: 1-4 and a light chain comprising an amino acid sequence that is at least 95% at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 5. In some embodiments, the antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain comprising an amino acid sequence that is at least 95% at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 5. In some embodiments, the antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 2 and a light chain comprising an amino acid sequence that is at least 95% at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 5. In some embodiments, the antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 3 and a light chain comprising an amino acid sequence that is at least 95% at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 5. In some embodiments, the antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 4 and a light chain comprising an amino acid sequence that is at least 95% at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 5.

[0246] In some embodiments, the antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of any one of SEQ ID NO: 6-9 and a light chain variable region comprising an amino acid sequence that is at least 95% at least 96%,

at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 10. In some embodiments, the antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of any one of SEQ ID NO: 6 and a light chain variable region comprising an amino acid sequence that is at least 95% at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 10. In some embodiments, the antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of any one of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence that is at least 95% at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 10. In some embodiments, the antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of any one of SEQ ID NO: 8 and a light chain variable region comprising an amino acid sequence that is at least 95% at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 10. In some embodiments, the antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of any one of SEQ ID NO: 9 and a light chain variable region comprising an amino acid sequence that is at least 95% at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 10.

[0247] In some embodiments, the antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 19 and a light chain variable region comprising an amino acid sequence that is at least 95% at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 20.

[0248] In some embodiments, an antibody provided herein binds to EphA2. In some embodiments, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequences of SEQ ID NOs: 21, 22, 23, 24, 25, and 26, respectively.

[0249] In some embodiments, the anti-EphA2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 27 and a

light chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 28. In some embodiments, the anti-EphA2 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 29 or SEQ ID NO: 30 and a light chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of the amino acid sequence of SEQ ID NO: 31. In some embodiments, the anti-EphA2 antibody comprises a heavy chain comprising the amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 32 or SEQ ID NO: 33 and a light chain comprising the amino acid sequence of SEQ ID NO: 34. In some embodiments, the anti-EphA2 antibody comprises a heavy chain that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 35 or SEQ ID NO: 36 and a light chain comprising the amino acid sequence of SEQ ID NO: 37. In some embodiments, the antibody is h1C1 or 1C1.

[0250] In some embodiments, the anti-EphA2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 28.

[0251] In some cases, an antibody provided herein binds to CD30. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 38, 39, 40, 41, 42, and 43, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 38, 39, 40, 41, 42, and 43, respectively. In some embodiments, the anti-CD30 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of either SEQ ID NO: 46 or 47 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 48. In some embodiments, the anti-CD30 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino

acid sequence of SEQ ID NO: 44 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 45.

[0252] In some cases, an antibody provided herein binds to CD228. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 49, 50, 51, 52, 53, and 54, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 49, 50, 51, 52, 53, and 54, respectively. In some embodiments, the anti-CD228 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 55 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 56. In some embodiments, the anti-CD228 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of either of SEQ ID NO: 57 or 58 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 59. In some embodiments, the anti-CD228 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of either of SEQ ID NO: 60 or 61 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 62.

[0253] In some cases, an antibody provided herein binds to avB6. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 63, 64, 65, 66, 67, and 68, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 63, 64, 65, 66, 67, and 68, respectively. In some embodiments, the anti-H2A2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or

99% identical to the amino acid sequence of SEQ ID NO: 69 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 70. In some embodiments, the anti-H2A2 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of either SEQ ID NO: 71 or 72 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 73. In some embodiments, the anti-H2A2 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of either SEQ ID NO: 74 or 75 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 76.

[0254] In some cases, an antibody provided herein binds to B7H4. In some cases, the antibody comprises a set of CDR sequences (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3, respectively) of which each sequence comprises at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, at least 95%, or 100% sequence identity to amino acid sequences from a set of amino acid sequences selected from the group consisting of SEQ ID NOs: 77-82, SEQ ID NOs: 91-96, SEQ ID NOs: 99-104, SEQ ID NOs: 107-112, SEQ ID NOs: 115-120, SEQ ID NOs: 123-128, SEQ ID NOs: 131-136, SEQ ID NOs: 139-144, SEQ ID NOs: 147-152, SEQ ID NOs: 155-160, SEQ ID NOs: 163-168, SEQ ID NOs: 171-176, SEQ ID NOs: 179-184, SEQ ID NOs: 187-192, SEQ ID NOs: 195-200, SEQ ID NOs: 203-208, SEQ ID NOs: 211-216, SEQ ID NOs: 219-224, SEQ ID NOs: 227-232, SEQ ID NOs: 235-240, and SEQ ID NOs: 243-248. In some cases, the antibody comprises a set of CDR sequences (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3, respectively) each comprising at most one mutation relative to an amino acid sequence from a set of amino acid sequences selected from the group consisting of SEQ ID NOs: 77-82, SEQ ID NOs: 91-96, SEQ ID NOs: 99-104, SEQ ID NOs: 107-112, SEQ ID NOs: 115-120, SEQ ID NOs: 123-128, SEQ ID NOs: 131-136, SEQ ID NOs: 139-144, SEQ ID NOs: 147-152, SEQ ID NOs: 155-160, SEQ ID NOs: 163-168, SEQ ID NOs: 171-176, SEQ ID NOs: 179-184, SEQ ID NOs: 187-192, SEQ ID NOs: 195-200, SEQ ID NOs: 203-208, SEQ ID NOs: 211-216, SEQ ID NOs: 219-224, SEQ ID NOs: 227-232, SEQ ID NOs: 235-240, and SEQ ID NOs: 243-248. In some cases, the anti-B7H4 antibody comprises a heavy chain and a light chain comprising amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 100% identical to the amino acid

sequences of SEQ ID NO: 85 and 87, SEQ ID NO: 86 and 87, SEQ ID NO: 88 and 90, SEQ ID NO: 89 and 90, SEQ ID NO: 251 and 252, , SEQ ID NO: 253 and 254, SEQ ID NO: 255 and 256, SEQ ID NO: 257 and 258, SEQ ID NO: 259 and 260, SEQ ID NO: 261 and 262, SEQ ID NO: 263 and 264, SEQ ID NO: 265 and 266, SEQ ID NO: 267 and 268, SEQ ID NO: 269 and 270, SEQ ID NO: 271 and 272, SEQ ID NO: 273 and 274, SEQ ID NO: 275 and 276, SEQ ID NO: 277 and 278, SEQ ID NO: 279 and 280, SEQ ID NO: 281 and 282, SEQ ID NO: 283 and 284, SEQ ID NO: 285 and 286, SEQ ID NO: 287 and 288, or SEQ ID NO: 289 and 290, respectively. In some embodiments, the anti-B7H4 antibody comprises a heavy chain variable region and a light chain variable region comprising amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 100% identical to the amino acid sequences of SEQ ID NO: 83 and 84, SEQ ID NO: 97 and 98, SEQ ID NO: 105 and 106, SEQ ID NO: 113 and 114, SEQ ID NO: 121 and 122, SEQ ID NO: 129 and 130, SEQ ID NO: 137 and 138, SEQ ID NO: 153 and 154, SEQ ID NO: 161 and 162, SEQ ID NO: 169 and 170, SEQ ID NO: 177 and 178, SEQ ID NO: 185 and 186, SEQ ID NO: 193 and 194, SEQ ID NO: 201 and 202, SEQ ID NO: 209 and 210, SEQ ID NO: 217 and 218, SEQ ID NO: 225 and 226, SEQ ID NO: 233 and 234, SEQ ID NO: 241 and 242, or SEQ ID NO: 249 and 250, respectively.

[0255] In some cases, an antibody provided herein binds to CD70. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 291, 292, 293, 294, 295, and 296, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 291, 292, 293, 294, 295, and 296, respectively. In some embodiments, the anti-CD70 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 297 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 298. In some embodiments, the anti-CD70 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 299 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 300.

[0256] In some cases, an antibody provided herein binds to TROP2. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 301, 302, 303, 304, 305, and 306, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 301, 302, 303, 304, 305, and 306, respectively. In some cases, an antibody provided herein binds to TROP2. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 309, 310, 311, 312, 313, and 314 respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 309, 310, 311, 312, 313, and 314, respectively. In some embodiments, the anti-TROP2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 307 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 308. In some embodiments, the anti-TROP2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 315 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 316.

[0257] In some cases, an antibody provided herein binds to MICA. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 317, 318, 319, 320, 321, and 322, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 317, 318, 319, 320, 321, and 322, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino

acid sequences of SEQ ID NOs: 325, 326, 327, 328, 329, and 330, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 325, 326, 327, 328, 329, and 330, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 333, 334, 335, 336, 337, and 338, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 333, 334, 335, 336, 337, and 338, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 341, 342, 343, 344, 345, and 346, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 341, 342, 343, 344, 345, and 346, respectively. In some embodiments, the anti-MICA antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 323 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 324. In some embodiments, the anti-MICA antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 331 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 332. In some embodiments, the anti-MICA antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 340 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 340. In some embodiments, the anti-MICA antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 347 and a light chain variable region

comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 348.

[0258] In some cases, an antibody provided herein binds to CD51. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 349, 350, 351, 352, 353, and 354, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 349, 350, 351, 352, 353, and 354, respectively. In some cases, an antibody provided herein binds to CD51. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 357, 358, 359, 360, 361, and 362, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 357, 358, 359, 360, 361, and 362, respectively. In some embodiments, the anti-CD51 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 355 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 356. In some embodiments, the anti-CD51 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 363 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 364.

[0259] In some cases, an antibody provided herein binds to gpA33. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 365, 366, 367, 368, 369, and 370, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 365, 366, 367, 368, 369, and 370, respectively. In some embodiments, the anti-gpA33 antibody comprises a heavy chain variable

region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 371 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 372.

[0260] In some cases, an antibody provided herein binds to IL1Rap. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 373, 374, 375, 376, 377, and 378, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 373, 374, 375, 376, 377, and 378, respectively. In some embodiments, the anti-IL1Rap antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 379 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 380.

[0261] In some cases, an antibody provided herein binds to EpCAM. In some cases, the antibody comprises a set of CDR sequences (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3, respectively) of which each sequence comprises at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, at least 95%, or 100% sequence identity to amino acid sequences from a set of amino acid sequences selected from the group consisting of SEQ ID NOs: 381-386, SEQ ID NOs: 389-394, SEQ ID NOs: 397-402, SEQ ID NOs: 405-410, SEQ ID NOs: 413-418, or SEQ ID NOs: 421-426. In some embodiments, the anti-EpCAM antibody comprises a heavy chain variable region and a light chain variable region comprising amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 100% identical to the amino acid sequences of SEQ ID NO: 387 and 388, SEQ ID NO: 395 and 396, SEQ ID NO: 403 and 404, SEQ ID NO: 411 and 412, SEQ ID NO: 419 and 420, or SEQ ID NO: 427 and 428, respectively.

[0262] In some cases, an antibody provided herein binds to CD352. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 429, 430, 431, 432, 433, and 434, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation

relative to the amino acid sequences of SEQ ID NOs: 429, 430, 431, 432, 433, and 434, respectively. In some embodiments, the anti-CD352 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 435 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 436.

[0263] In some cases, an antibody provided herein binds to CS1. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 437, 438, 439, 440, 441, and 442, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 437, 438, 439, 440, 441, and 442, respectively. In some embodiments, the anti-CS1 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 443 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 444.

[0264] In some cases, an antibody provided herein binds to CD38. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 445, 446, 447, 448, 449, and 450, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 445, 446, 447, 448, 449, and 450, respectively. In some embodiments, the anti-CD38 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 451 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 452.

[0265] In some cases, an antibody provided herein binds to CD25. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 453, 454,

455, 456, 457, and 458, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 453, 454, 455, 456, 457, and 458, respectively. In some embodiments, the anti-CD25 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 459 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 460.

[0266] In some cases, an antibody provided herein binds to ADAM9. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 461, 462, 463, 464, 465, and 466, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 461, 462, 463, 464, 465, and 466, respectively. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 469, 470, 471, 472, 473, and 474, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 469, 470, 471, 472, 473, and 474, respectively. In some embodiments, the anti-ADAM9 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 467 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 468. In some embodiments, the anti-ADAM9 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 475 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 476.

[0267] In some cases, an antibody provided herein binds to CD59. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences

comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 477, 478, 479, 480, 481, and 482, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 477, 478, 479, 480, 481, and 482, respectively. In some embodiments, the anti-CD59 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 483 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 484.

[0268] In some cases, an antibody provided herein binds to CD19. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 485, 486, 487, 488, 489, and 490, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 485, 486, 487, 488, 489, and 490, respectively. In some embodiments, the anti-CD19 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 491 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 492. In some embodiments, the anti-CD19 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 493 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 494.

[0269] In some cases, an antibody provided herein binds to CD138. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 495, 496, 497, 498, 499, and 500, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 495, 496, 497, 498, 499, and 500,

respectively. In some embodiments, the anti-CD138 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 501 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 502.

[0270] In some cases, an antibody provided herein binds to CD166. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 503, 504, 505, 506, 507, and 508, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 503, 504, 505, 506, 507, and 508, respectively. In some embodiments, the anti-CD166 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 509 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 510.

[0271] In some cases, an antibody provided herein binds to CD56. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 511, 512, 513, 514, 515, and 516, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 511, 512, 513, 514, 515, and 516, respectively. In some embodiments, the anti-CD56 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 517 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 518.

[0272] In some cases, an antibody provided herein binds to CD74. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 519, 520, 521, 522, 523, and 524, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2,

CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 519, 520, 521, 522, 523, and 524, respectively. In some embodiments, the anti-CD74 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 525 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 526.

[0273] In some cases, an antibody provided herein binds to CEACAM5. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 527, 528, 529, 530, 531, and 532, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 527, 528, 529, 530, 531, and 532, respectively. In some embodiments, the anti-CEACAM5 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 533 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 534.

[0274] In some cases, an antibody provided herein binds to CanAg. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 535, 536, 537, 538, 539, and 540, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 535, 536, 537, 538, 539, and 540, respectively. In some embodiments, the anti-CanAg antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 541 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 542.

[0275] In some cases, an antibody provided herein binds to DLL-3. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences

comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 543, 544, 545, 546, 547, and 548, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 543, 544, 545, 546, 547, and 548, respectively. In some embodiments, the anti-DLL-3 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 549 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 550.

[0276] In some cases, an antibody provided herein binds to DPEP-3. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 551, 552, 553, 554, 555, and 556, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 551, 552, 553, 554, 555, and 556, respectively. In some embodiments, the anti-DPEP-3 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 557 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 558.

[0277] In some cases, an antibody provided herein binds to EGFR. In some cases, the antibody comprises a set of CDR sequences (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3, respectively) of which each sequence comprises at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, at least 95%, or 100% sequence identity to amino acid sequences from a set of amino acid sequences selected from the group consisting of SEQ ID NOs: 559-564, SEQ ID NOs: 567-572, SEQ ID NOs: 575-580, and SEQ ID NOs: 895-900. In some embodiments, the anti-EGFR antibody comprises a heavy chain variable region and a light chain variable region comprising amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 100% identical to the amino acid sequences of SEQ ID NO: 565 and 566, SEQ ID NO: 573 and 574, SEQ ID NO: 581 and 582, or SEQ ID NO: 901 and 902, respectively.

[0278] In some cases, an antibody provided herein binds to FRa. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 583, 584, 585, 586, 587, and 588, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 583, 584, 585, 586, 587, and 588, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 591, 592, 593, 594, 595, and 596, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 591, 592, 593, 594, 595, and 596, respectively. In some embodiments, the anti-FRa antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 589 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 590. In some embodiments, the anti-FRa antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 597 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 598.

[0279] In some cases, an antibody provided herein binds to MUC-1. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 599, 600, 601, 602, 603, and 604, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 599, 600, 601, 602, 603, and 604, respectively. In some embodiments, the anti-MUC-1 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 605 and a light

chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 606.

[0280] In some cases, an antibody provided herein binds to Mesothelin. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 607, 608, 609, 610, 611, and 612, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 607, 608, 609, 610, 611, and 612, respectively. In some embodiments, the anti-Mesothelin antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 613 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 614.

[0281] In some cases, an antibody provided herein binds to ROR-1. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 615, 616, 617, 618, 619, and 620, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 615, 616, 617, 618, 619, and 620, respectively. In some embodiments, the anti-ROR-1 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 621 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 622.

[0282] In some cases, an antibody provided herein binds to B7H3. In some cases, the antibody comprises a set of CDR sequences (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3, respectively) of which each sequence comprises at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, at least 95%, or 100% sequence identity to amino acid sequences from a set of amino acid sequences selected from the group consisting of SEQ ID NOs: 623-628, SEQ ID NOs: 631-636, SEQ ID NOs: 639-644, SEQ ID NOs: 647-652, SEQ ID NOs: 655-660, SEQ ID NOs: 663-668, SEQ ID NOs: 671-676, SEQ ID NOs: 679-684,

SEQ ID NOs: 687-692, SEQ ID NOs: 695-700, and SEQ ID NOs: 705-710. In some embodiments, the anti-B7H3 antibody comprises a heavy chain variable region and a light chain variable region comprising amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 100% identical to the amino acid sequences of SEQ ID NO: 629 and 630, SEQ ID NOs: 637 and 638, SEQ ID NOs: 645 and 646, SEQ ID NOs: 653 and 654, SEQ ID NOs: 661 and 662, SEQ ID NOs: 669 and 670, SEQ ID NOs: 677 and 678, SEQ ID NOs: 685 and 686, SEQ ID NOs: 693 and 694, SEQ ID NOs: 701 and 702, SEQ ID NOs: 703 and 704, SEQ ID NOs: 711 and 712, SEQ ID NOs: 713 and 714, and SEQ ID NOs: 715 and 716, respectively.

[0283] In some cases, an antibody provided herein binds to HER3. In some embodiments, the anti-HER3 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 717 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 718. In some cases, an antibody provided herein binds to HER3. In some embodiments, the anti-HER3 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 719 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 720. In some cases, an antibody provided herein binds to HER3. In some embodiments, the anti-HER3 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 721 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 722. In some cases, an antibody provided herein binds to HER3. In some embodiments, the anti-HER3 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 723 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 724.

[0284] In some cases, an antibody provided herein binds to PTK7. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 725, 726, 727, 728,

729, and 730, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 725, 726, 727, 728, 729, and 730, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 733, 734, 735, 736, 737, and 738, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 733, 734, 735, 736, 737, and 738, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 741, 742, 743, 744, 745, and 746, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 741, 742, 743, 744, 745, and 746, respectively. In some cases, the anti-PTK7 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 731 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 732. In some cases, the anti-PTK7 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 739 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 740. In some cases, the anti-PTK7 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 747 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 748.

[0285] In some cases, an antibody provided herein binds to ZIP6. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 749, 750, 751, 752, 753, and 754, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3,

CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 749, 750, 751, 752, 753, and 754, respectively. In some cases, the anti-ZIP6 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 755 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 756. In some embodiments, the anti-ZIP6 antibody comprises a heavy chain comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 757 and a light chain comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 758.

[0286] In some cases, an antibody provided herein binds to Integrin αvβ6. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 759, 760, 761, 762, 763, and 764, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 759, 760, 761, 762, 763, and 764, respectively. In some embodiments, the anti- Integrin αvβ6 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 765 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 766.

[0287] In some cases, an antibody provided herein binds to CD48. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 767, 768, 769, 770, 771, and 772, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 767, 768, 769, 770, 771, and 772, respectively. In some embodiments, the anti-CD48 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or

99% identical to the amino acid sequence of SEQ ID NO: 773 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 774.

[0288] In some cases, an antibody provided herein binds to IGF-1R. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 775, 776, 777, 778, 779, and 780, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 775, 776, 777, 778, 779, and 780, respectively. In some embodiments, the anti-IGF-1R antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 781 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 782.

[0289] In some cases, an antibody provided herein binds to Claudin-18.2. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 783, 784, 785, 786, 787, and 788, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 783, 784, 785, 786, 787, and 788, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 791, 792, 793, 794, 795, and 796, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 791, 792, 793, 794, 795, and 796, respectively. In some embodiments, the anti-Claudin-18.2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 789 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 790. In some embodiments, the anti-Claudin-18.2 antibody

comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 797 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 798.

[0290] In some cases, an antibody provided herein binds to Nectin-4. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 799, 800, 801, 802, 803, and 804, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 799, 800, 801, 802, 803, and 804, respectively. In some embodiments, the anti-Nectin-4 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 805 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 806.

[0291] In some cases, an antibody provided herein binds to SLTRK6. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 807, 808, 809, 810, 811, and 812, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 807, 808, 809, 810, 811, and 812, respectively. In some embodiments, the anti-SLTRK6 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 813 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 814.

[0292] In some cases, an antibody provided herein binds to CD142. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 815, 816, 817, 818, 819, and 820, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2,

CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 815, 816, 817, 818, 819, and 820, respectively. In some embodiments, the anti-CD142 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 821 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 822.

[0293] In some cases, an antibody provided herein binds to Sialyl-Thomsen-nouveau antigen (STn). In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 823, 824, 825, 826, 827, and 828, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 823, 824, 825, 826, 827, and 828, respectively.

[0294] In some embodiments, the anti-STn antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 829 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 830.

[0295] In some cases, an antibody provided herein binds to CD20. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 831, 832, 833, 834, 835, and 836, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 831, 832, 833, 834, 835, and 836, respectively. In some embodiments, the anti-CD20 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 837 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 838.

[0296] In some cases, an antibody provided herein binds to HER2. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences

comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 839, 840, 841, 842, 843, and 844, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 839, 840, 841, 842, 843, and 844, respectively. In some embodiments, the anti-HER2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 845 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 846.

[0297] In some cases, an antibody provided herein binds to CD79b. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 847, 848, 849, 850, 851, and 852, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 847, 848, 849, 850, 851, and 852, respectively. In some embodiments, the anti-CD79b antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 853 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 854.

[0298] In some cases, an antibody provided herein binds to NaPi2B. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 855, 856, 857, 858, 859, and 860, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 855, 856, 857, 858, 859, and 860, respectively. In some embodiments, the anti-NaPi2B antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 861 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 862.

[0299] In some cases, an antibody provided herein binds to Muc16. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 863, 864, 865, 866, 867, and 868, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 863, 864, 865, 866, 867, and 868, respectively. In some embodiments, the anti-Muc16 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 869 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 870.

[0300] In some cases, an antibody provided herein binds to STEAP1. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 871, 872, 873, 874, 875, and 876, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 871, 872, 873, 874, 875, and 876, respectively. In some embodiments, the anti-STEAP1 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 877 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 878.

[0301] In some cases, an antibody provided herein binds to BCMA. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 879, 880, 881, 882, 883, and 884, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 879, 880, 881, 882, 883, and 884, respectively. In some embodiments, the anti-BCMA antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 885 and a light

chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 886.

[0302] In some cases, an antibody provided herein binds to c-Met. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 887, 888, 889, 890, 891, and 892, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 887, 888, 889, 890, 891, and 892, respectively. In some embodiments, the anti-c-Met antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 893 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 893.

[0303] In some cases, an antibody provided herein binds to SLAMF7. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 903, 904, 905, 906, 907, and 908, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 903, 904, 905, 906, 907, and 908, respectively. In some embodiments, the anti-SLAMF7 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 909 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 910.

[0304] In some cases, an antibody provided herein binds to C4.4a. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 911, 912, 913, 914, 915, and 916, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 911, 912, 913, 914, 915, and 916, respectively. In some embodiments, the anti-C4.4a antibody comprises a heavy chain variable

region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 917 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 918.

[0305] In some cases, an antibody provided herein binds to GCC. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 919, 920, 921, 922, 923, and 924, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 919, 920, 921, 922, 923, and 924, respectively. In some embodiments, the anti-GCC antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 925 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 926.

[0306] In some cases, an antibody provided herein binds to Axl. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 927, 928, 929, 930, 931, and 932, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 927, 928, 929, 930, 931, and 932, respectively. In some embodiments, the anti-Axl antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 933 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 933.

[0307] In some cases, an antibody provided herein binds to transmembrane glycoprotein NMB (gpNMB). In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 935, 936, 937, 938, 939, and 940, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences

each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 935, 936, 937, 938, 939, and 940, respectively. In some embodiments, the anti-gpNMB antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 941 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 942. In some embodiments, the anti-gpNMB antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 943 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 944.

[0308] In some cases, an antibody provided herein binds to Prolactin receptor. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 945, 946, 947, 948, 949, and 950, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 945, 946, 947, 948, 949, and 950, respectively. In some embodiments, the anti-Prolactin receptor antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 951 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 952.

[0309] In some cases, an antibody provided herein binds to FGFR2. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 953, 954, 955, 956, 957, and 958, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 953, 954, 955, 956, 957, and 958, respectively. In some embodiments, the anti-FGFR2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least

95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 959 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 960.

[0310] In some cases, an antibody provided herein binds to CDCP1. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 961, 962, 963, 964, 965, and 966, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 969, 970, 971, 972, 973, and 974, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 961, 962, 963, 964, 965, and 966, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 969, 970, 971, 972, 973, and 974, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 977, 978, 979, 980, 981, and 982, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 977, 978, 979, 980, 981, and 982, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 985, 986, 987, 988, 989, and 990, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 985, 986, 987, 988, 989, and 990, respectively. In some embodiments, the anti-CDCP1 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 967 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 968.

In some embodiments, the anti-CDCP1 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 975 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 976. In some embodiments, the anti-CDCP1 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 983 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 984. In some embodiments, the anti-CDCP1 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 991 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 992.

[0311] In some cases, an antibody provided herein binds to ASCT2. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 997, 998, 999, 1000, 1001, and 1002, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 997, 998, 999, 1000, 1001, and 1002, respectively. In some embodiments, the anti-ASCT2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 993 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 994. In some embodiments, the anti-ASCT2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 995 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 996. In some embodiments, the anti-ASCT2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%,

or 99% identical to the amino acid sequence of SEQ ID NO: 1003 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1004.

[0312] In some cases, an antibody provided herein binds to CD123. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 1005, 1006, 1007, 1008, 1009, and 1010, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 1005, 1006, 1007, 1008, 1009, and 1010, respectively. In some embodiments, the anti-CD123 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1011 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1012.

[0313] In some cases, an antibody provided herein binds to GPC3. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 1013, 1014, 1015, 1016, 1017, and 1018 respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 1013, 1014, 1015, 1016, 1017, and 1018, respectively. In some embodiments, the anti-TIGIT antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1027 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1028.

[0314] In some cases, an antibody provided herein binds to TIGIT. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 1021, 1022, 1023, 1024, 1025, and 1026, respectively. In some cases, the antibody comprises CDR-H1,

CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 1021, 1022, 1023, 1024, 1025, and 1026, respectively. In some embodiments, the anti-BCMA antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1043 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1044.

[0315] In some cases, an antibody provided herein binds to CD33. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 1029, 1030, 1031, 1032, 1033, and 1034, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 1029, 1030, 1031, 1032, 1033, and 1034, respectively. In some embodiments, the anti-CD33 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1035 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1036.

[0316] In some cases, an antibody provided herein binds to BCMA. In some such cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences comprising at least 80% sequence identity, at least 85% sequence identity, at least 90% sequence identity, or at least 95% sequence identity to the amino acid sequences of SEQ ID NOs: 1037, 1038, 1039, 1040, 1041, and 1042, respectively. In some cases, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences each comprising at most one mutation relative to the amino acid sequences of SEQ ID NOs: 1037, 1038, 1039, 1040, 1041, and 1042, respectively. In some embodiments, the anti-BCMA antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1043 and a light chain variable region comprising an amino acid sequence that is at least 80% at least 85%, at least 90%, at least 95%, at least 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 1044.

(iv) Non-Targeted Antibodies

[0317] In some cases, the antibody is a non-targeted antibody, for example, a non-binding or control antibody. In some cases, the antibody comprises an Fc fragment without fragment antigen-binding (fab) regions.

Linkers

[0318] As described herein, linkers (L) are optional groups that can connect D with Ab. In some embodiments, the linker (L) comprises a cleavable group. The cleavable group can be configured for cleavage by particular enzymes or under specific physiological conditions. When coupled to targeting antibodies which direct coupling to or uptake by specific cells or tissues, such linkers (L) can ensure location-specific payload release. For example, the cleavable group can be configured for cleavage at low pH, such as that typically present in a tumor microenvironment; or in an oxidizing environment, such as those of lysosomes and some endosomes. Examples of such cleavable groups can include ortho-esters, ketals, acetals, hydrazones, imines, and maleic acid amides.

[0319] The cleavable group can be configured for enzymatic cleavage. When the enzymes for such cleavage are localized within specific tissues, cells, or sub-cellular compartments, the cleavable group can exhibit location specific cleavage, thereby preventing payload release outside of desired locations. Examples of such cleavable groups include protease and hydrolase cleavage sites. In some cases, the cleavable group includes a cleavable glycosidic group. In some cases, the cleavable glycosidic group comprises β -D-glucuronide, β -D-galactose, β -D-glucose, β -D-xylose, hexamaltose, β -L-gulose, β -L-allose, β -mannose-6-phosphate, β -L-fucose, α-E-mannose, β -D-fucose, 6-deoxy-β-D-glucose, β-mannose-6-phosphate, lactose, maltose, cellobiose, gentiobiose, maltotriose, β-D-GlcNAc, and β-D-GalNAc. For example, the cleavable group can comprise β-glucuronidase or α-mannosidase-cleavage sites cleavable by lysosomal β-glucuronidases or α-mannosidases, thereby rendering the linker (L) inert prior to lysosomal uptake and cleavable subsequent to lysosomal uptake. In some cases, the cleavable group comprises an enzymatically cleavable glycosidic bond, peptide bond, carbamate, or quaternary amine. In some cases, the enzyme for such cleavage is associated with a cancer cell, such as extracellular cathepsin.

[0320] The linker (L) can be configured to promote specific tissue, cell, or sub-cellular localization. In some cases, the linker (L) is lipophilic to promoting endocytic uptake when in proximity of a target cell. For example, in certain embodiments disclosed herein, the linker (L) comprises polyethylene glycol (PEG), non-charged and non-polar peptides, and/or other membrane-permeable groups.

[0321] For many of the ADCs disclosed herein, the linker comprises a length of between 5 and 80 atoms as defined by the pathway between D and Ab through the fewest number of bonds. In some cases, the linker comprises a length of between 10 and 40 atoms as defined by the pathway between D and Ab through the fewest number of bonds. In some cases, the linker comprises a length of between 15 and 30 atoms as defined by the pathway between D and Ab through the fewest number of bonds. In some cases, the linker comprises a length of between 15 and 25 atoms as defined by the pathway between D and Ab through the fewest number of bonds.

[0322] Some embodiments provide 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 consistent with the present disclosure;

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;

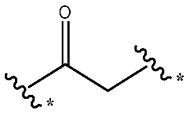
L has the formula $–M\text{-}(A)_a\text{-}(W)_w\text{-}(Y)_y\text{-}(X)_x–$, wherein:

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 (e.g., ), a disulfide, a dihydropyridazine, or a triazole;

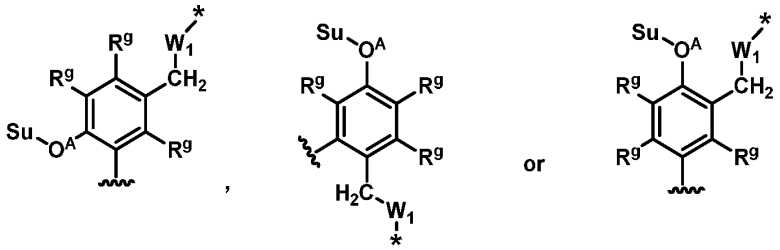
A is a $C_{2\text{-}20}$ alkylene optionally substituted with 1-4 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1};

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: $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ haloalkyl, $C_{1\text{-}6}$ alkoxy, $C_{1\text{-}6}$ haloalkoxy, halogen, -OH, $-NR^{d1}R^{e1}$, $-(C_{1\text{-}6}$ 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^{d1} and R^{e1} are independently hydrogen or $C_{1\text{-}3}$ 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;

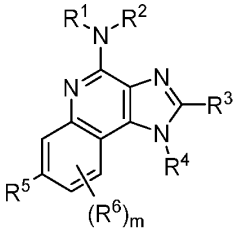
* represents covalent attachment to X, Y, or D;

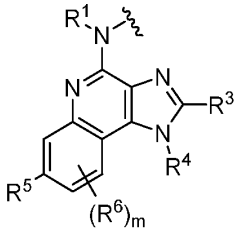
Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety;

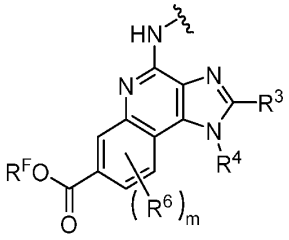
X is a C_1-C_6 alkylene or a 3-6 membered heteroalkylene;

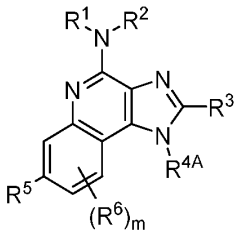
L is optionally substituted with a PEG Unit from PEG1 to PEG72;

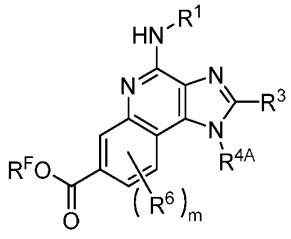
each D has the structure of any one of Formulae (I)-(VIII), (IIa), (IIIa), or (A) as defined herein:

 (I);

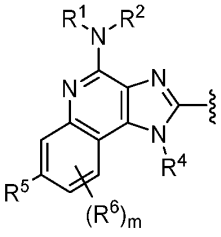
 (II);

 (IIa);

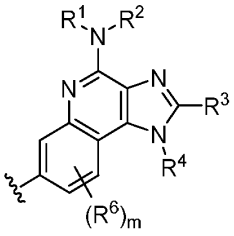
 (III);



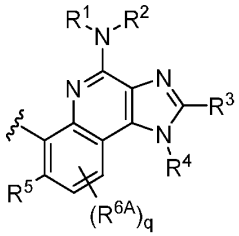
(IIIa);



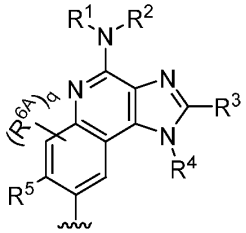
(IV);



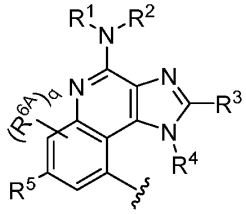
(V);



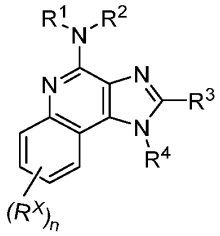
(VI);



(VII);



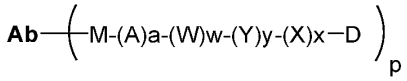
(VIII); and



(A); and

each instance of R^X, R^1, R^2, R^3, R^4, R^{4A}, R^5, R^6, R^{6A}, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, n, m, and q is as defined herein.

[0323] Some embodiments provide an antibody drug conjugate (ADC) having the structure:



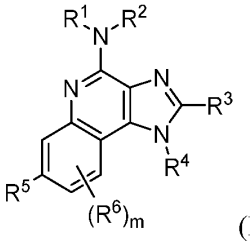
or a pharmaceutically acceptable salt thereof,

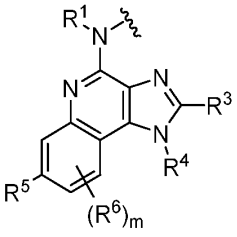
wherein:

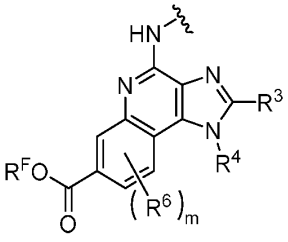
Ab is an antibody;

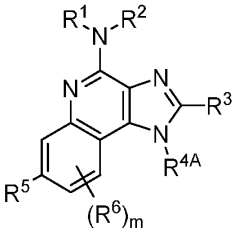
subscript p is an integer from 1 to 16;

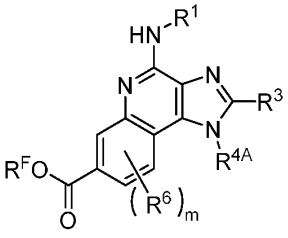
each D has the structure of any one of Formulae (I)-(VIII), (IIa), (IIIa), or (A) as defined herein:

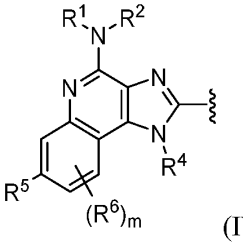

(I);

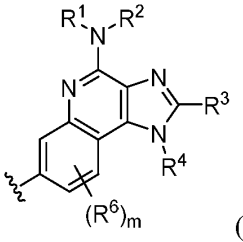

(II);

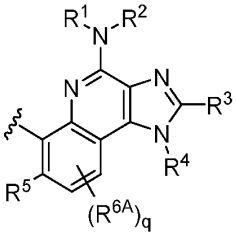

(IIa);

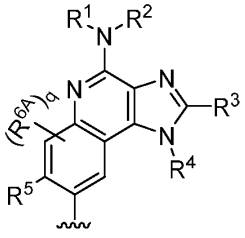

(III);

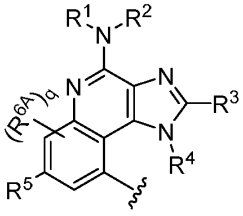

(IIIa);

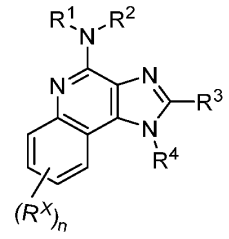

(IV);


(V);


(VI);


(VII);

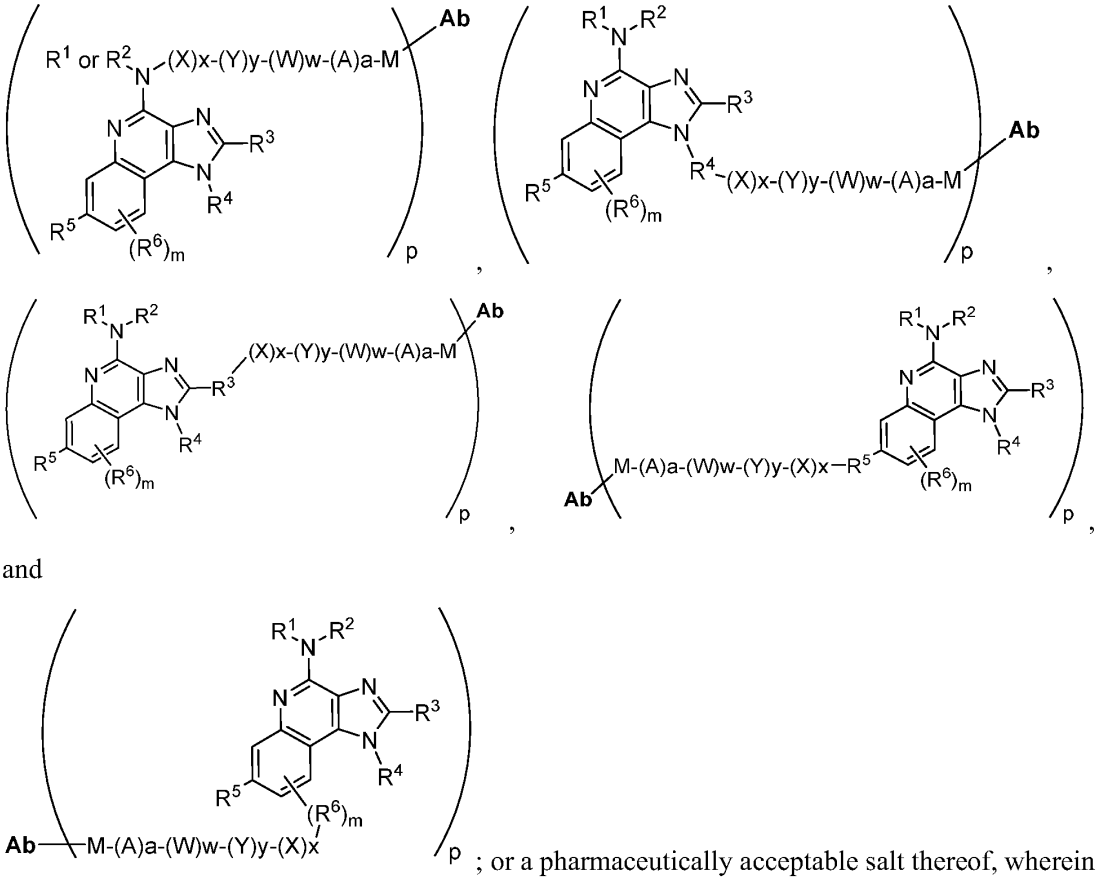

(VIII); and



(A); and

each instance of R^X, R^1, R^2, R^3, R^4, R^{4A}, R^5, R^6, R^{6A}, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, n, m, and q is as defined herein.

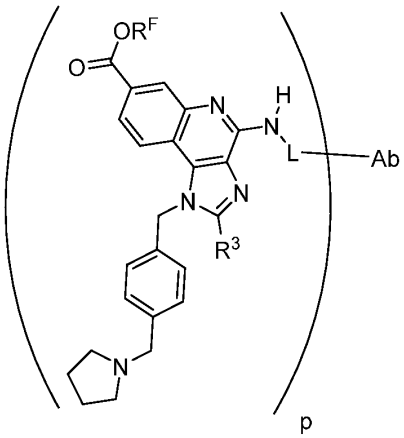
[0324] In some embodiments, the ADC is selected from the group consisting of:



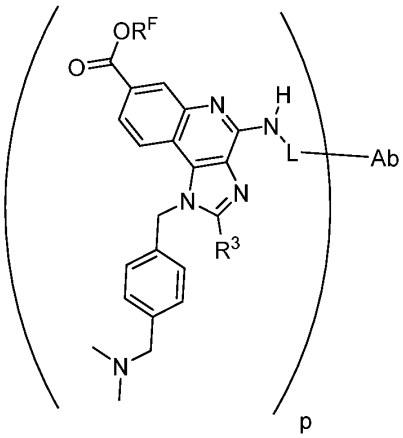
and

; or a pharmaceutically acceptable salt thereof, wherein Ab is an antibody and the remaining variables are as defined herein.

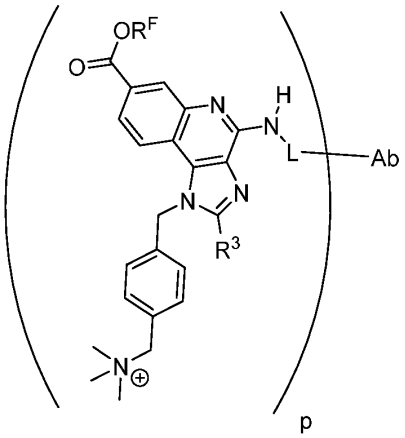
[0325] In some embodiments, the ADC is selected from the group consisting of:



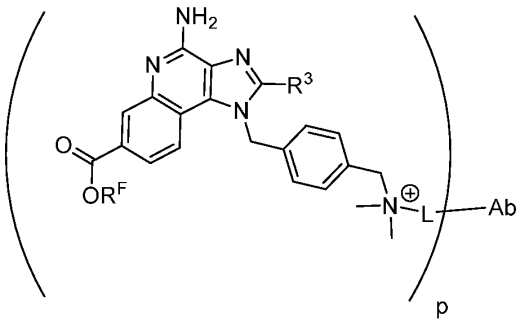
,



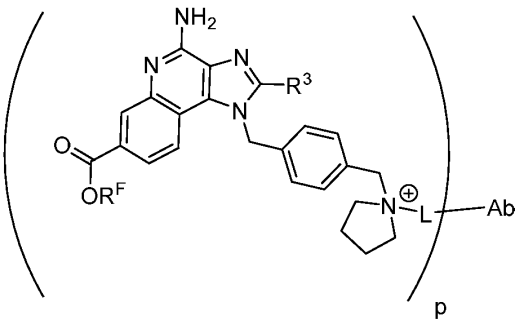
,



,



, and



; or a pharmaceutically acceptable salt thereof, wherein Ab is an antibody, L is a linker, and R^3, R^F, and subscript p are as defined herein.

In some embodiments, the ADCs described herein are present in the form of a salt. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0326] In some embodiments subscript p is an integer from 1 to 8; from 4 to 12; or from 8 to 16. In some embodiments, subscript p is an even number. In some embodiments, subscript p is 2, 4, 6, 8, 10, 12, 14, or 16. In some embodiments, subscript p is 2, 4, 6, or 8.

[0327] In some embodiments, each L is covalently attached to Ab via a sulfur atom of a cysteine residue. In some embodiments, one or more of the cysteine residues is an engineered

cysteine residue. In some embodiments, each cysteine residue is an engineered cysteine residue. In some embodiments, one or more of the cysteine residues is a native cysteine residue. In some embodiments, each cysteine residue is a native cysteine residue. In some embodiments, each sulfur atom is from a cysteine residue from a reduced interchain disulfide bond. In some embodiments, each L is covalently attached to Ab via an ϵ-amino group of a lysine residue.

[0328] In some embodiments, the linker (L) has the formula $–M-(A)_a-(W)_w-(Y)_y-(X)_x–$, wherein:

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

subscript x is 0 or 1;

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

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};

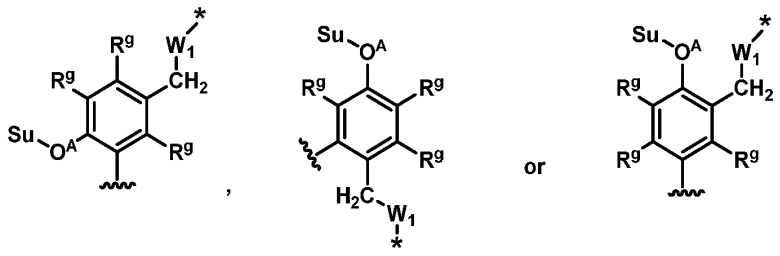
each R^{a1} is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, halogen, -OH, =O, $-NR^{d1}R^{e1}$, $-(C_{1-6}$ alkylene$)-NR^{d1}R^{e1}$, $-C(=O)NR^{d1}R^{e1}$, $-C(=O)(C_{1-6}$ alkyl), and $-C(=O)O(C_{1-6}$ alkyl);

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

subscript a is 0 or 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 Y, X, or D;

subscript w is 0 or 1;

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

subscript y is 0 or 1.

[0329] In some embodiments, the linker (L) has the formula –M-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$–, wherein:

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

subscript x is 0 or 1;

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

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};

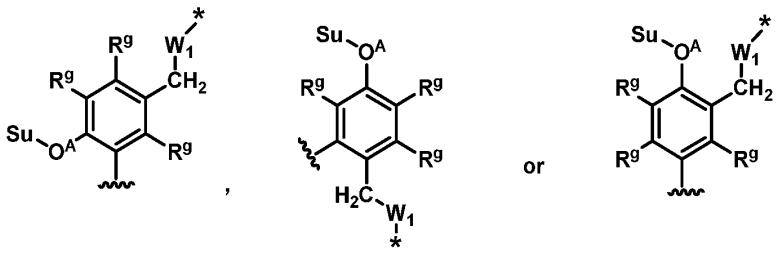
each R^{a1} is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, halogen, -OH, =O, $-NR^{d1}R^{e1}$, -(C_{1-6} alkylene)-$NR^{d1}R^{e1}$, $-C(=O)NR^{d1}R^{e1}$, -C(=O)(C_{1-6} alkyl), and -C(=O)O(C_{1-6} alkyl);

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

subscript a is 0 or 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 Y, X, or D;

subscript w is 0 or 1;

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

subscript y is 0 or 1.

[0330] In some embodiments, -O^A- represents the oxygen atom of a glycosidic bond. In some embodiments, the glycosidic bond provides a β-glucuronidase or a α-mannosidase-cleavage site. In some embodiments, the β-glucuronidase-cleavage site is cleavable by human lysosomal β-glucuronidase. In some embodiments, the α-mannosidase-cleavage site is cleavable by human lysosomal α-mannosidase.

[0331] In some embodiments, subscript x is 0. In some embodiments, subscript x is 1. In some embodiments, subscript a is 0. In some embodiments, subscript a is 1. In some embodiments, subscript w is 0. In some embodiments, subscript w is 1. In some embodiments, subscript y is 0. In some embodiments, subscript y is 1. In some embodiments, subscripts a + y + w = 1. In some embodiments, subscripts a + y + w = 2. In some embodiments, subscripts a + y + w = 3. In some embodiments, subscripts a + y + w = 0. In some embodiments, subscripts x + a + y + w = 0 (i.e., the linker (L) is M).

[0332] In some embodiments, X is a C_1-C_6 alkylene. In some embodiments, X is a C_1-C_3 alkylene. In some embodiments, X is a 3-4 membered heteroalkylene. In some embodiments, X is *-CH_2-N(CH_2CH_3)-, wherein the * represents covalent attachment to D.

[0333] In some embodiments, A is a C_{2-20} alkylene optionally substituted with 1-4 R^{a1}. In some embodiments, A is a C_{2-10} alkylene optionally substituted with 1-4 R^{a1}. In some embodiments, A is a C_{4-10} alkylene optionally substituted with 1-4 R^{a1}. In some embodiments, A is a C_{2-20} alkylene substituted with one R^{a1}. In some embodiments, A is a C_{2-10} alkylene substituted with one R^{a1}. In some embodiments, A is a C_{2-10} alkylene substituted with one R^{a1}.

[0334] In some embodiments, 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, -$NR^{d1}R^{e1}$, -$C(=O)NR^{d1}R^{e1}$, -$C(=O)(C_{1-6}$ alkyl), and -$C(=O)O(C_{1-6}$ alkyl). In some embodiments, each R^{a1} is C_{1-6} alkyl. In some embodiments, each R^{a1} is C_{1-6} haloalkyl. In some embodiments, each R^{a1} is C_{1-6} alkoxy. In some embodiments, each R^{a1} is C_{1-6} haloalkoxy. In some embodiments, each R^{a1} is halogen. In some embodiments, each R^{a1} is –OH. In some embodiments, each R^{a1} is =O. In some embodiments, each R^{a1} is -$NR^{d1}R^{e1}$. In some embodiments, each R^{a1} is -(C_{1-6} alkylene)-$NR^{d1}R^{e1}$. In some embodiments, each R^{a1} is -$C(=O)NR^{d1}R^{e1}$. In some embodiments, each R^{a1} is -$C(=O)(C_{1-6}$ alkyl). In some embodiments, each R^{a1} is -$C(=O)O(C_{1-6}$ alkyl). In some embodiments, one

occurrence of R^{a1} is $-NR^{d1}R^{e1}$. In some embodiments, one occurrence of R^{a1} is -(C_{1-6} alkylene)-$NR^{d1}R^{e1}$. In some embodiments, one occurrence of R^{a1} is -(C_{1-2} alkylene)-$NR^{d1}R^{e1}$. In some embodiments, A is a C_{2-20} alkylene substituted with 1 or 2 R^{a1}, each of which is =O.

[0335] In some embodiments, R^{d1} and R^{e1} are independently hydrogen or C_{1-3} alkyl. In some embodiments, one of R^{d1} and R^{e1} is hydrogen, and the other of R^{d1} and R^{e1} is C_{1-3} alkyl. In some embodiments, R^{d1} and R^{e1} are both hydrogen or C_{1-3} alkyl. In some embodiments, R^{d1} and R^{e1} are both C_{1-3} alkyl. In some embodiments, R^{d1} and R^{e1} are both methyl.

[0336] In some embodiments, A is a C_{2-20} alkylene. In some embodiments, A is a C_{2-10} alkylene. In some embodiments, A is a C_{2-10} alkylene. In some embodiments, A is a C_{2-6} alkylene. In some embodiments, A is a C_{4-10} alkylene.

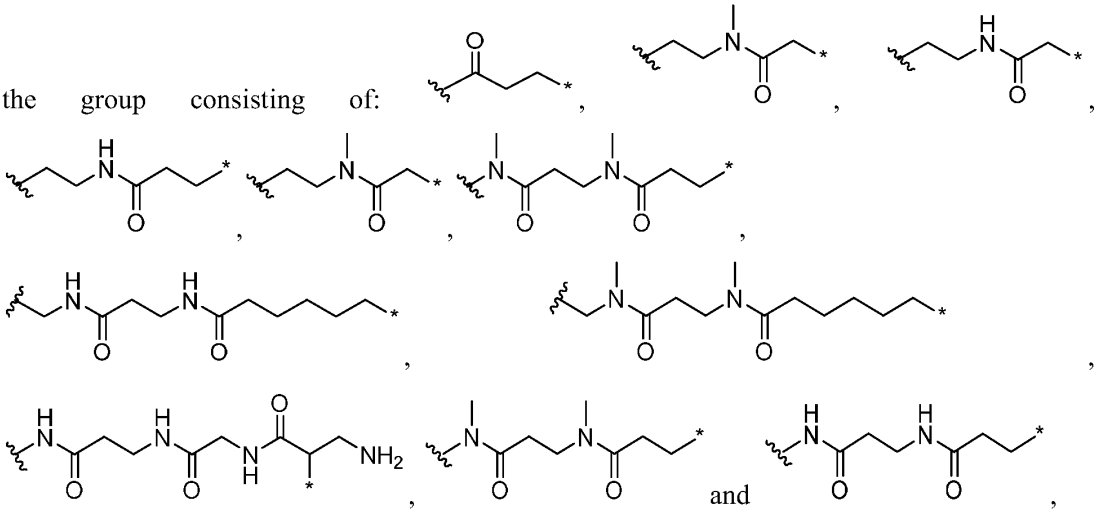
[0337] In some embodiments, A is a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1}. In some embodiments, A is a 2 to 20 membered heteroalkylene optionally substituted with 1-4 R^{b1}. In some embodiments, A is a 2 to 12 membered heteroalkylene optionally substituted with 1-4 R^{b1}. In some embodiments, A is a 4 to 12 membered heteroalkylene optionally substituted with 1-4 R^{b1}. In some embodiments, A is a 4 to 8 membered heteroalkylene optionally substituted with 1-4 R^{b1}. In some embodiments, A is a 2 to 40 membered heteroalkylene substituted with one R^{b1}. In some embodiments, A is a 2 to 20 membered heteroalkylene substituted with one R^{b1}. In some embodiments, A is a 2 to 12 membered heteroalkylene substituted with one R^{b1}. In some embodiments, A is a 4 to 12 membered heteroalkylene substituted with one R^{b1}. In some embodiments, A is a 4 to 8 membered heteroalkylene substituted with one R^{b1}.

[0338] In some embodiments, 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). In some embodiments, each R^{b1} is C_{1-6} alkyl. In some embodiments, each R^{b1} is C_{1-6} haloalkyl. In some embodiments, each R^{b1} is C_{1-6} alkoxy. In some embodiments, each R^{b1} is C_{1-6} haloalkoxy. In some embodiments, each R^{b1} is halogen. In some embodiments, each R^{b1} is –OH. In some embodiments, each R^{b1} is $-NR^{d1}R^{e1}$. In some embodiments, each R^{b1} is -(C_{1-6} alkylene)-$NR^{d1}R^{e1}$. In some embodiments, each R^{b1} is $C(=O)NR^{d1}R^{e1}$. In some embodiments, each R^{b1} is -C(=O)(C_{1-6} alkyl). In some embodiments, each R^{b1} is -C(=O)O(C_{1-6} alkyl). In some embodiments, one occurrence of R^{b1} is $-NR^{d1}R^{e1}$. In some embodiments, one occurrence of R^{b1} is -(C_{1-6} alkylene)-$NR^{d1}R^{e1}$. In some embodiments, one occurrence of R^{b1} is -(C_{1-2} alkylene)-$NR^{d1}R^{e1}$.

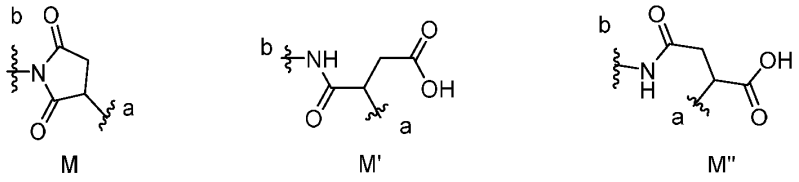
[0339] In some embodiments, R^{d1} and R^{e1} are independently hydrogen or C_{1-3} alkyl. In some embodiments, one of R^{d1} and R^{e1} is hydrogen, and the other of R^{d1} and R^{e1} is C_{1-3} alkyl. In some

embodiments, R^{d1} and R^{e1} are both hydrogen or C_{1-3} alkyl. In some embodiments, R^{d1} and R^{e1} are both C_{1-3} alkyl. In some embodiments, R^{d1} and R^{e1} are both methyl.

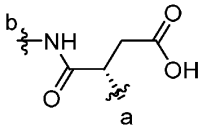
[0340] In some embodiments, A is a 2 to 40 membered heteroalkylene. In some embodiments, A is a 2 to 20 membered heteroalkylene. In some embodiments, A is a 2 to 12 membered heteroalkylene. In some embodiments, A is a 4 to 12 membered heteroalkylene. In some embodiments, A is a 4 to 8 membered heteroalkylene. In some embodiments, A is selected from the group consisting of:

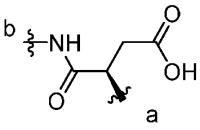
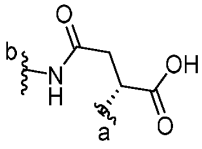
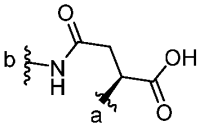


wherein ~~~ represents covalent attachment to W, Y, X, or D, and * represents covalent linkage to M. In some embodiments, M is a succinimide. In some embodiments, M is a hydrolyzed succinimide. It will be understood that a hydrolyzed succinimide may exist in two regioisomeric form(s). Those forms are exemplified below for hydrolysis of M, wherein the structures representing the regioisomers from that hydrolysis are formula M' and M''; wherein wavy line a indicates the point of covalent attachment to the antibody, and wavy line b indicates the point of covalent attachemtnt to A.

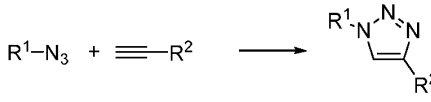
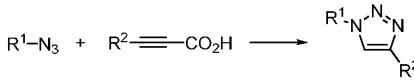
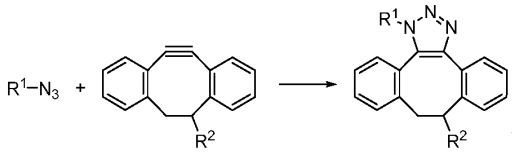
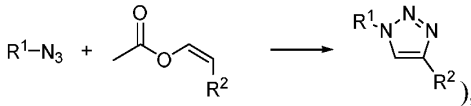


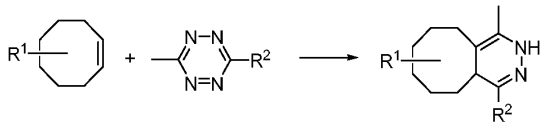
M M' M"

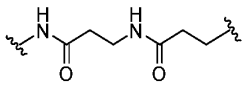
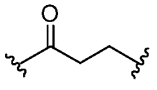


[0341] In some embodiments, M' is . In some embodiments, M' is  . In some embodiments, M" is  . In some embodiments, M" is  .

[0342] In some embodiments, M is a succinimide, a hydrolyzed succinimide, an amide, or a triazole. In some embodiments, M is a succinimide or a hydrolyzed succinimide.

[0343] In some embodiments, M is a triazole. In some cases, the triazole is a 1,2,3-triazole, such as those formed by some click chemistry cycloadditions, including copper-, copper iron bimetallic-, and ruthenium-catalyzed cycloadditions (e.g., ); copper-catalyzed decarboxylative cycloadditions (e.g., ); copper-free azide-DBCO cycloadditions (e.g., ), copper-free azide-DIFO cycloadditions, copper-free azide-BCN cycloadditions, copper-free azide-DICO cycloadditions, and copper-free azide-vinyl acetate cycloadditions (e.g., ), and variations with derivatives thereof.

[0344] In some cases, M is a dihydropyridazine, such as those formed from certain tricyclooctine-tetrazine cycloadditions (e.g., ).

[0345] In some embodiments, M is an amide. In some embodiments, A is a PEG4 to PEG12. In some embodiments, A is a PEG4 to PEG8. Representative A groups include, but are not limited to:  and  .

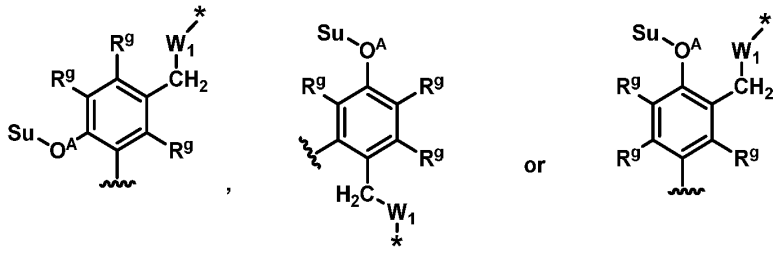
[0346] In some embodiments, M is a methyl ketone.

[0347] In some embodiments, subscript w is 0. In some embodiments subscript w is 1.

[0348] In some embodiments, W is a single amino acid. In some embodiments, W is a single natural amino acid. In some embodiments, W is a peptide including from 2-12 amino acids, wherein each amino acid is independently a natural or unnatural amino acid. In some embodiments, each amino acid is independently a natural amino acid. In some embodiments, W is a dipeptide. In some embodiments, W is a tripeptide. In some embodiments, W is a tetrapeptide. In some embodiments, W is a pentapeptide. In some embodiments, W is a hexapeptide. In some embodiments, W is 7, 8, 9, 10, 11, or 12 amino acids. In some embodiments, each amino acid of W is independently selected from the group consisting of valine, alanine, β-alanine, glycine, lysine, leucine, phenylalanine, proline, aspartic acid, serine, glutamic acid, homoserine methyl ether, aspartate methyl ester, *N,N*-dimethyl lysine, arginine, valine-alanine, valine-citrulline, phenylalanine-lysine, and citrulline. In some embodiments, W is an aspartic acid. In some embodiments, W is a lysine. In some embodiments, W is a glycine. In some embodiments, W is an alanine. In some embodiments, W is aspartate methyl ester. In some embodiments, W is a *N,N*-dimethyl lysine. In some embodiments, W is a homoserine methyl ether. In some embodiments, W is a serine. In some embodiments, W is a valine-alanine.

[0349] In some embodiments, W is from 1-12 amino acids; and the bond between W and the X^B or between W and Y is enzymatically cleavable by a tumor-associated protease. In some embodiments, the tumor-associated protease is a cathepsin. In some embodiments, the tumor-associated protease is cathepsin B, C, or D.

[0350] In some embodiments, W has the structure of:



wherein Su is a Sugar moiety;

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

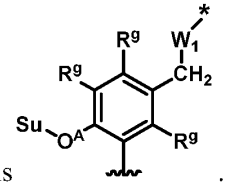
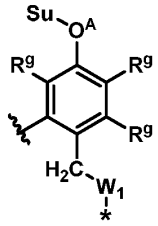
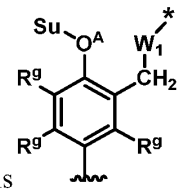
each R^g is independently hydrogen, halogen, C_1-C_6 alkoxy, -N(C_1-C_6 alkyl)$_2$, -NHC(=O)(C_1-C_6 alkyl), -CN, -CF_3, acyl, carboxamido, C_1-C_6 alkyl, or -NO_2;

W_1 is absent, *–C(=O)-O–, or *–O-C(=O)–;

 represents covalent attachment to A or M; and

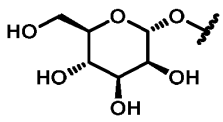
the * represents covalent attachment to Y, X, or D.

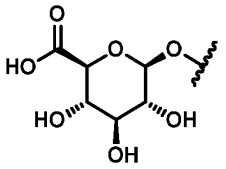
In some embodiments, -O^A- represents the oxygen atom of a glycosidic bond. In some embodiments, the glycosidic bond provides a β-glucuronidase or a α-mannosidase-cleavage site. In some embodiments, the β-glucuronidase or a α-mannosidase-cleavage site is cleavable by human lysosomal β-glucuronidase or by human lysosomal α-mannosidase.

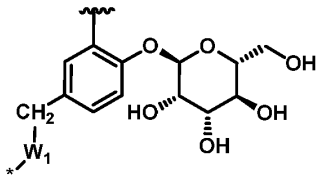
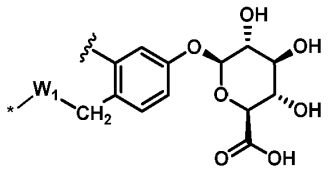
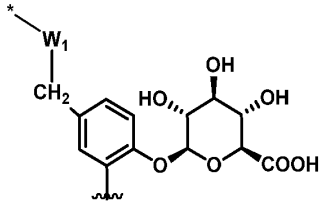
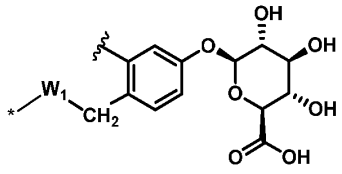
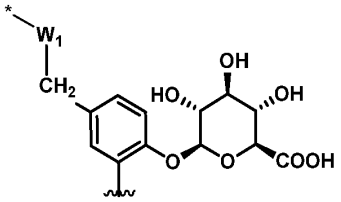
[0351] In some embodiments, W is  . In some embodiments, W is  . In some embodiments, W is  .

[0352] In some embodiments, each R^g is hydrogen. In some embodiments, one R^g is hydrogen, and the remaining R^g are independently 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. In some embodiments, two R^g are hydrogen, and the remaining 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.

[0353] In some embodiments, 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 other R^g are hydrogen.

[0354] In some embodiments, O^A-Su is charged neutral at physiological pH. In some embodiments, O^A-Su is mannose. In some embodiments, O^A-Su is  . In some

embodiments, O^A-Su comprises a carboxylate moiety. In some embodiments, O^A-Su is glucuronic acid. In some embodiments, O^A-Su is  .

In some embodiments, W is  . In some embodiments, W is  or  . In some embodiments, W is  . In some embodiments, W is  .

[0355] In some embodiments, W_1 is absent. In some embodiments, W_1 is *–C(=O)-O–. In some embodiments, W_1 is absent or *–O-C(=O)–. In some embodiments, W_1 is *–O-C(=O)–.

[0356] In some embodiments, the linker comprises a cleavable unit. In some embodiments, W is a Cleavable Unit. In some embodiments, W is a Peptide Cleavable Unit. In some embodiments, W is a Glucuronide Unit.

[0357] In some embodiments, subscript a is 0.

[0358] In some embodiments, subscript y is 0. In some embodiments subscript y is 1.

[0359] In some embodiments, Y is a self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety. In some embodiments, Y is a self-immolative moiety or a non-self-immolative releasable moiety. In some embodiments, Y is a self-immolative moiety. In some embodiments, Y is a non-self-immolative moiety.

[0360] A non-self-immolative moiety is one which requires enzymatic cleavage, and in which part or all of the group remains bound to the Drug Unit after cleavage from the ADC, thereby forming free drug. Examples of a non-self-immolative moiety include, but are not limited to: -glycine- and -glycine-glycine. When an ADC having Y is -glycine- or -glycine-glycine- undergoes

enzymatic cleavage (for example, via a cancer-cell-associated protease or a lymphocyte-associated protease), the Drug Unit is cleaved from the ADC such that the free drug includes the glycine or glycine-glycine group from Y. In some embodiments, an independent hydrolysis reaction takes place within, or in proximity to, the target cell, further cleaving the glycine or glycine-glycine group from the free drug. For example, an ADC with a non-self-immolative linker with a PAB optionally substituted with 1-4 substituents independently selected from halogen, cyano, and nitro, can undergo enzymatic cleavage of the linker (for example, via a cancer-cell-associated protease or a lymphocyte-associated protease), releasing a free drug which includes the optionally substituted PAB. This compound may further undergo 1,6-elimination of the PAB, removing any portion of Y from the free drug. *See,* e.g., Told et al., 2002, *J. Org. Chem.* 67:1866-1872. In some embodiments, enzymatic cleavage of the non-self-immolative moiety, as described herein, and does not result in any further hydrolysis step(s).

[0361] A self-immolative moiety refers to a bifunctional chemical moiety that is capable of covalently linking together two spaced chemical moieties into a normally stable tripartite molecule. The self-immolative moiety will spontaneously separate from the second chemical moiety if its bond to the first moiety is cleaved. For example, a self-immolative moiety includes a p-aminobenzyl alcohol (PAB) optionally substituted with one or more 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. Other examples of self-immolative moieties include, but are not limited to, aromatic compounds that are electronically similar to the PAB group such as 2-aminoimidazol-5-methanol derivatives (*see,* e.g., Hay et al., 1999, *Bioorg. Med. Chem. Lett.* 9:2237), ortho or para-aminobenzylacetals, substituted and unsubstituted 4-aminobutyric acid amides (*see,* e.g., Rodrigues et al., 1995, *Chemistry Biology* 2:223), appropriately substituted bicyclo[2.2.1] and bicyclo[2.2.2] ring systems (*see,* e.g., Storm et al., 1972, *J. Amer. Chem. Soc.* 94:5815), 2-aminophenylpropionic acid amides (*see*, e.g., Amsberry et al., 1990, *J. Org. Chem.* 55:5867), and elimination of amine-containing drugs that are substituted at the α-position of glycine (*see,* e.g., Kingsbury et al., 1984, *J. Med. Chem.* 27:1447).

[0362] In some embodiments, Y is a p-aminobenzyl alcohol (PAB) optionally substituted with 1-4 substituents independently selected from 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. In some embodiments, Y is an unsubstituted p-aminobenzyl alcohol (PAB).

[0363] In some embodiments, Y is a para-aminobenzyloxy-carbonyl (PABC) group optionally substituted with a sugar moiety. In some embodiments, Y is -glycine- or -glycine-

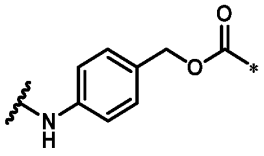
glycine-. In some embodiments, Y is a branched bis(hydroxymethyl)styrene (BHMS) unit, which is capable of incorporating (and releasing) multiple Drug Units.

[0364] In some embodiments, –M-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$– is a non-self-immolative releasable linker, which provides release of the free drug once the ADC has been internalized into the target cell. In some embodiments, –M-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$– is a releasable linker, which provides release of the free drug with, or in the vicinity, of targeted cells. In some embodiments, releasable linkers possess a recognition site, such as a peptide cleavage site, sugar cleavage site, or disulfide cleavage site. In some embodiments, each releasable linker is a di-peptide. In some embodiments, each releasable linker is a disulfide. In some embodiments, each releasable linker is a hydrazone. In some embodiments, each releasable linker is independently selected from the group consisting of Val-Cit-, -Phe-Lys-, and -Val-Ala-. In some embodiments, each releasable linker, when bound to a succinimide or hydrolyzed succinimide, is independently selected from the group consisting of succinimido-caproyl (mc), succinimido-caproyl-valine-citrulline (sc-vc), succinimido-caproyl-valine-citrulline-paraaminobenzyloxycarbonyl (sc-vc-PABC), and SDPr-vc (where "S" refers to succinimido).

[0365] In some embodiments, –M-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$– comprises a non-cleavable linker. Non-cleavable linkers are known in the art and can be adapted for use with the ADCs described herein as the "Y" group. A non-cleavable linker is capable of linking a Drug Unit to an antibody in a generally stable and covalent manner and is substantially resistant to cleavage, such as acid-induced cleavage, light-induced cleavage, peptidase- or esterase-induced cleavage, and disulfide bond cleavage. The free drug can be released from the ADCs containing non-cleavable linkers via alternative mechanisms, such as proteolytic antibody degradation. In some embodiments, the Drug Unit can exert a biological effect as a part of the ADC (i.e., while still conjugated to the antibody via a linker).

[0366] Reagents that form non-cleavable linker-maleimide and non-cleavable linker-succinimide compounds are known in the art and can adapted for use herein. Exemplary reagents comprise a maleimido or haloacetyl-based moiety, such as 6-maleimidocaproic acid N-hydroxy succinimide ester (MCC), N-succinimidyl 4-(maleimidomethyl)cyclohexanecarboxylate (SMCC), N-succinimidyl-4-(N-maleimidomethyl)-cyclohexane-1-carboxy-(6-amidocaproate) (LC-SMCC), maleimidoundecanoic acid N-succinimidyl ester (KMUA), γ-maleimidobutyric acid N-succinimidyl ester (GMBS), c-maleimidocaproic acid N-hydroxysuccinimide ester (EMCS), m-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), N-(α-maleimidoacetoxy)-succinimide ester [AMAS], succinimidyl-6-(β-maleimidopropionamido)hexanoate (SMPH), N-succinimidyl-4-(p-maleimidophenyl)-butyrate (SMPB), and N-(p-maleimidophenyl)isocyanate (PMPI), N-

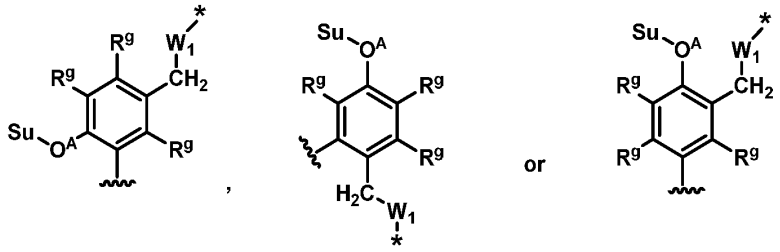
succinimidyl-4-(iodoacetyl)-aminobenzoate (STAB), N-succinimidyl iodoacetate (SIA), N-succinimidyl bromoacetate (SBA) and N-succinimidyl 3-(bromoacetamido)propionate (SBAP). Additional "A-M" groups for use in the ADCs described herein can be found, for example, in U.S. Pat. No. 8,142,784, incorporated herein by reference in its entirety.

[0367] In some embodiments, Y is  , wherein ~~~ represents connection to W, A, or M; and the * represents connection to X or D, in the ADCs described herein.

[0368] In some embodiments, $-M-(A)_a-(W)_w-(Y)_y-(X)_x-$, comprises a non-releasable linker, wherein the free drug is released from the ADC only after the ADC has been degraded, liberating the free drug. Such ADCs often degrade following cellular uptake, for example following micropinocytosis.

[0369] In some embodiments, subscript x is 0; subscript y is 0; subscript w is 1; subscript a is 1; and M is a succinimide or a hydrolyzed succinimide.

[0370] In some embodiments, subscript x is 0; subscript y is 0; subscript w is 1; subscript a is 1; M is a succinimide or a hydrolyzed succinimide; and W has the structure of:



wherein Su is a Sugar moiety;

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

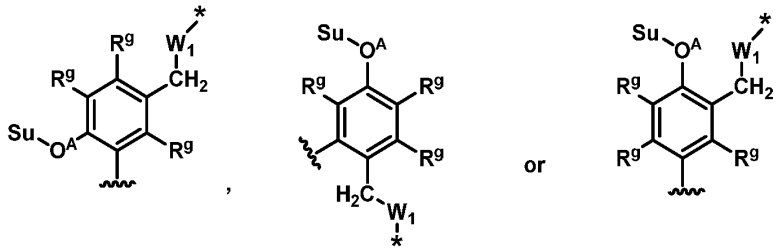
each R^g is independently hydrogen, halogen, C_1-C_6 alkoxy, $-N(C_1$-C_6 alkyl$)_2$, $-NHC(=O)(C_1$-C_6 alkyl), -CN, $-CF_3$, acyl, carboxamido, C_1-C_6 alkyl, or $-NO_2$;

W_1 is absent;

~~~ represents covalent attachment to A; and

the * represents covalent attachment to D.

[0371] In some embodiments, subscript x is 0; subscript y is 0; subscript w is 1; subscript a is 1; M is a succinimide or a hydrolyzed succinimide; and W has the structure of:
~~~



wherein Su is a Sugar moiety;

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

each R^g is independently hydrogen, halogen, 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 *–C(=O)-O–;

 represents covalent attachment to A; and

the * represents covalent attachment to D.

[0372] In some embodiments, subscript x is 0; subscript y is 1; subscript w is 1; subscript a is 1; and M is a succinimide or a hydrolyzed succinimide. In some embodiments, Y is a PAB group and W is a dipeptide.

[0373] In the linkers described herein, A, when present, is covalently attached to M; Y, when present, is attached to X, when present; and M is attached to Ab.

[0374] In some embodiments, the linker (L) is substituted with a polyethylene glycol moiety selected from the group consisting of PEG2 to PEG20. In some embodiments, L is substituted with a polyethylene glycol moiety selected from the group consisting of PEG2, PEG4, PEG6, PEG8, PEG10, PEG12, PEG16, and PEG20. In some embodiments, L is not substituted with a polyethylene glycol moiety selected from the group consisting of PEG2 to PEG20.

[0375] In some embodiments, A is substituted with a polyethylene glycol moiety selected from the group consisting of PEG2 to PEG20. In some embodiments, W is substituted with a polyethylene glycol moiety selected from the group consisting of PEG2 to PEG20. In some embodiments, Y is substituted with a polyethylene glycol moiety selected from the group consisting of PEG2 to PEG20. In some embodiments, X is substituted with a polyethylene glycol moiety selected from the group consisting of PEG2 to PEG20. In some embodiments, the linker (L) is substituted with one polyethylene glycol moiety. In some embodiments, the linker (L) is substituted with 2 or 3 independently selected polyethylene glycol moieties.

[0376] Polydisperse PEGs, monodisperse PEGs and discrete PEGs can be used to make the ADCs and intermediates thereof. Polydisperse PEGs are a heterogeneous mixture of sizes and molecular weights whereas monodisperse PEGs are typically purified from heterogeneous

mixtures and therefore provide a single chain length and molecular weight. Discrete PEGs are synthesized in step-wise fashion and not via a polymerization process. Discrete PEGs provide a single molecule with defined and specified chain length. The number of $-CH_2CH_2O-$ subunits of a PEG Unit ranges, for example, from 8 to 24 or from 12 to 24, referred to as PEG8 to PEG24 and PEG12 to PEG24, respectively.

[0377] The PEG moieties provided herein, which are also referred to as PEG Units, comprise one or multiple polyethylene glycol chains. The polyethylene glycol chains are linked together, for example, in a linear, branched or star shaped configuration. Typically, at least one of the polyethylene glycol chains of a PEG Unit is derivatized at one end for covalent attachment to an appropriate site on a component of the ADC (e.g., L). Exemplary attachments to ADCs are by means of non-conditionally cleavable linkages or via conditionally cleavable linkages. Exemplary attachments are via amide linkage, ether linkages, ester linkages, hydrazone linkages, oxime linkages, disulfide linkages, peptide linkages or triazole linkages. In some embodiments, attachment to ADC is by means of a non-conditionally cleavable linkage. In some embodiments, attachment to the ADC is not via an ester linkage, hydrazone linkage, oxime linkage, or disulfide linkage. In some embodiments, attachment to the ADC is not via a hydrazone linkage.

[0378] A conditionally cleavable linkage refers to a linkage that is not substantially sensitive to cleavage while circulating in plasma but is sensitive to cleavage in an intracellular or intratumoral environment. A non-conditionally cleavable linkage is one that is not substantially sensitive to cleavage in any biologically relevant environment in a subject that is administered the ADC. Chemical hydrolysis of a hydrazone, reduction of a disulfide bond, and enzymatic cleavage of a peptide bond or glycosidic bond of a Glucuronide Unit as described by WO 2007/011968 (which is incorporated by reference in its entirety) are examples of conditionally cleavable linkages.

[0379] In some embodiments, the PEG Unit is directly attached to the ADC (or an intermediate thereof) at L. In those embodiments, the other terminus (or termini) of the PEG Unit is free and untethered (i.e., not covalently attached), and in some embodiments, is a methoxy, carboxylic acid, alcohol or other suitable functional group. The methoxy, carboxylic acid, alcohol or other suitable functional group acts as a cap for the terminal polyethylene glycol subunit of the PEG Unit. By untethered, it is meant that the PEG Unit will not be covalently attached at that untethered site to a Drug Unit, to an antibody, or to a linking component to a Drug Unit and/or an antibody. Such an arrangement can allow a PEG Unit of sufficient length to assume a parallel orientation with respect to the drug in conjugated form, i.e., as a Drug Unit (D). For those embodiments in which the PEG Unit comprises more than one polyethylene glycol chain, the

multiple polyethylene glycol chains are independently chosen, e.g., are the same or different chemical moieties (e.g., polyethylene glycol chains of different molecular weight or number of -CH_2CH_2O- subunits). A PEG Unit having multiple polyethylene glycol chains is attached to the ADC at a single attachment site. The skilled artisan will understand that the PEG Unit, in addition to comprising repeating polyethylene glycol subunits, may also contain non-PEG material (e.g., to facilitate coupling of multiple polyethylene glycol chains to each other or to facilitate coupling to the ADC). Non-PEG material refers to the atoms in the PEG Unit that are not part of the repeating –CH_2CH_2O- subunits. In some embodiments provided herein, the PEG Unit comprises two monomeric polyethylene glycol chains attached to each other via non-PEG elements. In other embodiments provided herein, the PEG Unit comprises two linear polyethylene glycol chains attached to a central core that is attached to the ADC (i.e., the PEG Unit itself is branched).

[0380] There are a number of PEG attachment methods available to those skilled in the art: *see,* for example: Goodson, et al. (1990) *Bio/Technology* 8:343 (PEGylation of interleukin-2 at its glycosylation site after site-directed mutagenesis); EP 0 401 384 (coupling PEG to G-CSF); Malik, et al., (1992) *Exp. Hematol.* 20:1028-1035 (PEGylation of GM-CSF using tresyl chloride); ACT Pub. No. WO 90/12874 (PEGylation of erythropoietin containing a recombinantly introduced cysteine residue using a cysteine-specific mPEG derivative); U.S. Pat. No. 5,757,078 (PEGylation of EPO peptides); U.S. Pat. No. 5,672,662 (Poly(ethylene glycol) and related polymers monosubstituted with propionic or butanoic acids and functional derivatives thereof for biotechnical applications); U.S. Pat. No. 6,077,939 (PEGylation of an N-terminal α-carbon of a peptide); Veronese et al., (1985) *Appl. Biochem. Bioechnol* 11:141-142 (PEGylation of an N-terminal α-carbon of a peptide with PEG-nitrophenylcarbonate ("PEG-NPC") or PEG-trichlorophenylcarbonate); and Veronese (2001) *Biomaterials* 22:405-417 (Review article on peptide and protein PEGylation).

[0381] For example, a PEG Unit may be covalently bound to an amino acid residue via reactive groups of a polyethylene glycol-containing compound and the amino acid residue. Reactive groups of the amino acid residue include those that are reactive to an activated PEG molecule (e.g., a free amino or carboxyl group). For example, N-terminal amino acid residues and lysine (K) residues have a free amino group; and C-terminal amino acid residues have a free carboxyl group. Thiol groups (e.g., as found on cysteine residues) are also useful as a reactive group for forming a covalent attachment to a PEG. In addition, enzyme-assisted methods for introducing activated groups (e.g., hydrazide, aldehyde, and aromatic-amino groups) specifically at the C-terminus of a polypeptide have been described. *See* Schwarz, et al. (1990) *Methods*

Enzymol. 184:160; Rose, et al. (1991) *Bioconjugate Chem.* 2:154; and Gaertner, et al. (1994) *J. Biol. Chem.* 269: 7224.

[0382] In some embodiments, a polyethylene glycol-containing compound forms a covalent attachment to an amino group using methoxylated PEG ("mPEG") having different reactive moieties. Non-limiting examples of such reactive moieties include succinimidyl succinate (SS), succinimidyl carbonate (SC), mPEG-imidate, para-nitrophenylcarbonate (NPC), succinimidyl propionate (SPA), and cyanuric chloride. Non-limiting examples of such mPEGs include mPEG-succinimidyl succinate (mPEG-SS), $mPEG_2$-succinimidyl succinate ($mPEG_2$-SS); mPEG-succinimidyl carbonate (mPEG-SC), $mPEG_2$-succinimidyl carbonate ($mPEG_2$-SC); mPEG-imidate, mPEG-para-nitrophenylcarbonate (mPEG-NPC), mPEG-imidate; $mPEG_2$-para-nitrophenylcarbonate ($mPEG_2$-NPC); mPEG-succinimidyl propionate (mPEG-SPA); $mPEG_2$-succinimidyl propionate (mPEG--SPA); mPEG-N-hydroxy-succinimide (mPEG-NHS); $mPEG_2$-N-hydroxy-succinimide ($mPEG_2$--NHS); mPEG-cyanuric chloride; $mPEG_2$-cyanuric chloride; $mPEG_2$-Lysinol-NPC, and $mPEG_2$-Lys-NHS.

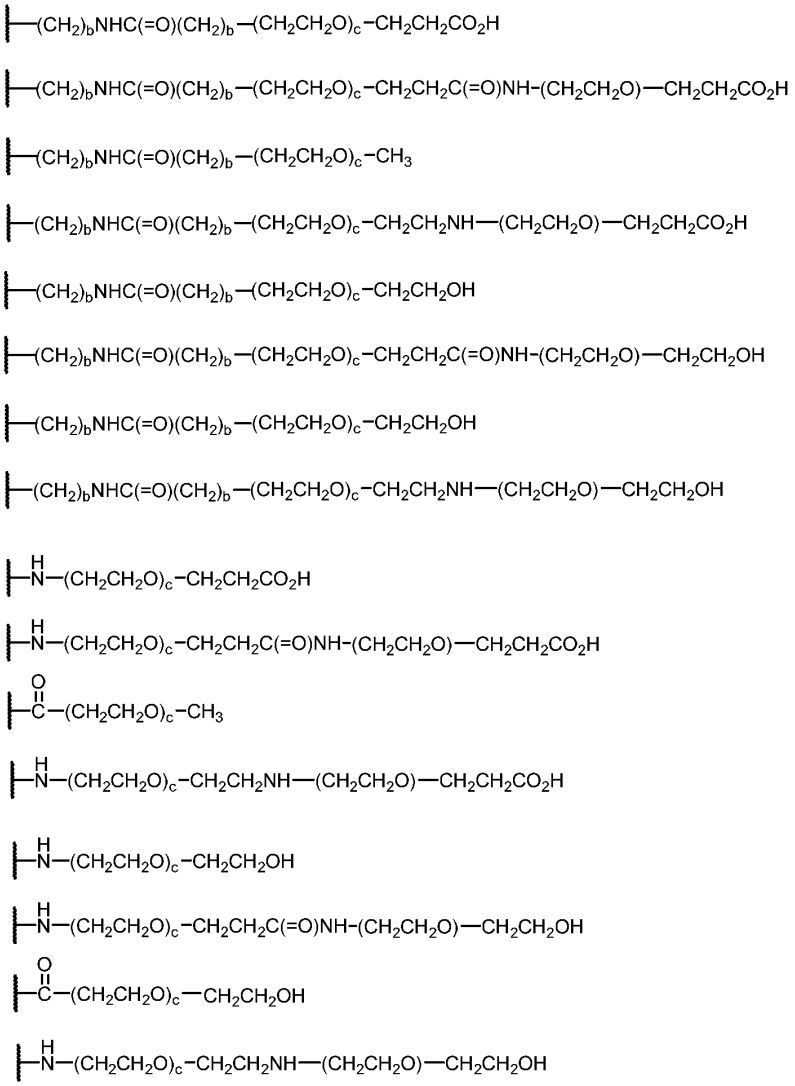
[0383] In some instances, at least one of the polyethylene glycol chains that make up the PEG is functionalized to provide covalent attachment to the ADC. Functionalization of the polyethylene glycol-containing compound that is the precursor to the PEG includes, for example, via an amine, thiol, NHS ester, maleimide, alkyne, azide, carbonyl, or other functional group. In some embodiments, the PEG further comprises non-PEG material (i.e., material not comprised of $-CH_2CH_2O-$) that provides coupling to the ADC or in constructing the polyethylene glycol-containing compound or PEG facilitates coupling of two or more polyethylene glycol chains.

[0384] In some embodiments, the presence of the PEG Unit in an ADC is capable of having two potential impacts upon the pharmacokinetics of the resulting ADC. One impact is a decrease in clearance (and consequent increase in exposure) that arises from the reduction in non-specific interactions induced by the exposed hydrophobic elements of the Drug Unit. The second impact is a decrease in volume and rate of distribution that sometimes arises from the increase in the molecular weight of the ADC. Increasing the number of polyethylene glycol subunits increases the hydrodynamic radius of a conjugate, typically resulting in decreased diffusivity. In turn, decreased diffusivity typically diminishes the ability of the ADC to penetrate into a tumor. *See* Schmidt and Wittrup, *Mol Cancer Ther* 2009; 8:2861-2871. Because of these two competing pharmacokinetic effects, it can be desirable to use a PEG Unit that is sufficiently large to decrease the ADC clearance thus increasing plasma exposure, but not so large as to greatly diminish its diffusivity to an extent that it interferes with the ability of the ADC to reach the intended target cell population. *See,* e.g., Examples 1, 18, and 21 of US 2016/0310612, which is incorporated by

reference herein (e.g., for methodology for selecting an optimal size of a PEG Unit for a particular Drug Unit, Linker, and/or drug-linker compound).

[0385] In some embodiments, the PEG Unit comprises one or more linear polyethylene glycol chains each having at least 2 subunits, at least 3 subunits, at least 4 subunits, at least 5 subunits, at least 6 subunits, at least 7 subunits, at least 8 subunits, at least 9 subunits, at least 10 subunits, at least 11 subunits, at least 12 subunits, at least 13 subunits, at least 14 subunits, at least 15 subunits, at least 16 subunits, at least 17 subunits, at least 18 subunits, at least 19 subunits, at least 20 subunits, at least 21 subunits, at least 22 subunits, at least 23 subunits, or at least 24 subunits. In some embodiments, the PEG comprises a combined total of at least 8 subunits, at least 10 subunits, or at least 12 subunits. In some such embodiments, the PEG comprises no more than a combined total of about 72 subunits. In some such embodiments, the PEG comprises no more than a combined total of about 36 subunits. In some embodiments, the PEG comprises about 8 to about 24 subunits (referred to as PEG8 to PEG24).

[0386] In some embodiments, the PEG Unit comprises a combined total of from 2 to 72, 2 to 60, 2 to 48, 2 to 36 or 2 to 24 subunits, from 3 to 72, 3 to 60, 3 to 48, 3 to 36 or 3 to 24 subunits, from 4 to 72, 8 to 60, 4 to 48, 4 to 36 or 4 to 24 subunits, from 5 to 72, 5 to 60, 5 to 48, 5 to 36 or 5 to 24 subunits, from 6 to 72, 6 to 60, 6 to 48, 6 to 36 or 6 to 24 subunits, from 7 to 72, 7 to 60, 7 to 48, 7 to 36 or 7 to 24 subunits, from 8 to 72, 8 to 60, 8 to 48, 8 to 36 or 8 to 24 subunits, from 9 to 72, 9 to 60, 9 to 48, 9 to 36 or 9 to 24 subunits, from 10 to 72, 10 to 60, 10 to 48, 10 to 36 or 10 to 24 subunits, from 11 to 72, 11 to 60, 11 to 48, 11 to 36 or 11 to 24 subunits, from 12 to 72, 12 to 60, 12 to 48, 12 to 36 or 12 to 24 subunits, from 13 to 72, 13 to 60, 13 to 48, 13 to 36 or 13 to 24 subunits, from 14 to 72, 14 to 60, 14 to 48, 14 to 36 or 14 to 24 subunits, from 15 to 72, 15 to 60, 15 to 48, 15 to 36 or 15 to 24 subunits, from 16 to 72, 16 to 60, 16 to 48, 16 to 36 or 16 to 24 subunits, from 17 to 72, 17 to 60, 17 to 48, 17 to 36 or 17 to 24 subunits, from 18 to 72, 18 to 60, 18 to 48, 18 to 36 or 18 to 24 subunits, from 19 to 72, 19 to 60, 19 to 48, 19 to 36 or 19 to 24 subunits, from 20 to 72, 20 to 60, 20 to 48, 20 to 36 or 20 to 24 subunits, from 21 to 72, 21 to 60, 21 to 48, 21 to 36 or 21 to 24 subunits, from 22 to 72, 22 to 60, 22 to 48, 22 to 36 or 22 to 24 subunits, from 23 to 72, 23 to 60, 23 to 48, 23 to 36 or 23 to 24 subunits, or from 24 to 72, 24 to 60, 24 to 48, 24 to 36 or 24 subunits. In some embodiments, the PEG Unit comprises a combined total of from 2 to 24 subunits, 2 to 16 subunits, 2 to 12 subunits, 2 to 8 subunits, or 2 to 6 subunits. Illustrative linear PEGs that can be used in any of the embodiments provided herein are as follows:



wherein the wavy line indicates the site of attachment to the ADC; each subscript b is independently selected from the group consisting of 2 to 12; and each subscript c is independently selected from the group consisting of 1 to 72, 8 to 72, 10 to 72, 12 to 72, 6 to 24, or 8 to 24. In some embodiments, each subscript b is 2 to 6. In some embodiments, each subscript c is about 2, about 4, about 8, about 12, or about 24.

[0387] As described herein, the PEG Unit can be selected such that it improves clearance of the resultant ADC but does not significantly impact the ability of the ADC to penetrate into the tumor.

[0388] In some embodiments, the PEG is from about 300 daltons to about 5 kilodaltons; from about 300 daltons to about 4 kilodaltons; from about 300 daltons to about 3 kilodaltons; from about 300 daltons to about 2 kilodaltons; from about 300 daltons to about 1 kilodalton; or any

value in between. In some embodiments, the PEG has at least 8, 10 or 12 subunits. In some embodiments, the PEG Unit is PEG8 to PEG72, for example, PEG8, PEG10, PEG12, PEG16, PEG20, PEG24, PEG28, PEG32, PEG36, PEG48, or PEG72.

[0389] In some embodiments, apart from the PEGylation of the ADC, there are no other PEG subunits present in the ADC (i.e., no PEG subunits are present as part of any of the other components of the conjugates and linkers provided herein, such as A and X^B). In some embodiments, apart from the PEG, there are no more than 8, no more than 7, no more than 6, no more than 5, no more than 4, no more than 3, no more than 2 or no more than 1 other polyethylene glycol (-CH_2CH_2O-) subunits present in the ADC, or intermediate thereof (i.e., no more than 8, 7, 6, 5, 4, 3, 2, or 1 other polyethylene glycol subunits in other components of the ADCs (or intermediates thereof) provided herein).

[0390] It will be appreciated that when referring to polyethylene glycol subunits of a PEG Unit, and depending on context, the number of subunits can represent an average number, e.g., when referring to a population of ADCs or intermediates thereto and/or using polydisperse PEGs.

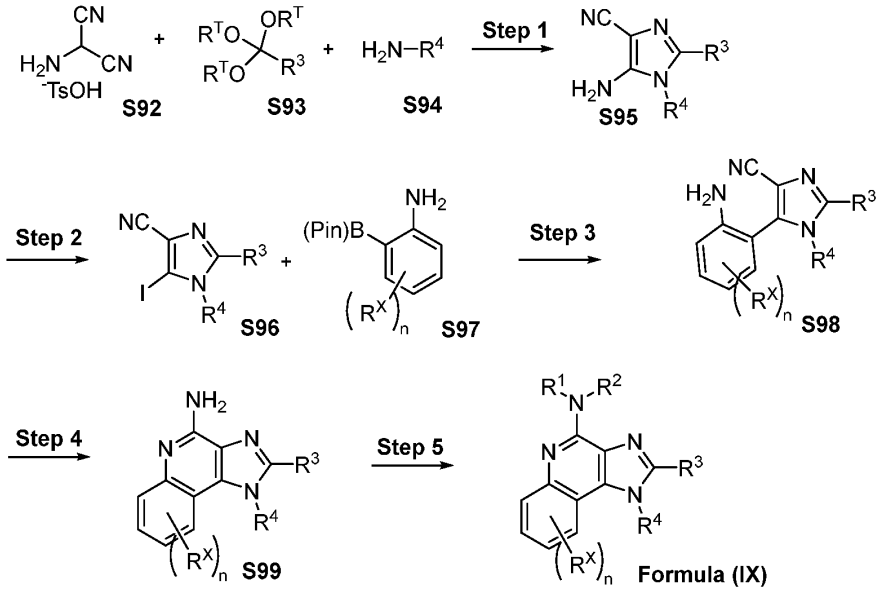
Methods of Making Compounds of the Present Disclosure

[0391] Further embodiments of the present disclosure provide methods of preparing compounds of Formulae (A), (I)-(X), (IIa), and (IIIa) and are illustrated by the following procedures in which the meanings of the generic radicals are as given above unless otherwise qualified. Certain compounds of Formulae (A), (I)-(X), (IIa), and (IIIa) can be useful as intermediates for preparing other compounds of Formulae (A), (I)-(X), (IIa), and (IIIa). In cases where compounds are sufficiently basic or acidic, a pharmaceutically acceptable salt of a compound of Formulae (A), (I)-(X), (IIa), and (IIIa) can be useful as an intermediate for isolating or purifying a compound of Formulae (A), (I)-(X), (IIa), and (IIIa).

[0392] General synthetic approaches toward imidazoquinolines (e.g., as shown in Formulae (A), (I)-(X), (IIa), and (IIIa)) are provided in *Bioorg. Med. Chem. Lett.* 59 (2022) 128548 and *Molbank* 2021, *2021*, M1305, which are herein incorporated by reference. As such syntheses can be limited in their abilities to produce versatile functional group patterns on imidazoquinoline cores, some embodiments provided herein provide improved synthetic routes toward such imidazoquinoline structures as shown in Formulae (A), (I)-(X), (IIa), and (IIIa).

[0393] In certain embodiments, substituted imidazoquinoline compounds Formula (IX), can be synthesized according to SCHEME 70 below:

SCHEME 70



wherein:

R^1, R^2, R^3, R^4, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, R^X, and n are as defined herein, and wherein R^1, R^2, R^3, R^4, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, R^X are not coupled to a linker (L).

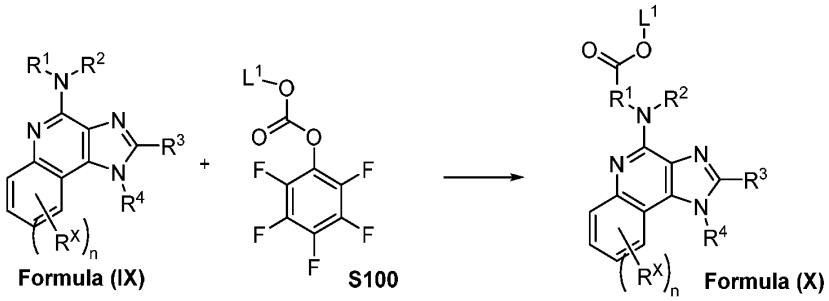
[0394] Such a procedure can begin with a condensation (Step 1) between an aminomalontrile S92, and orthoester containing R^3 S93, and an amine containing R^4 S94, yielding a 4-cyano-5-imidazole intermediate S95 bearing R^3 and R^4. Step 1 can be performed under mild reflux conditions (e.g., 40-50°C) in basic organic solvent, such as DCM with a tertiary amine. In Step 2, activation of S95 and conversion to S96 can be achieved with a Sandmeyer Reaction. In Step Step 3, S97 can then be combined with an R^5 and R^6 substituted 2-amino phenylboronic acid S98 through a cross-coupling step to form S99. A compound of Formula (IX) can then be generated via acid catalyzed cyclization of S99 (Step 4). In an optional subsequent step (Step 5), the imidazoquinoline 4-amino group can be substituted with R^1 and/or R^2.

[0395] In many cases, a compound of Formula (IX) can be converted to a compound of Formula (X). As outlined in SCHEMES 71A-F below, a linker intermediate (L^1) can be coupled to R^1 or R^2, R^3, R^4, R^5, R^6, or the imidazoquinoline C4 amine of Formula (IX). Such a step can comprise site selective nucleophilic substitution by any of R^1-R^6, or the imidazoquinoline C4 amine. The reagent nucleophilic substitution can include a linker intermediate (L^1) coupled to a carbonate (e.g., pentafluorophenyl carbonate (S100)), a carbamate (e.g., tosyl carbamate), a urea, a thiocarbonate, a thiocarbamate, an alkylbromide, an alkyl iodide, or an iodoketone. In some

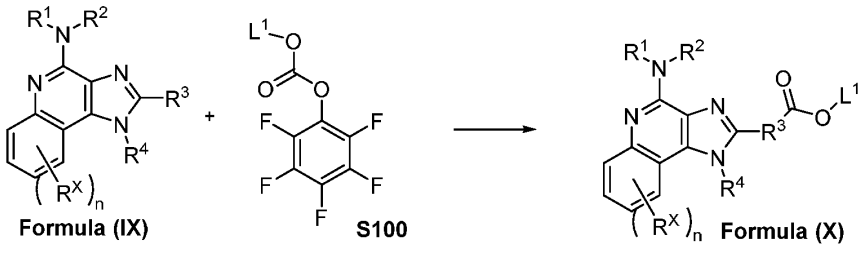
cases, the reagent for nucleophilic substitution comprises the linker intermediate (L^1) coupled to a carbonate or a carbamate. In some cases, the reagent for nucleophilic substitution comprises the linker intermediate (L^1) coupled to a carbonate. In some cases, the reagent for nucleophilic substitution comprises the linker intermediate (L^1) coupled to a pentafluorophenyl carbonate. In some cases, an amine, a thiol, or an enol of R^1-R^6 couples to the nucleophilic substitution reagent (e.g., S100). In some cases, an amine of R^1-R^6 couples to the nucleophilic substitution reagent. In some cases, the imidazoquinoline C4 amine is protected prior to R^1, R^2, R^3, R^4, R^5, or R^6 coupling to the nucleophilic substitution reagent.

[0396] SCHEME 71A depicts coupling between a representative reagent for nucleophilic substitution (S100) and R^1 of Formula (IX) to form Formula (X). While reaction between R^2 of Formula (IX) and S100 is not shown, such a reaction can be achieved in an analogous manner. SCHEME 71B depicts coupling between a representative reagent for nucleophilic substitution (S100) and R^3 of Formula (IX) to form Formula (X). SCHEME 71C depicts coupling between a representative reagent for nucleophilic substitution (S100) and R^4 of Formula (IX) to form Formula (X). SCHEME 71D depicts coupling between a representative reagent for nucleophilic substitution (S100) and R^5 of Formula (IX) to form Formula (X). SCHEME 71E depicts coupling between a representative reagent for nucleophilic substitution (S100) and R^6 of Formula (IX) to form Formula (X). SCHEME 71F depicts coupling between a representative reagent for nucleophilic substitution (S100) and the imidazoquinoline C4 amine of Formula (IX) to form Formula (X).

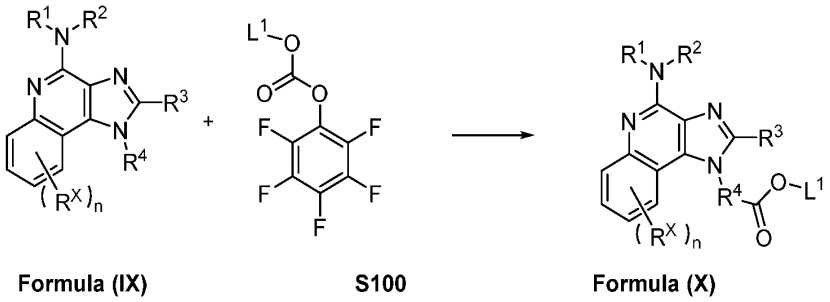
SCHEME 71A



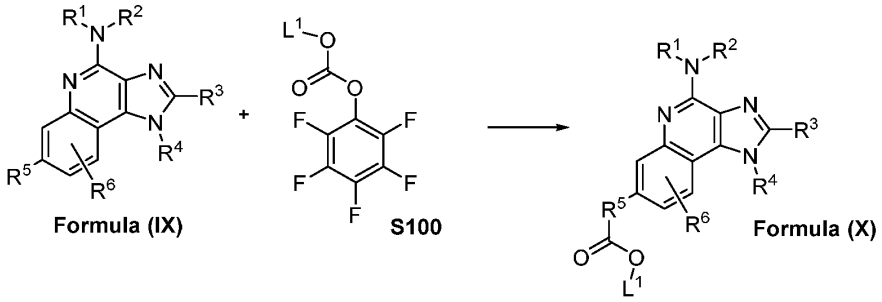
SCHEME 71B



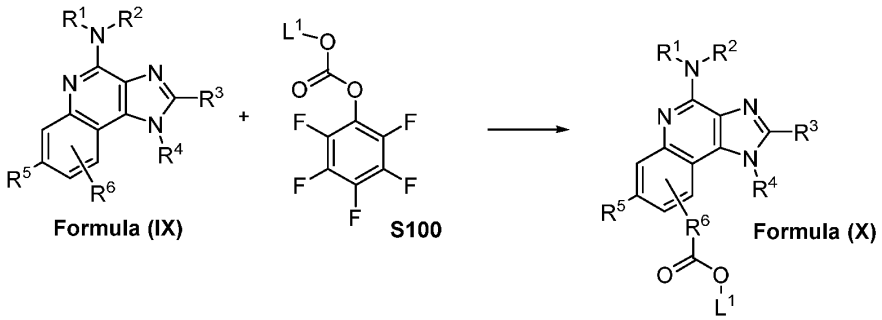
SCHEME 71C



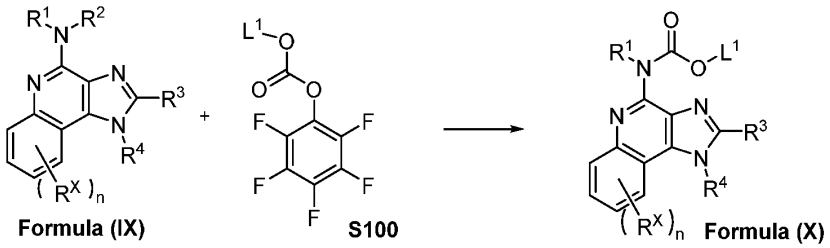
SCHEME 71D



SCHEME 71E



SCHEME 71F

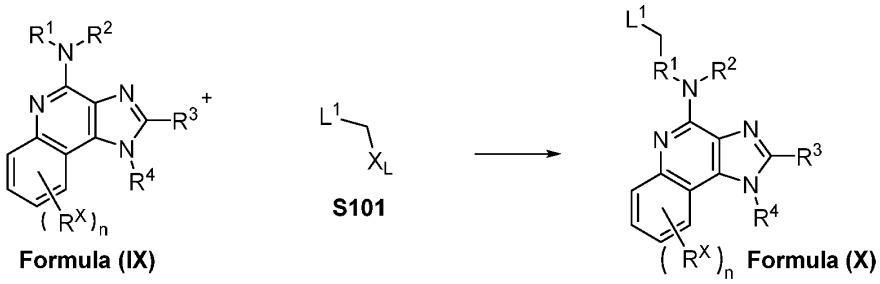


[0397] Alternative nucleophilic substitution schemes for forming Formula (X) by attaching a linker intermediate (L^1) to Formula (IX) are provided in **SCHEMES 72A-F**. As outlined in these schemes, R^1, R^2, R^3, R^4, R^5, R^6, or an imidazoquinoline amine (e.g., N1 or a C4 amine) can couple to an sp3 carbon of S101 through nucleophilic substitution, thereby displacing leaving group X_L.

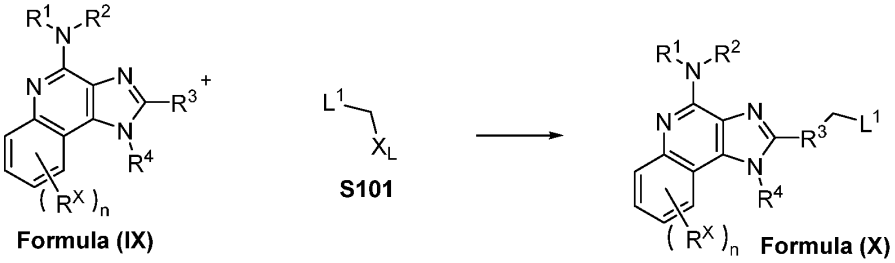
Examples of leaving groups (X_L) suitable for this step include chlorine, bromine, iodine, hydroxyl, nitrates, phosphates, alkoxides, phenoxides, and tosylates. In some cases, R^1, R^2, R^3, R^4, R^5, or R^6 of Formula (IX) couple through an amine. In some cases, the amine is a tertiary amine. In some cases, the amine comprises the formula -$N(Me)_2$. In some cases, reaction of the R^1, R^2, R^3, R^4, R^5, or R^6 amine with S101 forms a quaternary amine. In some cases, reaction of the R^1, R^2, R^3, R^4, R^5, or R^6 amine with S101 forms a secondary or tertiary amine.

[0398] **SCHEME 72A** depicts coupling between a S101 and R^1 of Formula (IX) to form Formula (X). While reaction between R^2 of Formula (IX) and S101 is not shown, such a reaction can be achieved in an analogous manner. **SCHEME 72B** depicts coupling between S101 and R^3 of Formula (IX) to form Formula (X). **SCHEME 72C** depicts coupling between S101 and R^4 of Formula (IX) to form Formula (X). **SCHEME 72D** depicts coupling between S101 and R^5 of Formula (IX) to form Formula (X). **SCHEME 72E** depicts coupling between S101 and R^6 of Formula (IX) to form Formula (X). **SCHEME 72F** depicts coupling between S101 and the imidazoquinoline C4 amine of Formula (IX) to form Formula (X).

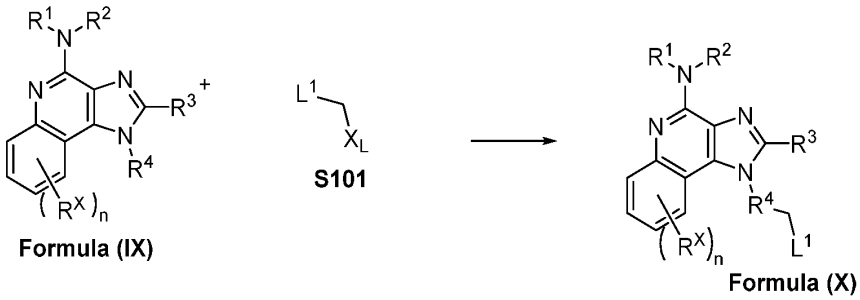
SCHEME 72A



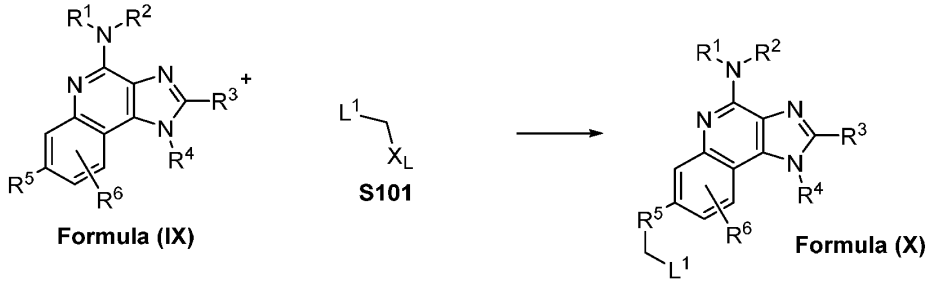
SCHEME 72B



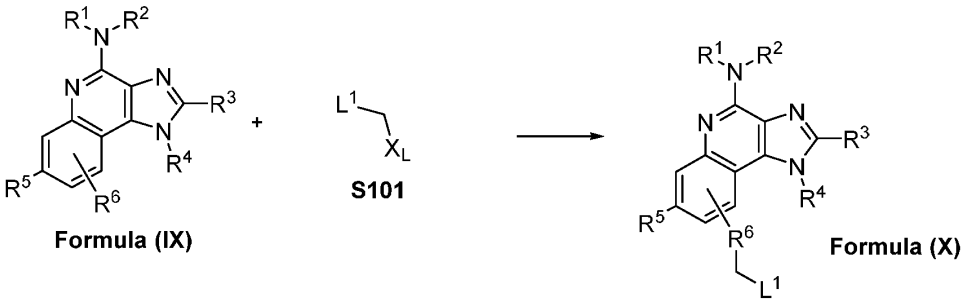
SCHEME 72C



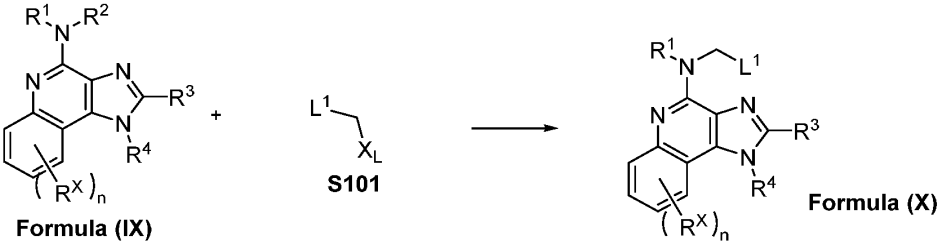
SCHEME 72D



SCHEME 72E



SCHEME 72F



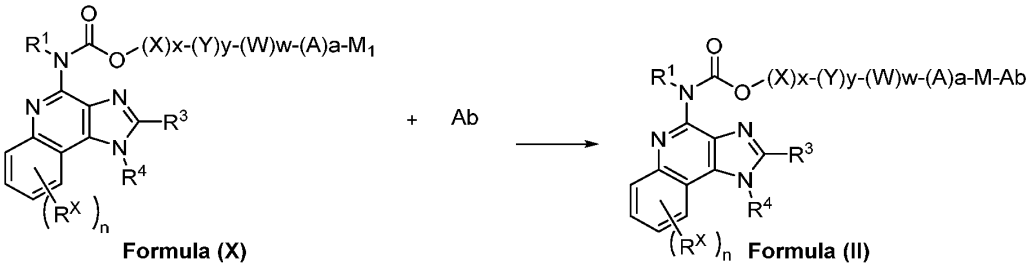
[0399] Formula (X) can be coupled to a biomolecule via the linker intermediate (CH_2-L^1) to form any of Formulae (A), (I)-(VIII), (IIa), or (IIIa). While SCHEME 73 depicts the formation of Formula (II) with a C4 amine-coupled linker, this scheme can be generalized for all of Formulae (A), (I)-(VIII), (IIa), or (IIIa). The linker intermediate can have the formula M^1-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$–; wherein:

M^1 comprises a functional group that will react with a protein (e.g., an antibody) to form a covalent bond;

subscripts a, w, y, and x are each independently 0 or 1; wherein the sum of subscripts a, w, y, and x is greater than or equal to 1; and

A, W, Y, X, are as defined for the linker (L).

SCHEME 73



[0400] In some embodiments, M^1 comprises a functional group that will react with an antibody to form a covalent bond (the Ab-M bond). In some embodiments, M^1 is selected from the group consisting of 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. In some embodiments, M^1 is selected from the group consisting of maleimido, azido, C_1-C_6 alkynyl, cycloalkynyl optionally substituted with 1 or 2 fluoro (e.g., cyclooctynyl or DIFO), sulfhydryl, and succinimidyl esters.

[0401] In some embodiments, M^1 is configured to react with lysyl amines. In some embodiments, M^1 is configured to react with cysteine thiols. In some embodiments, M^1 is configured to react with lysyl amines and cysteine thiols. In some embodiments, M^1 is not reactive towards lysyl amines or cysteine thiols. In such cases, M^1 can be configured to couple with functionalized protein residues, for example with an alkyne or azide for click chemistry mediated coupling.

Methods of Using Compounds of the Present Disclosure

[0402] In some embodiments, the ADCs described herein, or pharmaceutically acceptable salts thereof, are used to deliver the conjugated drug to a target tissue, cancer site, or cell. Without being bound by theory, in some embodiments, an ADC associates with an antigen on the surface of a target cell or in proximity to a target tissue, cancer site, or cell (e.g., an exosome surface

protein in a tumor microenvironment), thereby localizing the ADC to the target tissue, cancer site, or cell.

[0403] In certain embodiments, an ADC as disclosed herein can elicit cancer-site specific immunostimulation. Cancer cells often generate immunosuppressive microenvironments, preventing recognition, immune cell activation, and cytotoxic activities that would otherwise remediate the cancer. In particular, many cancers generate localized concentrations of immune checkpoint inhibitors which can diminish the responsiveness of immune cells (e.g., T-cells), and in some cases actively recruit and transform them to promote further tumor growth and block responses from other immune cells. Accordingly, localized immune activation at cancer sites, as provided by certain ADCs of the present disclosure, can be critical for successful therapy.

[0404] In certain embodiments, the ADC is configured to bind to or near a cancer cell without undergoing cancer-cell uptake. In such cases, the ADC can be configured to release a drug unit outside of the cancer cell. For example, the ADC can comprise a linker which undergoes cleavage in high pH cancer microenvironments, but which is otherwise stable during circulation. Alternatively or additionally thereto, the ADC can comprise a linker with a cleavage sequence for a protease overexpressed by the cancer cell, for example a serine protease overexpressed by a prostate cancer cell.

[0405] In certain embodiments, an ADC of the present disclosure targets a cancer cell. In certain embodiments, the ADC is configured to internalize within the cancer cell (e.g., undergo endocytosis) or a tumor associated immune cell (e.g., a tumor associated macrophage). The ADC can comprise a linker which is configured for cleavage inside of the cancer cell, but inert outside of the cancer cell. The ADC can comprise a drug (e.g., a compound of any of Formulae (A), (I), (II), (IIa), (III), (IIIa), (IV), (V), (VI), (VII), (VIII), or (IX)) with low uptake efficiency but high potency, for example certain imidazoquinolines with negative C7 functionalization.

[0406] In many cases, the ADC is configured for uptake by an immune cell. In many such cases, the ADC may target a cancer cell, but comprises a mechanism for uptake by proximal immune cells. As demonstrated in **EXAMPLES 46** and **47**, TLR7/8 agonists often elicit minimal responses in cancer cells, and instead affect immune activation in proximal T-cells and B-cells which express TLR7 and/or TLR8. As TLR7 and TLR8 are often primarily endosomal, antibody assisted endocytosis and micropinocytosis can deliver TLR7/8 agonists directly to sites with high abundances of TLR7 and TLR8 within immune cells, thereby affecting tumor microenvironment immune activation. In some cases, ADC tumor cell binding enhances immune cell uptake. For example, FcγIII receptor-mediated immune cell uptake may be more than an order of magnitude higher for cancer cell bound antibodies than for free circulating antibodies.

[0407] Alternatively or in addition thereto, an ADC can be configured to undergo transcytosis upon binding to a target cell or tissue. Such an ADC can target a receptor or comprise a structure (e.g., an IgA immunoglobulin) which facilitates transport across a cell barrier. For example, upon binding to a receptor on a tumor associated macrophage (TAM), such an ADC may transcytose, thereby passing through a passivating TAM layer and reaching underlying cancer cells.

[0408] In some embodiments, an ADC targets a surface antigen of a cell. The ADC can be configured to localize to the cell (e.g., bind to the cell and not internalize within the cell, or bind to the cell to increase uptake into the cell). In some such cases, the ADC can release its drug payload while in proximity to the cell. For example, the ADC can comprise a linker with a peptide portion that is cleavable by a protease excreted by the cell. The ADC can also be configured to internalize within the cell. For example, the ADC may endocytose within the cell upon binding to the surface antigen.

[0409] In certain cases, the surface antigen is associated with a cancer cell. Often, the cancer cell is proximal to an immune cell comprising TLR7 and/or TLR8. In certain cases, the surface antigen is expressed by the cancer cell and the immune cell. In other cases, the surface antigen is expressed by the cancer cell and is not expressed by the immune cell. In certain cases, the surface antigen is expressed by the immune cell. In some cases, the immune cell is a $CD8^+$ T-cell, a $CD4^+$ T-Cell, a T-regulatory cell, a macrophage, or a natural killer cell. In certain cases, the immune cell is a tumor associated immune cell (e.g., a tumor associated macrophage). In certain cases, the immune cell is a macrophage. In some cases, the immune cell expresses TLR7, TLR8, or TLR7 and TLR8. In some cases, the cancer cell does not express TLR7, TLR8, or TLR7 and TLR8.

[0410] ADC internalization can enable drug localization to otherwise inaccessible targets. As many signalling pathways are primarily intracellular (e.g., the majority of signalling proteins and signal transduction events occur inside of a cell), signal modulation often requires effective drug internalization and subcellular localization. As many drugs exhibit poor cellular uptake and non-specific subcellular localization, many targets remain inaccessible for drug targeting. Archetypal examples of such targets are TLR7 and TLR8, whose endosomal localizations are inaccessible to many treatments.

[0411] Certain ADCs disclosed herein overcome this challenge by mediating uptake and subcellular localization to deliver high payload concentrations at select target sites. In some cases, ADC binding to a cell surface antigen mediates uptake into the cell. In specific cases, an ADC is configured to endocytose into a target cell, thereby accessing endosomally compartmentalized species, such as TLR7 and TLR8. In some cases, a linker (L) of an ADC is configured to undergo cleavage subsequent to internalizing within the target cell. In some cases, the linker (L) of an ADC

is configured to undergo cleavage within a specific subcellular space. For example, a linker (L) of an ADC can comprise a peptide with a cleavage sequence specific for a lysosomal protease.

[0412] Some embodiments provide a method of treating a viral or bacterial infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an ADC described herein, or a pharmaceutically acceptable salt thereof.

[0413] Some embodiments provide a method of treating viral or bacterial infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition comprising an ADC described herein, or a pharmaceutically acceptable salt thereof.

[0414] Some embodiments provide a method of inducing an anti-viral or anti-bacterial immune response in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition comprising an ADC described herein, or a pharmaceutically acceptable salt thereof.

[0415] Some embodiments provide a method of inducing an anti-viral or anti-bacterial immune response in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an ADC described herein, or a pharmaceutically acceptable salt thereof.

[0416] Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an ADC described herein, or a pharmaceutically acceptable salt thereof.

[0417] Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition comprising an ADC described herein, or a pharmaceutically acceptable salt thereof.

[0418] Some embodiments provide 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 a composition comprising an ADC described herein, or a pharmaceutically acceptable salt thereof.

[0419] Some embodiments provide 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 an ADC described herein, or a pharmaceutically acceptable salt thereof.

[0420] In some embodiments of treating a cancer or inducing an anti-tumor response in a subject in need thereof, the cancer (e.g., cancer cells or tumor cells against which the anti-tumor response is directed) does not express CD4, CD8, an immune checkpoint, or a combination thereof. It was surprisingly determined herein that a lack of CD4, CD8 and immune checkpoint expression by tumor cells can enhance their responsiveness to treatment with immune stimulants

(e.g., as overviewed in **EXAMPLE 53**). Building upon this discovery, specific embodiments disclosed herein include treatment of CD4, CD8, and/or immune checkpoint negative cancers. For example, a method consistent with the present disclosure can include a step of determining that a cancer does not include CD4, CD8, and/or immune checkpoint expression, and identifying a subject with the cancer as suitable for treatment with a method disclosed herein. In some cases, the cancer does not express CD4. In some cases, the cancer does not express CD8, in some cases, the cancer does not express the immune checkpoint. In some cases, immune cells associated with the cancer (e.g., present in a tumor microenvironment of the cancer) express CD4, CD8, an immune checkpoint, or a combination thereof.

[0421] As used herein, the term "does not express" can denote a lack of detectable expression of a particular biomolecule or class of biomolecules. The expression can be an expression level of the biomolecule or an expression level of mRNA encoding the biomolecule. For example, a cell that does not express a specific cell surface protein may provide an immunofluorescence signal for the cell surface protein or a qPCR signal for mRNA encoding the cell surface protein that is not statistically distinguishable from a baseline for the immunofluorescence or qPCR measurement. As some biomolecules have non-zero baseline expression levels, "does not express" can also denote that a cell expresses less than about 10%, less than about 5%, less than about 2%, or less than about 1% of the amount of a biomolecule relative to a reference cell with active or upregulated expression of that biomarker. For example, a lymphocyte that does not express CD4 may express less than about 10%, less than about 5%, less than about 2%, or less than about 1% of the amount of CD4 as a CD4+ T cell.

[0422] In particular cases, the term "does not express", in reference to a biomolecule, denotes that a below-threshold percentage of cells from a population of cells express the biomolecule. For example, a population of cancer cells may be identified as cancer cells that do not express a specific biomolecule if less than 10% of the cancer cells express the biomolecule. Accordingly, in some embodiments disclosed herein, less than about 10%, less than about 7.5%, less than about 5%, less than about 4.5%, less than about 4%, less than about 3.5%, less than about 3%, less than about 2.5%, less than about 2%, less than about 1.5%, less than about 1%, or less than about 0.5% of cancer cells of the cancer express CD4, CD8, the immune checkpoint, or a combination thereof. In particular embodiments, less than about 10%, less than about 7.5%, less than about 5%, less than about 4.5%, less than about 4%, less than about 3.5%, less than about 3%, less than about 2.5%, less than about 2%, less than about 1.5%, less than about 1%, or less than about 0.5% of cancer cells of the cancer express CD4. In further embodiments, less than about 10%, less than about 7.5%, 5%, less than about 4.5%, less than about 4%, less than about 3.5%, less than about

3%, less than about 2.5%, less than about 2%, less than about 1.5%, less than about 1%, or less than about 0.5% of cancer cells of the cancer express CD8. In certain embodiments, less than about 10%, less than about 7.5%, less than about 5%, less than about 4.5%, less than about 4%, less than about 3.5%, less than about 3%, less than about 2.5%, less than about 2%, less than about 1.5%, less than about 1%, or less than about 0.5% of cancer cells of the cancer express the immune checkpoint.

[0423] In some embodiments, CD4 expression, CD8 expression, immune checkpoint expression, or a combination thereof is membrane expression, wherein the expression denotes CD4, CD8, immune checkpoints, or combination thereof that are displayed in cell membranes, and does not include CD4, CD8, or immune checkpoints disposed within other portions of a cell (e.g., immune checkpoint precursors localized inside of a cell). In such embodiments, measurement of CD4, CD8, and/or immune checkpoint expression can include whole cell (rather than homogenate) analysis, for example with immunohistochemical staining, fluorescence-activated cell sorting (FACS), or affinity-based cell sorting.

[0424] In some embodiments, the immune checkpoint is PDL1, PD1, CTLA-4, B7H4, B7H3, TIGIT, TIM-3, VISTA, GITR/GITRL, CD80/CD86, CD155, PDL1, PDL2, galectin 9, CD40, OX40L, 4-1BB/4-1BBL, ICOS/ICOSL, CD70, or a combination thereof. In particular embodiments, the immune checkpoint is PDL1.

[0425] The cancer cells can be derived from a biological sample from the subject. The cancer cells can be analyzed while disposed within the biological sample. For example, cancer cells can be stained and imaged from a tissue slice culture. The cancer cells can also be collected or isolated from the biological sample. In some cases, the cancer cells are derived from a tumor. In some cases, the cancer cells are derived from a liquid biological sample such as whole blood, serum, plasma, urine, or synovial fluid. In some cases, the cancer cells are circulating tumor cells. CD4, CD8, and/or immune checkpoint expression can be analyzed in whole cells or in homogenate. In particular cases, CD4 expression, CD8 expression, immune checkpoint expression, or a combination thereof is in cancer cells derived from a tumor. In some cases, the cancer cells derived from the tumor comprise tumor-associated immune cells. In further cases, the cancer cells derived from the tumor do not comprise tumor-associated immune cells. In some cases, the cancer cells derived from the tumor comprise stromal cells from the tumor. In other cases, the cancer cells derived from the tumor do not comprise stromal cells from the tumor.

[0426] Any method suitable for protein or nucleic acid detection may be used to determine expression of CD4, CD8 and immune checkpoints. As non-limiting examples, expression measurements can include flow cytometry, immunohistochemistry, immunocytochemistry,

immunofluorescence, immunoprecipitation, western blotting, ELISA, or mRNA analysis. As further non-limiting examples, mRNA analysis (e.g., for mRNA encoding CD4, CD8, or an immune checkpoint) can include quantitative polymerase chain reaction (qPCR), reverse transcription qPCR (RT-qPCR), RNA sequencing, microarray analysis, in situ hybridization, or sequential gene expression analysis.

[0427] Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an ADC as described herein, or a pharmaceutically acceptable salt thereof, in combination with another anticancer therapy (e.g., surgery and radiation therapy) and/or anticancer agent (e.g., an immunotherapy such as nivolumab or pembrolizumab). The ADCs described herein can be administered to the subject before, during, or after administration of the anticancer therapy and/or anticancer agent and/or surgery. In some embodiments, the ADCs described herein can be administered to the subject following treatment with radiation and/or after surgery.

[0428] Some embodiments provide a method for delaying or preventing acquired resistance to an anticancer agent, comprising administering to the subject a therapeutically effective amount of an ADC as described herein, or a pharmaceutically acceptable salt thereof, to a patient at risk for developing or having acquired resistance to an anticancer agent. In some embodiments, the patient is administered a dose of the anticancer agent (e.g., at substantially the same time as a dose of an ADC as described herein, or a pharmaceutically acceptable salt thereof is administered to the patient).

[0429] Some embodiments provide a method of delaying and/or preventing development of cancer resistant to an anticancer agent in a subject, comprising administering to the subject a therapeutically effective amount of an ADC as described herein, or a pharmaceutically acceptable salt thereof, before, during, or after administration of a therapeutically effective amount of the anticancer agent.

[0430] The ADCs described herein are useful for inhibiting the multiplication of a cancer cell, causing apoptosis in a cancer cell, for increasing phagocytosis of a cancer cell, and/or for treating cancer in a subject in need thereof. The ADCs can be used accordingly in a variety of settings for the treatment of cancers. The ADCs can be used to deliver a drug to a cancer cell. Without being bound by theory, in some embodiments, the antibody of an ADC binds to or associates with a cancer-cell-associated antigen. The antigen can be attached to a cancer cell or can be an extracellular matrix protein associated with the cancer cell. The drug can be released in proximity to the cancer cell, thus recruiting/activating immune cells to attack the cancer cell. In some

embodiments, the Drug Unit is cleaved from the ADC outside the cancer cell. In some embodiments, the Drug Unit remains attached to the antibody bound to the antigen.

[0431] In some embodiments, the antibody binds to the cancer cell. In some embodiments, the antibody binds to a cancer cell antigen which is on the surface of the cancer cell. In some embodiments, the antibody binds to a cancer cell antigen which is an extracellular matrix protein associated with the tumor cell or cancer cell. In some embodiments, the antibody of an ADC binds to or associates with a cancer-associated cell or an antigen on a cancer-associated cell. In some embodiments, the cancer-associated cell is a stromal cell in a tumor, for example, a cancer-associated fibroblast (CAF).

[0432] In some embodiments, the antibody of an ADC binds to or associates with an immune cell or an immune-cell-associated antigen. The antigen can be attached to an immune cell or can be an extracellular matrix protein associated with the immune cell. The drug can be released in proximity to the immune cell, thus recruiting/activating the immune cell to attack a cancer cell. In some embodiments, the Drug Unit is cleaved from the ADC outside the immune cell. In some embodiments, the Drug Unit remains attached to the antibody bound to the antigen. In some embodiments, the immune cell is a lymphocyte, an antigen-presenting cell, a natural killer (NK) cell, a neutrophil, an eosinophil, a basophil, a mast cell, an innate lymphoid cell, or a combination of any of the foregoing. In some embodiments, the immune cell is selected from the group consisting of B cells, plasma cells, T cells, NKT cells, gamma delta T cells, monocytes, macrophages, dendritic cells, natural killer (NK) cells, neutrophils, eosinophils, basophils, mast cells, and a combination of any of the foregoing.

[0433] The specificity of the antibody for a particular cancer cell can be important for determining those tumors or cancers that are most effectively treated. For example, ADCs that target a cancer cell antigen present on hematopoietic cancer cells in some embodiments treat hematologic malignancies. In some embodiments, ADCs target a cancer cell antigen present on abnormal cells of solid tumors for treating such solid tumors. In some embodiments an ADC are directed against abnormal cells of hematopoietic cancers such as, for example, lymphomas (Hodgkin Lymphoma and Non-Hodgkin Lymphomas) and leukemias.

[0434] Cancers, including, but not limited to, a tumor, metastasis, or other disease or disorder characterized by abnormal cells that are characterized by uncontrolled cell growth in some embodiments are treated or inhibited by administration of an ADC.

[0435] In some embodiments, the subject has previously undergone treatment for the cancer. In some embodiments, the prior treatment is surgery, radiation therapy, administration of one or more anticancer agents, or a combination of any of the foregoing.

[0436] In any of the methods described herein, the cancer is selected from the group consisting of: adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myelocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal carcinoma in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, esophagus and stomach carcinoma, eye intraocular melanoma, eye intraocular squamous cell carcinoma, eye lacrimal duct carcinoma, fallopian tube serous carcinoma, gallbladder adenocarcinoma, gallbladder glomus tumor, gastroesophageal junction adenocarcinoma, head and neck adenoid cystic carcinoma, head and neck carcinoma, head and neck neuroblastoma, head and neck squamous cell carcinoma, kidney chromophore carcinoma, kidney medullary carcinoma, kidney renal cell carcinoma, kidney renal papillary carcinoma, kidney sarcomatoid carcinoma, kidney urothelial carcinoma, kidney carcinoma, leukemia lymphocytic, leukemia lymphocytic chronic, liver cholangiocarcinoma, liver hepatocellular carcinoma, liver carcinoma, lung adenocarcinoma, lung adenosquamous carcinoma, lung atypical carcinoid, lung carcinosarcoma, lung large cell neuroendocrine carcinoma, lung non-small cell lung carcinoma, lung sarcoma, lung sarcomatoid carcinoma, lung small cell carcinoma, lung small cell undifferentiated carcinoma, lung squamous cell carcinoma, upper aerodigestive tract squamous cell carcinoma, upper aerodigestive tract carcinoma, lymph node lymphoma diffuse large B cell, lymph node lymphoma follicular lymphoma, lymph node lymphoma mediastinal B-cell, lymph node lymphoma plasmablastic lung adenocarcinoma, lymphoma follicular lymphoma, lymphoma, non-Hodgkins, nasopharynx and paranasal sinuses undifferentiated carcinoma, ovary carcinoma, ovary carcinosarcoma, ovary clear cell carcinoma, ovary epithelial carcinoma, ovary granulosa cell tumor, ovary serous carcinoma, pancreas carcinoma, pancreas ductal adenocarcinoma, pancreas neuroendocrine carcinoma, peritoneum mesothelioma, peritoneum serous carcinoma, placenta choriocarcinoma, pleura mesothelioma, prostate acinar adenocarcinoma, prostate carcinoma, rectum adenocarcinoma, rectum squamous cell carcinoma, skin adnexal carcinoma, skin basal cell carcinoma, skin melanoma, skin Merkel cell carcinoma, skin squamous cell carcinoma, small intestine adenocarcinoma, small intestine gastrointestinal

stromal tumors (GISTs), large intestine/colon carcinoma, large intestine adenocarcinoma, soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epitheliod cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, lymphoid neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

[0437] In some embodiments, the subject is concurrently administered one or more additional anticancer agents with the ADCs described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is concurrently receiving radiation therapy with the ADCs described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is administered one or more additional anticancer agents after administration of the ADCs described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject receives radiation therapy after administration of the ADCs described herein, or a pharmaceutically acceptable salt thereof.

[0438] In some embodiments, the subject has discontinued a prior therapy, for example, due to unacceptable or unbearable side effects, wherein the prior therapy was too toxic, or wherein the subject developed resistance to the prior therapy.

[0439] Some embodiments provide a method for delaying or preventing a disease or disorder, comprising administering to the subject a therapeutically effective amount of an ADC as described herein, or a pharmaceutically acceptable salt thereof, and a vaccine against the disease or disorder, to a patient at risk for developing the disease or disorder. In some embodiments, the disease or disorder is cancer, as described herein. In some embodiments, the disease or disorder is a viral pathogen. In some embodiments, the vaccine is administered subcutaneously. In some embodiments, the vaccine is administered intramuscularly. In some embodiments, the ADC and the vaccine are administered via the same route (for example, the ADC and the vaccine are both administered subcutaneously). In some embodiments, the ADC, or a pharmaceutically acceptable salt thereof, and the vaccine are administered via different routes. In some embodiments, the

vaccine and the ADC, or a pharmaceutically acceptable salt thereof, are provided in a single formulation. In some embodiments, the vaccine and the ADC, or a pharmaceutically acceptable salt thereof, are provided in separate formulations.

[0440] In some embodiments, the ADCs described herein are present in the form of a salt. In some embodiments, the salt is a pharmaceutically acceptable salt.

Pharmaceutical Compositions of the Present Disclosure and Methods of Use Thereof

[0441] Some embodiments provide a composition comprising a distribution of ADCs, as described herein. In some embodiments, the composition comprises a distribution of ADCs, as described herein and at least one pharmaceutically acceptable carrier. In some embodiments, the route of administration is parenteral. Parenteral administration includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In some embodiments, the compositions are administered parenterally. In one of those embodiments, the ADCs are administered intravenously. Administration is typically through any convenient route, for example by infusion or bolus injection.

[0442] Compositions of an ADC can be formulated so as to allow the ADC to be bioavailable upon administration of the composition to a subject. Compositions can be in the form of one or more injectable dosage units.

[0443] Materials used in preparing the compositions can be non-toxic in the amounts used. It will be evident to those of ordinary skill in the art that the optimal dosage of the active ingredient(s) in the composition will depend on a variety of factors. Relevant factors include, without limitation, the type of animal (e.g., human), the particular form of the compound, the manner of administration, and the composition employed.

[0444] In some embodiments, the ADC composition is a solid, for example, as a lyophilized powder, suitable for reconstitution into a liquid prior to administration. In some embodiments, the ADC composition is a liquid composition, such as a solution or a suspension. A liquid composition or suspension is useful for delivery by injection and a lyophilized solid is suitable for reconstitution as a liquid or suspension using a diluent suitable for injection. In a composition administered by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent is typically included.

[0445] In some embodiments, the liquid compositions, whether they are solutions, suspensions or other like form, can also include one or more of the following: sterile diluents such as water for injection, saline solution, physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or digylcerides which can serve as the solvent or suspending medium, polyethylene glycols, glycerin, cyclodextrin, propylene glycol or other

solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as amino acids, acetates, citrates or phosphates; detergents, such as nonionic surfactants, polyols; and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral composition is typically enclosed in ampoule, a disposable syringe or a multiple-dose vial made of glass, plastic or other material. In some embodiments, the sterile diluent comprises physiological saline. In some embodiments, the sterile diluent is physiological saline. In some embodiments, the composition described herein are liquid injectable compositions that are sterile.

[0446] The amount of the ADC that is effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, which is usually determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays are sometimes employed to help identify optimal dosage ranges. The precise dose to be employed in the compositions will also depend on the route of parenteral administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each subject's circumstances.

[0447] In some embodiments, the compositions comprise an effective amount of an ADC such that a suitable dosage will be obtained. Typically, this amount is at least about 0.01% of the ADC by weight of the composition.

[0448] In some embodiments, the compositions dosage of an ADC administered to a subject is from about 0.01 mg/kg to about 100 mg/kg, from about 1 to about 100 mg of a per kg or from about 0.1 to about 25 mg/kg of the subject's body weight. In some embodiments, the dosage administered to a subject is about 0.01 mg/kg to about 15 mg/kg of the subject's body weight. In some embodiments, the dosage administered to a subject is about 0.1 mg/kg to about 15 mg/kg of the subject's body weight. In some embodiments, the dosage administered to a subject is about 0.1 mg/kg to about 20 mg/kg of the subject's body weight. In some embodiments, the dosage administered is about 0.1 mg/kg to about 5 mg/kg or about 0.1 mg/kg to about 10 mg/kg of the subject's body weight. In some embodiments, the dosage administered is about 1 mg/kg to about 15 mg/kg of the subject's body weight. In some embodiments, the dosage administered is about 1 mg/kg to about 10 mg/kg of the subject's body weight. In some embodiments, the dosage administered is about 0.1 to about 4 mg/kg, about 0.1 to about 3.2 mg/kg, or about 0.1 to about 2.7 mg/kg of the subject's body weight over a treatment cycle.

[0449] The term "carrier" refers to a diluent, adjuvant or excipient, with which a compound is administered. Such pharmaceutical carriers are liquids. Water is an exemplary carrier when the compounds are administered intravenously. Saline solutions and aqueous dextrose and glycerol

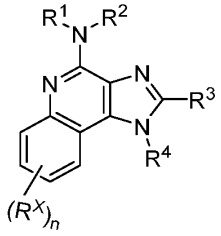
solutions are also useful as liquid carriers for injectable solutions. Suitable pharmaceutical carriers also include glycerol, propylene, glycol, or ethanol. The present compositions, if desired, will in some embodiments also contain minor amounts of wetting or emulsifying agents, and/or pH buffering agents.

[0450] In some embodiments, the ADCs are formulated in accordance with routine procedures as a composition adapted for intravenous administration to animals, particularly human beings. Typically, the carriers or vehicles for intravenous administration are sterile isotonic aqueous buffer solutions. In some embodiments, the composition further comprises a local anesthetic, such as lignocaine, to ease pain at the site of the injection. In some embodiments, the ADC and the remainder of the formulation are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where an ADC is to be administered by infusion, it is sometimes dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the ADCs are administered by injection, an ampoule of sterile water for injection or saline is typically provided so that the ingredients can be mixed prior to administration.

[0451] The compositions are generally formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

Compounds of Formula (IX)

[0452] Some embodiments provide a compound of Formula (IX):



(IX)

or a pharmaceutically acceptable salt thereof;

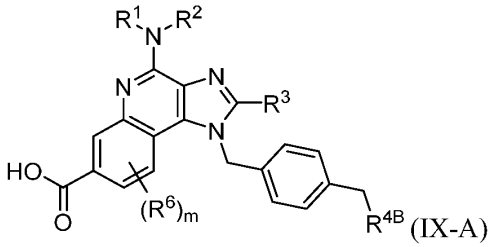
wherein:

R^1, R^2, R^3, R^4, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, R^X, and n are as defined herein, and where the compound or the pharmaceutically acceptable salt thereof is not coupled to a linker (L).

[0453] In some embodiments, the free drug, as described herein, is a compound of Formula (IX). In some embodiments, the free drug, as described herein, comprises a compound of Formula (IX).

[0454] In some embodiments, the free drug, as described herein, comprises a compound of Formula (IX) in prodrug form. In some cases, R^1 of the compound of Formula (IX) in prodrug form is 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. In some cases, R^1 of the compound of Formula (IX) in prodrug form is selected from the group consisting of C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, and C_1-C_6 carbamoyl. In some cases, R^1 of the compound of Formula (IX) in prodrug form is C_1-C_6 alkoxycarbonyl.

[0455] In some embodiments, the compound of Formula (IX) 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;

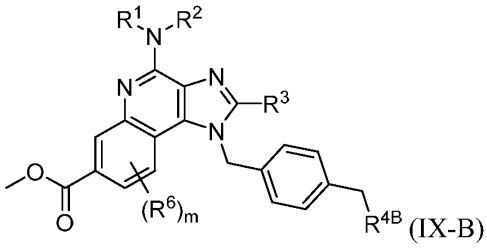
R^{4B} is selected from the group consisting of 5-10 membered heteroaryl, $-NR^DR^E$, and $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$;

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.

[0456] In some embodiments, the compound of Formula (IX) 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.

[0457] In some embodiments of Formula (IX), R^1 and R^2 are each independently selected C_1-C_6 alkyl. In some embodiments of Formula (IX), R^1 and R^2 are both methyl. In some embodiments of Formula (IX), one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is C_1-C_6 alkyl. In some

embodiments of Formula (IX), one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is methyl. In some embodiments of Formula (IX), R^1 and R^2 are both hydrogen.

In some embodiments of Formula (IX), R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 carbamoyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 carbamoyl, 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 $-NR^AR^B$. In some embodiments of Formula (IX), R^1 is 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 $-NR^AR^B$.

[0458] In some embodiments of Formula (IX), 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.

[0459] In some embodiments of Formula (IX), 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. In some embodiments of Formula (IX), 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. In some embodiments of Formula (IX), 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. In some embodiments of Formula (IX), R^3 is an unsubstituted C_1-C_6 alkyl. In some embodiments of Formula (IX), R^3 is n-butyl. In some embodiments of Formula (IX), R^3 is hydrogen.

[0460] In some embodiments of Formula (IX), R^4 is $-S(=O)2R^C$; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; or C_1-C_6 alkyl optionally substituted with a group selected from the group consisting of (i)-(xiv), as described herein. In some embodiments of Formula (IX), R^4 is $-C(=O)NR^DR^E$; $-C(=O)OR^C$; or C_1-C_6 alkyl optionally substituted with a group selected from the group consisting of (i)-(xiv), as described herein. In some embodiments of Formula (IX), R^4 is $-C(=O)NR^DR^E$ or $-C(=O)OR^C$. In some embodiments of Formula (IX), R^4 is $-C(=O)NR^DR^E$.

[0461] In some embodiments of Formula (IX), R^5 is selected from the group consisting of $-C(=O)OH$, $-NO_2$, $-CN$, $-CF_3$, and $-S(O_3)H$. In some embodiments of Formula (IX), R^5 is selected

from the group consisting of -C(=O)OH and -S(O_3)H. In some embodiments Formula (IX), R^5 is -C(=O)OH.

[0462] In some embodiments of Formula (IX), R^1 is not substituted with a solubilizing group (S_b). In some embodiments of Formula (IX), R^4 is not substituted with a solubilizing group (S_b). In some embodiments of Formula (IX), R^1 and R^4 are not substituted with solubilizing groups (S_b). In some embodiments of Formula (IX), only one of R^1 and R^4 is substituted with a solubilizing group (S_b). In some embodiments of Formula (IX), R^1 is not substituted with a solubilizing group if R^1 is a point of covalent attachment to L. In some embodiments of Formula (IX), R^4 is not substituted with a solubilizing group (S_b) if R^1 is a point of covalent attachment to L.

[0463] In some embodiments of Formulae (IX-A) and (IX-B), R^{4B} is $-NR^DR^E$.

[0464] In some embodiments of Formulae (IX-A) and (IX-B), R^{4B} is $-[N(C_1\text{-}C_6\ \text{alkyl})R^DR^E]^+$.

[0465] In some embodiments of Formulae (IX-A) and (IX-B), 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)-. In some embodiments of Formulae (IX-A) and (IX-B), 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.

[0466] In some embodiments of Formulae (IX-A) and (IX-B), R^D and R^E are each independently selected C_1-C_6 alkyl. In some embodiments of Formulae (IX-A) and (IX-B), R^D and R^E are both methyl. In some embodiments of Formulae (IX-A) and (IX-B), one of R^D and R^E is hydrogen and the other of R^D and R^E is C_1-C_6 alkyl. In some embodiments of Formulae (IX-A) and (IX-B), one of R^D and R^E is hydrogen and the other of R^D and R^E is methyl.

[0467] In some embodiments of Formulae (IX-A) and (IX-B), R^D and R^E are both hydrogen.

[0468] In some embodiments of Formulae (IX-A) and (IX-B), 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.

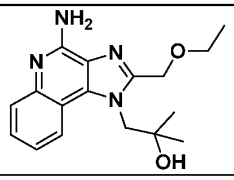
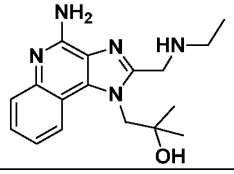
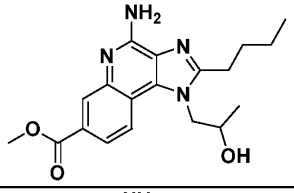
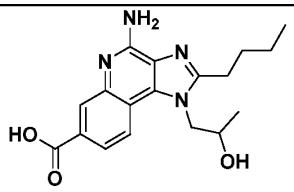
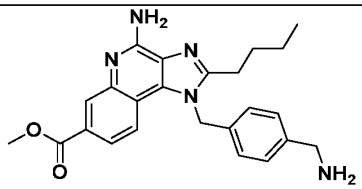
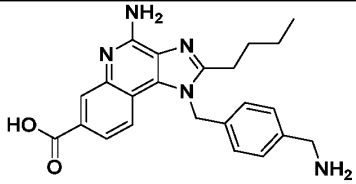
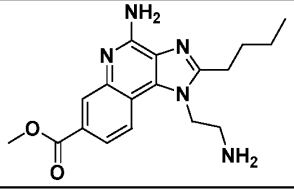
[0469] In some embodiments of Formulae (IX-A) and (IX-B), R^{4B} is 5-10 membered heteroaryl.

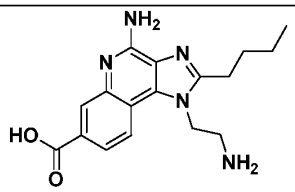
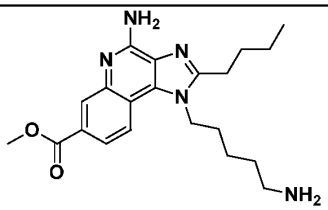
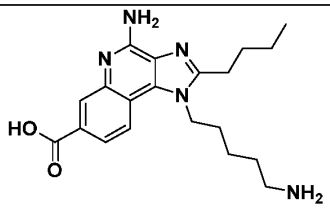
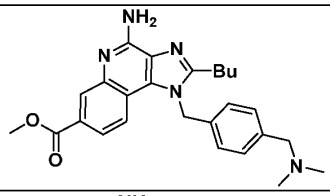
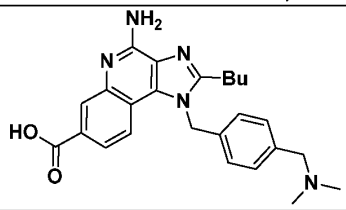
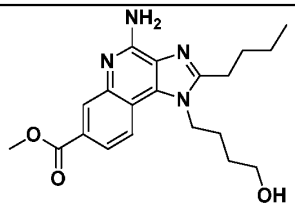
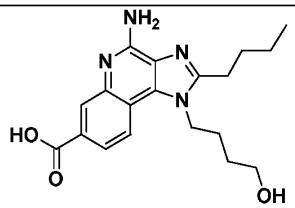
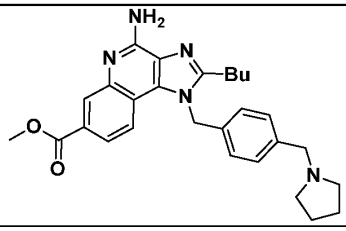
[0470] In some embodiments of Formula (IX), subscript m is 1. In some embodiments of Formula (IX), subscript m is 0.

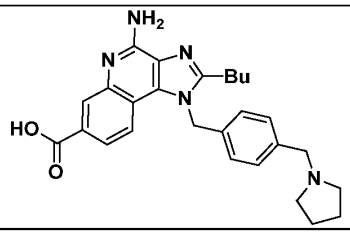
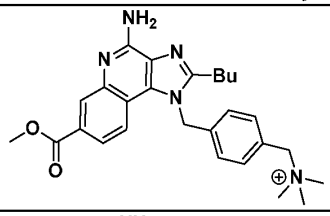
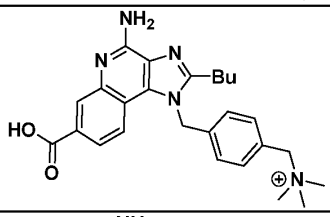
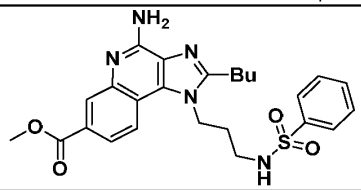
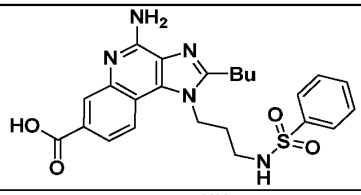
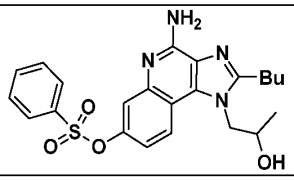
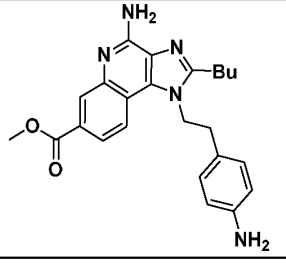
[0471] In some embodiments of Formula (IX), R^6 is selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy. In some embodiments of Formula (IX), R^6 is selected from the group consisting of halogen, hydroxyl, nitro, and cyano.

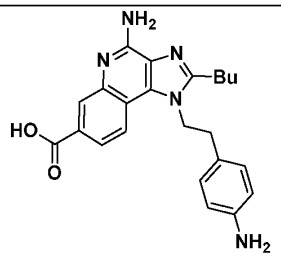
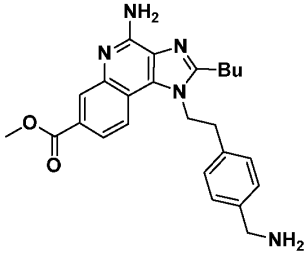
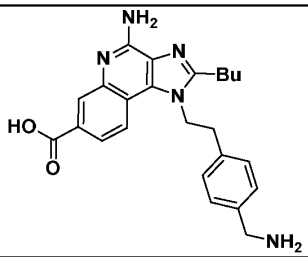
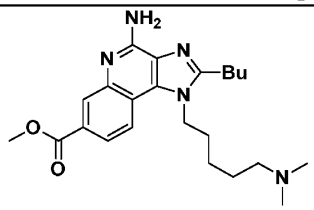
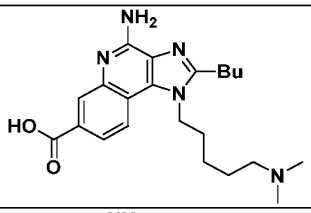
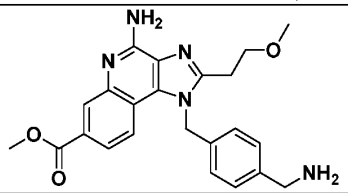
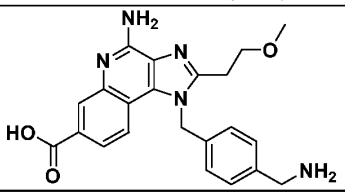
[0472] In some embodiments, the compound of Formula (IX) is selected from the compounds shown in TABLE 2, or a pharmaceutically acceptable salt thereof. In some embodiments, the compounds of Formula (IX) described herein are present in the form of a salt. In some embodiments, the salt is a pharmaceutically acceptable salt.

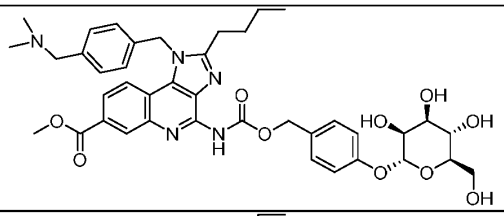
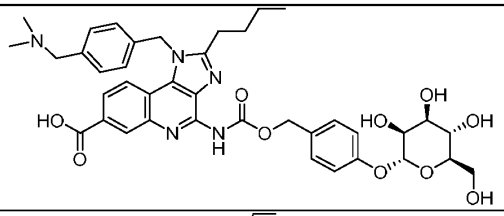
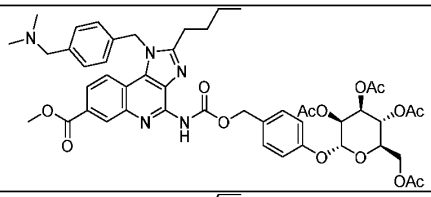
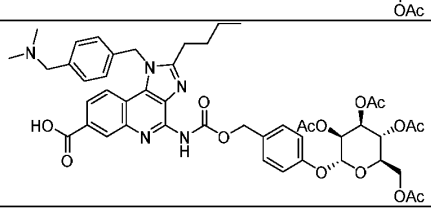
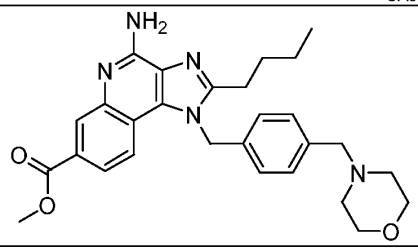
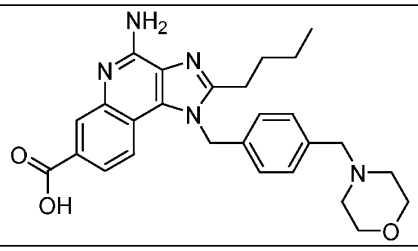
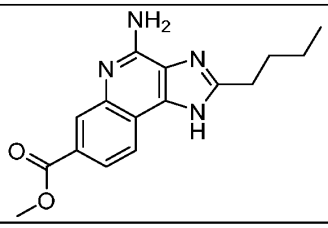
TABLE 2

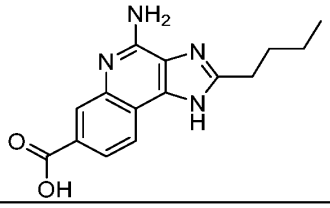
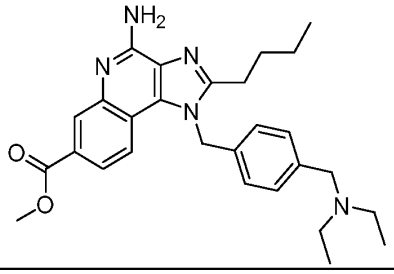
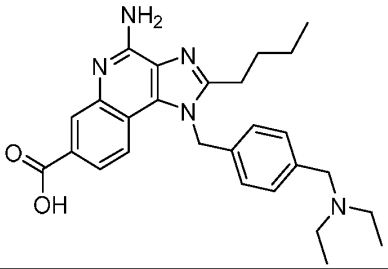
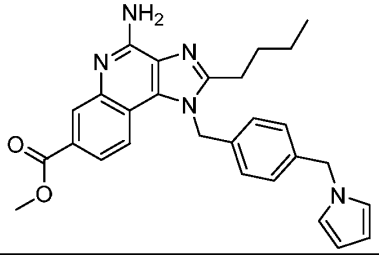
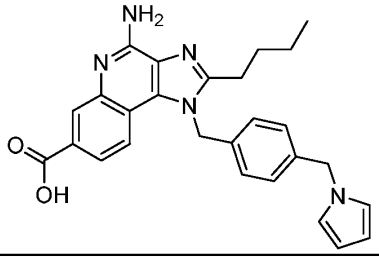
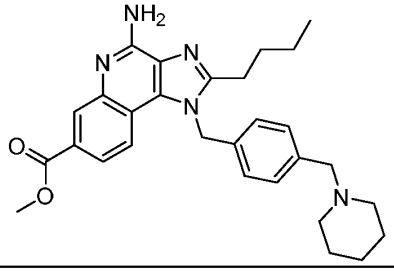
Cmpd No.	Structure
Resiquimod	
Gardiquimod	
S5a	
S5b	
S8a	
S8b	
S11a	

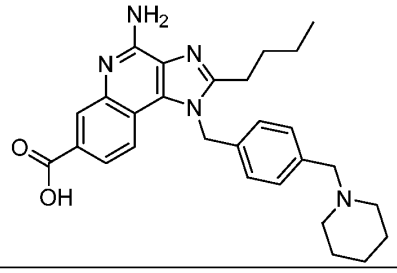
S11b	
S14a	
S14b	
S18a	
S18b	
S63a	
S63b	
S65a	

S65b	
S72a	
S72b	
S73a	
S73b	
S74a	
S75a	

S75b	
S76a	
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S77a	
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S79a	
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S80a	
S80b	
S81a	
S81b	
S82a	

S82b	
S83a	
S83b	
S84a	
S84b	
S85a	

S85b	

Methods of Use of Compounds of Formula (IX)

[0473] Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount a compound of Formula (IX), or a pharmaceutically acceptable salt thereof.

[0474] Some embodiments provide a method of treating a viral or bacterial infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (IX), or a pharmaceutically acceptable salt thereof.

[0475] Some embodiments provide a method of inducing an anti-viral or anti-bacterial immune response in a subject in need thereof, comprising administering to the subject a therapeutically effective amount a compound of Formula (IX), or a pharmaceutically acceptable salt thereof.

[0476] Some embodiments provide a method of inducing an anti-tumor immune response in a subject in need thereof, comprising administering to the subject a therapeutically effective amount a compound of Formula (IX), or a pharmaceutically acceptable salt thereof.

Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount a compound of Formula (IX), or a pharmaceutically acceptable salt thereof, in combination with another anticancer therapy (e.g., surgery and radiation therapy) and/or anticancer agent (e.g., an immunotherapy such as nivolumab or pembrolizumab). Compounds of Formula (IX) can be administered to the subject before, during, or after administration of the anticancer therapy and/or anticancer agent. In some embodiments, the compounds of Formula (IX) described herein can be administered to the subject following treatment with radiation and/or after surgery.

[0477] Some embodiments provide a method for delaying or preventing acquired resistance to an anticancer agent, comprising administering to the subject a therapeutically effective amount a compound of Formula (IX), or a pharmaceutically acceptable salt thereof, to a patient at risk for developing or having acquired resistance to an anticancer agent. In some embodiments, the patient is administered a dose of the anticancer agent (e.g., at substantially the same time as a dose of the

compound of Formula (IX), or a pharmaceutically acceptable salt thereof is administered to the patient).

[0478] Some embodiments provide a method of delaying and/or preventing development of cancer resistant to an anticancer agent in a subject, comprising administering to the subject a therapeutically effective amount a compound of Formula (IX), or a pharmaceutically acceptable salt thereof, before, during, or after administration of a therapeutically effective amount of the anticancer agent.

[0479] Compounds of Formula (IX) are useful for inhibiting the multiplication of a cancer cell, causing apoptosis in a cancer cell, for increasing phagocytosis of a cancer cell, and/or for treating cancer in a subject in need thereof. In some embodiments, the cancer is as described herein. In some embodiments, the subject has previously undergone treatment for the cancer. In some embodiments, the prior treatment is surgery, radiation therapy, administration of one or more anticancer agents, or a combination of any of the foregoing. In some embodiments, the subject has discontinued a prior therapy, for example, due to unacceptable or unbearable side effects, wherein the prior therapy was too toxic, or wherein the subject developed resistance to the prior therapy.

[0480] Some embodiments provide a method for delaying or preventing a disease or disorder, comprising administering to the subject a therapeutically effective amount of a compound of Formula (IX), or a pharmaceutically acceptable salt thereof, and a vaccine against the disease or disorder, to a patient at risk for developing the disease or disorder. In some embodiments, the disease or disorder is cancer, as described herein. In some embodiments, the disease or disorder is a viral pathogen. In some embodiments, the vaccine is administered subcutaneously. In some embodiments, the vaccine is administered intramuscularly. In some embodiments, the compound of Formula (IX), or a pharmaceutically acceptable salt thereof, and the vaccine are administered via the same route (for example, the compound of Formula (IX), or a pharmaceutically acceptable salt thereof, and the vaccine are both administered subcutaneously). In some embodiments, the compound of Formula (IX), or a pharmaceutically acceptable salt thereof, and the vaccine are administered via different routes. In some embodiments, the vaccine and the compound of Formula (IX), or a pharmaceutically acceptable salt thereof, are provided in a single formulation. In some embodiments, the vaccine and the compound of Formula (IX), or a pharmaceutically acceptable salt thereof, are provided in separate formulations.

[0481] In some embodiments, the compounds of Formula (IX) described herein are present in the form of a salt. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0482] In some embodiments, the compounds of Formula (IX) and ADCs of Formulae (A), (I)-(VIII), (IIa), and (IIIa) are provided as prodrugs. In some such embodiments, the prodrug comprises a functional group configured to hydrolytically cleave under specific physiological conditions (e.g., the low pH of a tumor microenvironment) or in the presence of hydrolytic enzymes (e.g., in the presence of human hydrolases or proteases associated with a target tissue or cell). In some embodiments of Formulae (A), (I)-(VIII), (IIa), and (IIIa), R^1, R^4, or R^1 and R^4 comprise a hydrolysable group. The hydrolysable group can be configured for cleavage within or in proximity to a target tissue or cell. Prior to cleavage, the hydrolysable group can prevent the drug unit from binding to its target (e.g., TLR7/8), thereby diminishing off-target activity and enhancing specificity for the target.

Compositions and Methods of Administration of Compounds of Formula (IX)

[0483] Some embodiments provide a composition comprising a compound of Formula (IX), or a pharmaceutically acceptable salt thereof, and one or more excipients, as described herein. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral.

[0484] Oral administration can include a dosage form formulated for once-daily or twice-daily (BID) administration. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. In making the compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such an excipient in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders. In some embodiments, the composition is formulated for oral administration. In some embodiments, the composition is a solid oral formulation. In some embodiments, the composition is formulated as a tablet or capsule.

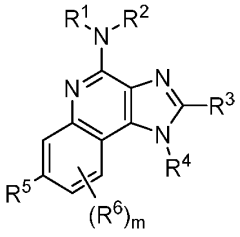
[0485] Suitable excipients are known in the art. Descriptions of some of these excipients can be found in *The Handbook of Pharmaceutical Excipients*, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

[0486] The compositions comprising a compound of Formula (IX), or a pharmaceutically acceptable salt thereof, can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other subjects, each unit containing a predetermined quantity of active material (i.e., a compound of Formula (IX), or a pharmaceutically acceptable salt thereof) calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[0487] An effective amount of the active material (i.e., a compound of Formula (IX), or a pharmaceutically acceptable salt of any of the foregoing) is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about 1000 mg/kg of body weight per day, or any range therein. Preferably, the range is from about 0.05 to about 500 mg/kg of body weight per day, or any range therein. More preferably, from about 0.1 to about 250 mg/kg of body weight per day, or any range therein. More preferably, from about 0.1 to about 100 mg/kg of body weight per day, or any range therein. In an example, the range can be from about 0.1 to about 50.0 mg/kg of body weight per day, or any amount or range therein. In another example, the range can be from about 0.01 to about 15.0 mg/kg of body weight per day, or any range therein. In yet another example, the range can be from about 0.05 to about 7.5 mg/kg of body weight per day, or any amount to range therein. In yet another example, the range can be from about 0.1 to about 5.0 mg/kg of body weight per day, or any amount to range therein. Pharmaceutical compositions comprising a compound of Formula (IX), or a pharmaceutically acceptable salt of any of the foregoing, can be administered on a regimen of 1 to 4 times per day or in a single daily dose.

Drug-Linker Intermediates (L^1-D)

[0488] Some embodiments provide 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: L^1 is a linker intermediate; 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 (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.

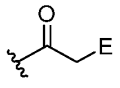
[0489] In some embodiments, the drug-linker intermediate compounds of Formula (X) is used to prepare the ADCs described herein.

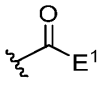
[0490] Each of R^1, R^2, R^3, R^4, R^5 R^A, R^6, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, and R^K, in compounds of Formula (X) are as described herein with respect to the compounds of Formulae (I)-(IX), with the exception that covalent attachment to L in those compounds corresponds to covalent attachment to L^1 in compounds of Formula (X).

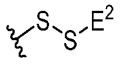
[0491] In some embodiments, the linker intermediate (L^1) has the formula M^1-$(A)_a$-$(W)_w$-$(Y)_y$-$(X)_x$–; wherein A, W, Y, X, are as defined for the linker (L); and wherein subscripts a, w, y, and x are each independently 0 or 1; wherein the sum of subscripts a, w, y, and x is greater than or equal to 1.

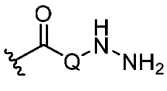
[0492] In some embodiments, M^1 comprises a functional group that will react with an antibody to form a covalent bond (the Ab-M bond). In some embodiments, M^1 is selected from the group consisting of maleimido, azido, C_1-C_6 alkynyl, cycloalkynyl optionally substituted with 1 or 2 fluoro (e.g., cyclooctynyl 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,

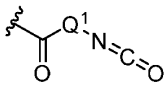
isothiocyanates, alpha-haloketones, alpha-O-sulfonate (e.g., mesyl or tosyl) ketones, alkyl hydrazines, hydrazides, hydroxylamines, and iodoketones. In some embodiments, M^1 is selected from the group consisting of maleimido, azido, C_1-C_6 alkynyl, cycloalkynyl optionally substituted with 1 or 2 fluoro (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. In some embodiments, M^1 is selected from the group consisting of maleimido, azido, C_1-C_6 alkynyl, cycloalkynyl optionally substituted with 1 or 2 fluoro (e.g., cyclooctynyl or DIFO), sulfhydryl, succinimidyl esters. Additional examples of functional groups that will react with an antibody to form an a covalent bond are described in PCT Publication No. WO2016/040684, which is hereby incorporated by reference in its entirety.

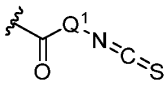
[0493] In some embodiments, M^1 is  ; wherein ~~~ indicates the covalent bond to the remainer of L^1 (e.g., A, W, Y, or X); and wherein E is halogen or $–O(SO_2)-E'$; wherein E' is alkyl, aryl, or aryl substituted with alkyl, as described herein (e.g., tosyl or mesyl).

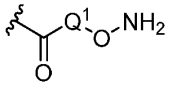
[0494] In some embodiments, M^1 is  ; wherein ~~~ indicates the covalent bond to the remainer of L^1 (e.g., A, W, Y, or X); wherein E^1 is halogen, -O-N-succinimide, -O-(aryl), wherein the aryl is substituted with nitro, 4 or 5 fluoro, -OC(=O)-O(C_1-C_6 alkyl), or -OC(=O)-O(aryl).

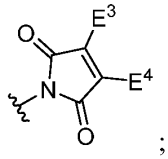
[0495] In some embodiments, M^1 is  ; wherein ~~~ indicates the covalent bond to the remainer of L^1 (e.g., A, W, Y, or X); wherein E^2 is aryl or heteroaryl, as described herein.

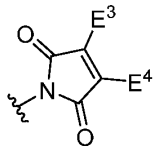
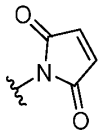
[0496] In some embodiments, M^1 is  ; wherein ~~~ indicates the covalent bond to the remainer of L^1 (e.g., A, W, Y, or X); and wherein Q is a bond or C_1-C_{10} alkylene.

[0497] In some embodiments, M^1 is  ; wherein ~~~ indicates the covalent bond to the remainer of L^1 (e.g., A, W, Y, or X); and wherein Q^1 is C_1-C_{10} alkylene.

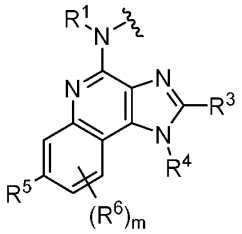
[0498] In some embodiments, M^1 is  ; wherein ~~~ indicates the covalent bond to the remainer of L^1 (e.g., A, W, Y, or X); and wherein Q^1 is C_1-C_{10} alkylene.

[0499] In some embodiments, M^1 is  ; wherein ~~~ indicates the covalent bond to the remainer of L^1 (e.g., A, W, Y, or X); and wherein Q^1 is C_1-C_{10} alkylene.

[0500] In some embodiments, M^1 is  ; wherein ~~~ indicates the covalent bond to the remainer of L^1 (e.g., A, W, Y, or X); and wherein E^3 and E^4 are independently selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, and $–O(SO_2)$-E^5; wherein E^5 is alkyl, aryl, or aryl substituted with alkyl, as described herein (e.g., tosyl or mesyl)..

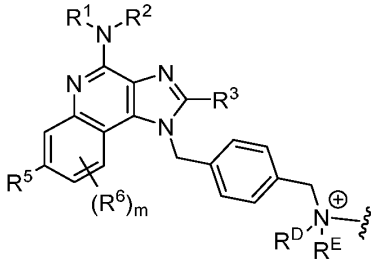
[0501] In some embodiments, M^1 is  , and E^3 and E^4 are both hydrogen. As such, in some embodiments M^1 is  (maleimido). In some embodiments, M^1 is maleimido.

[0502] In some embodiments, L^1-D has the structure:



or a pharmaceutically acceptable salt thereof; wherein ~~~ represents covalent attachment to L^1.

[0503] In some embodiments, L^1-D has the structure:



or a pharmaceutically acceptable salt thereof; wherein ~~~ represents covalent attachment to L^1.

[0504] In some embodiments, R^5 is $–C(=O)OR^F$. In some embodiments, R^F is C_1-C_6 alkyl. In some embodiments, R^F is methyl. In some embodiments, R^F is hydrogen.

[0505] Some embodiments of Formula (X), D is in prodrug form. In some cases, R^1 of the compound of Formula (X) in prodrug form is 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. In some cases, R^1 of the compound of Formula (X) in prodrug form is selected from the group consisting of C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, and C_1-C_6 carbamoyl. In some cases, R^1 of the compound of Formula (X) in prodrug form is C_1-C_6 alkoxycarbonyl.

[0506] In some embodiments of Formula (X), 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 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, 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 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, 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 $–NR^AR^B$.

[0507] In some embodiments of Formula (X), R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 carbamoyl, C_3-C_6 cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 carbamoyl, 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 $–NR^AR^B$. In some embodiments of Formula (X), R^1 is 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 $–NR^AR^B$.

[0508] In some embodiments of Formula (X), R^4 is $-S(=O)2R^C$; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; or C_1-C_6 alkyl optionally substituted with a group selected from the group consisting of (i)-(xiv), as described herein. In some embodiments of Formula (X), R^4 is $-C(=O)NR^DR^E$; $-C(=O)OR^C$; or C_1-C_6 alkyl optionally substituted with a group selected from the group consisting of (i)-(xiv), as described herein. In some embodiments of Formula (X), R^4 is $-C(=O)NR^DR^E$ or $-C(=O)OR^C$. In some embodiments of Formula (X), R^4 is $-C(=O)NR^DR^E$.

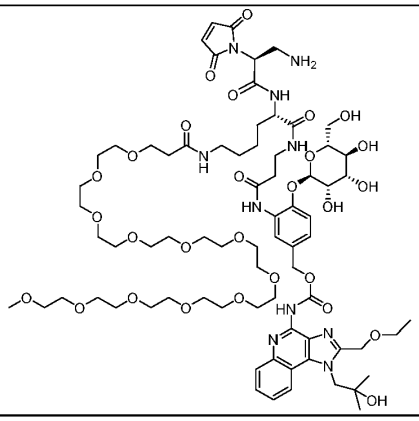
[0509] In some embodiments of Formula (X), R^5 is selected from the group consisting of $-C(=O)OH$, $-NO_2$, $-CN$, $-CF_3$, and $-S(O_3)H$. In some embodiments of Formula (X), R^5 is selected

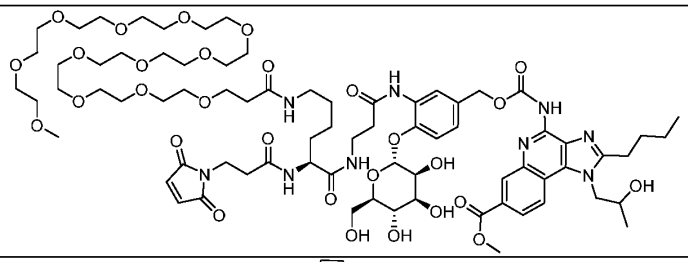
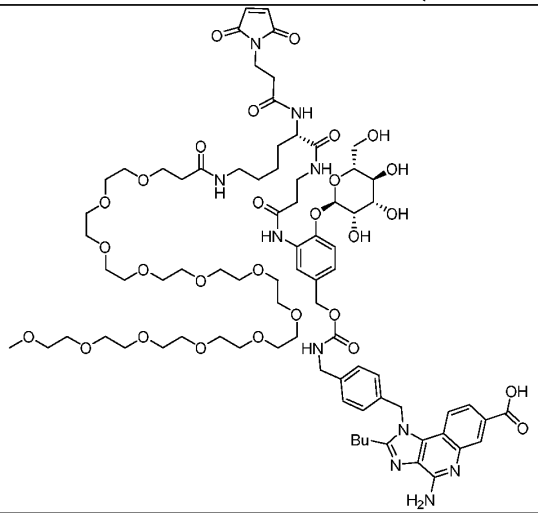
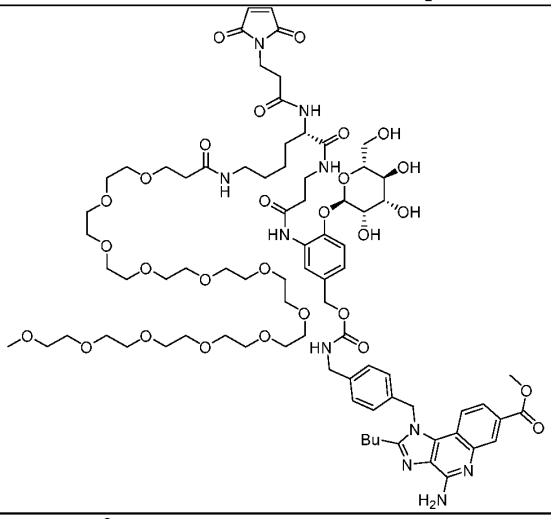
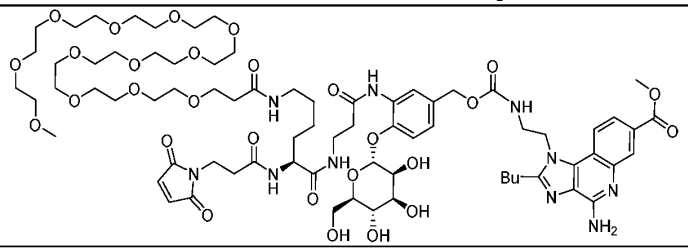
from the group consisting of -C(=O)OH and -S(O$_3$)H. In some embodiments Formula (X), R^5 is -C(=O)OH.

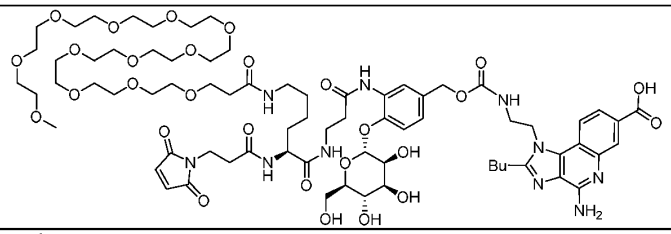
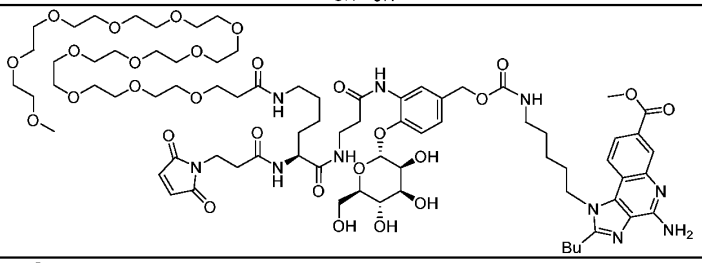
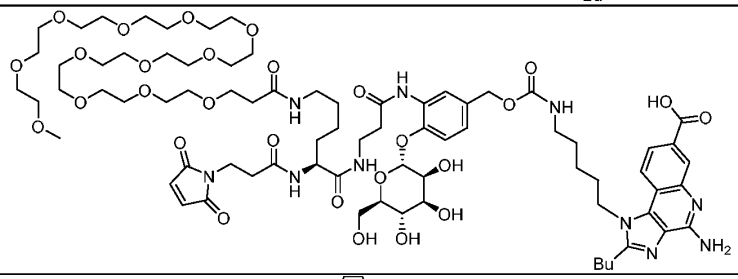
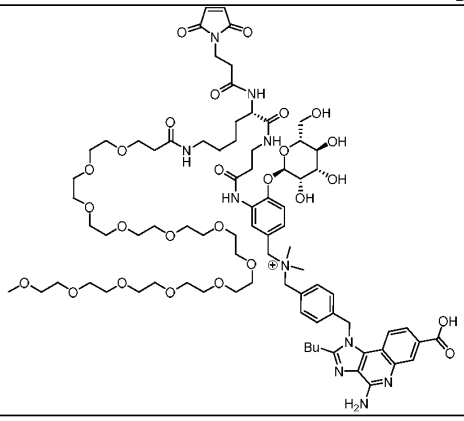
[0510] In some embodiments of Formula (X), R^1 is not substituted with a solubilizing group (S$_b$). In some embodiments of Formula (X), R^4 is not substituted with a solubilizing group (S$_b$). In some embodiments of Formula (X), R^1 and R^4 are not substituted with solubilizing groups (S$_b$). In some embodiments of Formula (X), only one of R^1 and R^4 is substituted with a solubilizing group (S$_b$). In some embodiments of Formula (X), R^1 is not substituted with a solubilizing group if R^1 is a point of covalent attachment to L. In some embodiments of Formula (X), R^4 is not substituted with a solubilizing group (S$_b$) if R^1 is a point of covalent attachment to L.

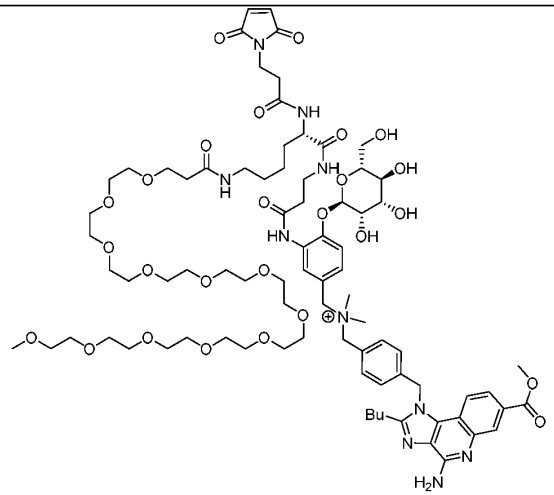
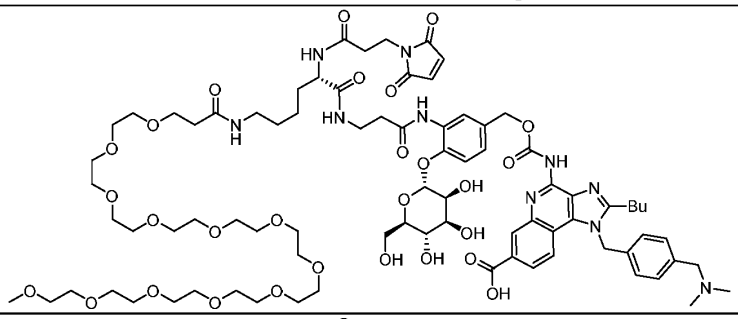
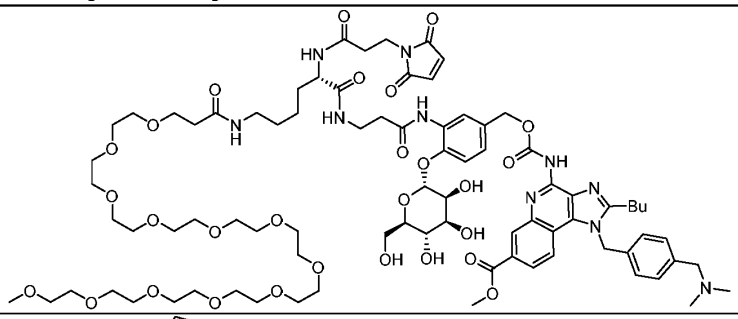
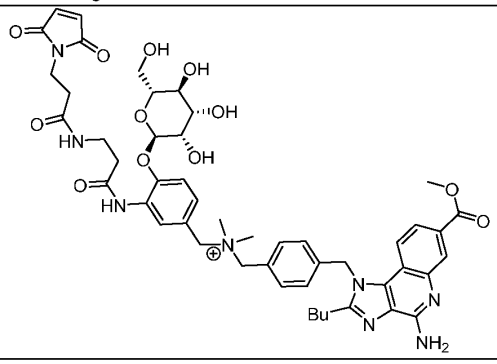
[0511] In some embodiments, subscript m is 0. In some embodiments, R^3 is C$_1$-C$_6$ alkyl. In some embodiments, R^3 is n-butyl. In some embodiments, R^1 is hydrogen or C$_1$-C$_6$ alkyl. In some embodiments, R^1 is hydrogen or methyl. In some embodiments, R^1 is hydrogen. In some embodiments, R^2 is hydrogen or C$_1$-C$_6$ alkyl. In some embodiments, R^2 is hydrogen or methyl. In some embodiments, R^2 is hydrogen. In some embodiments, R^D and R^E are independently C$_1$-C$_6$ alkyl. In some embodiments, R^D and R^E are both methyl. In some embodiments, 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. In some embodiments, R^D and R^E, together with the nitrogen atom to which they are attached form an unsubstituted 3-6 membered heterocyclyl. In some embodiments, the compound of L^1-D is selected from the compounds shown in **TABLE 3**, or a pharmaceutically acceptable salt thereof. In some embodiments, each L-D of Ab-(L-D)$_p$ is selected from the compounds shown in **TABLE 3**, or a pharmaceutically acceptable salt thereof, wherein each succinimide is coupled to a cysteine of Ab.

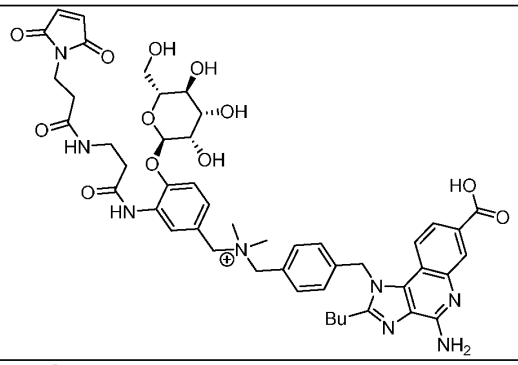
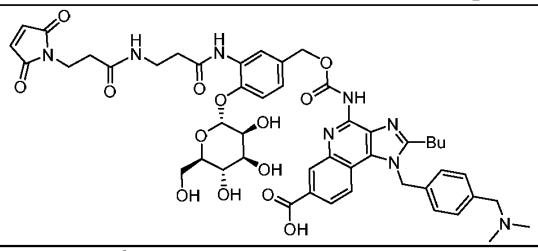
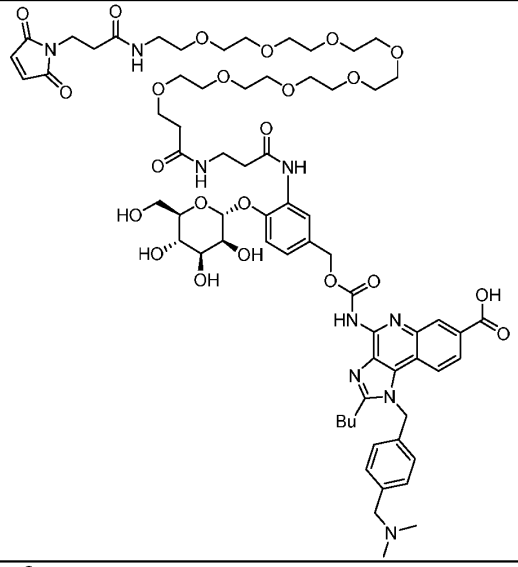
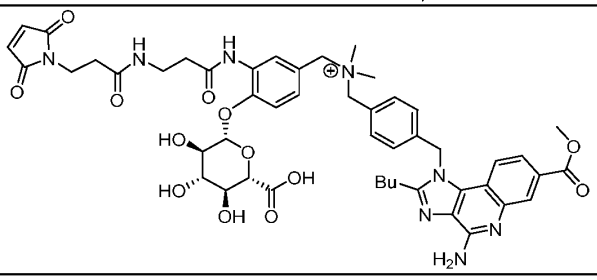
TABLE 3

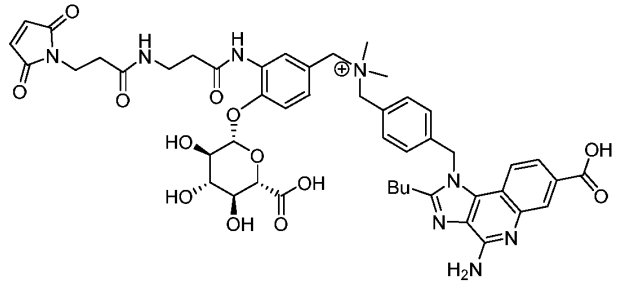
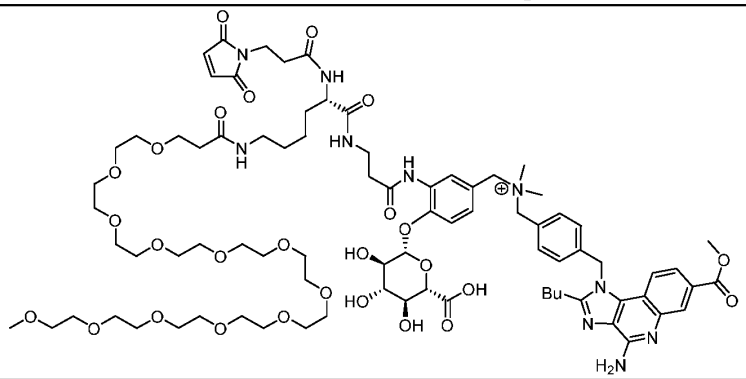
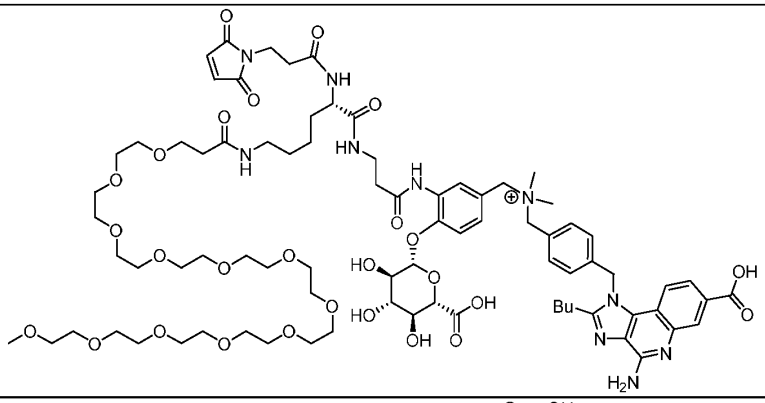
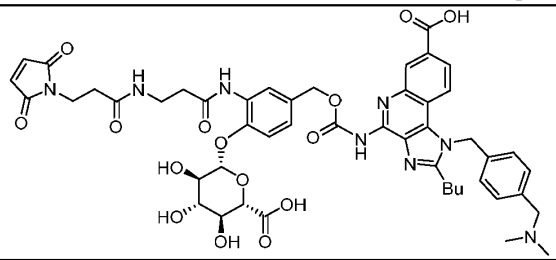
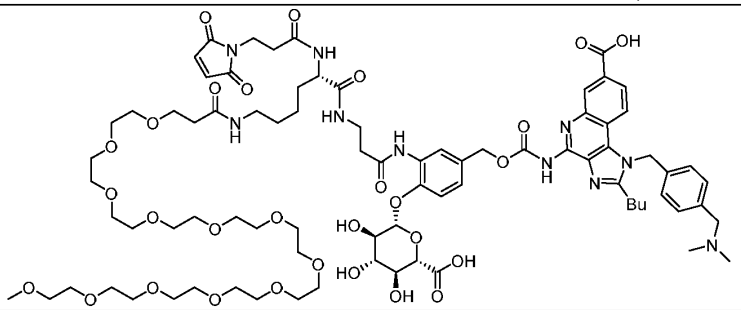
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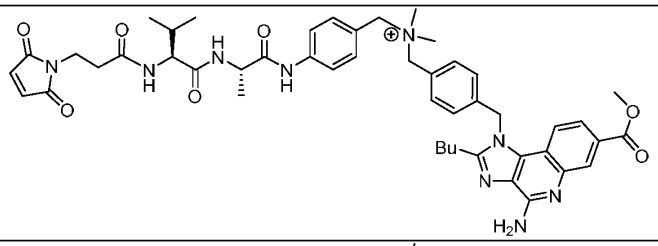
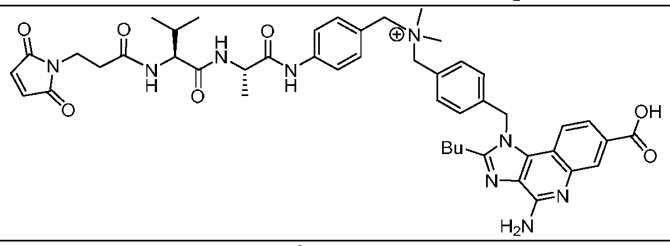
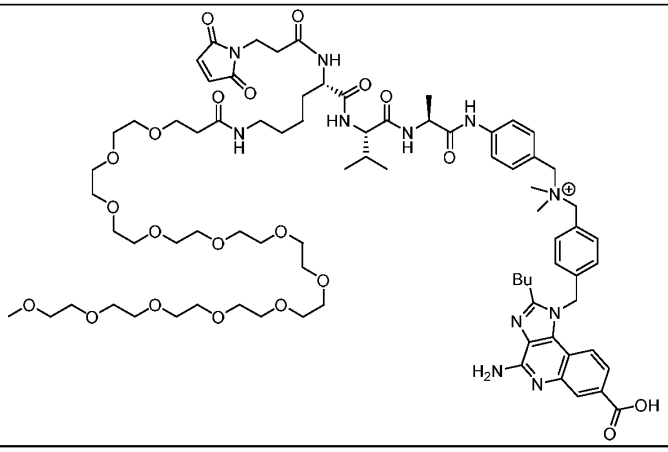
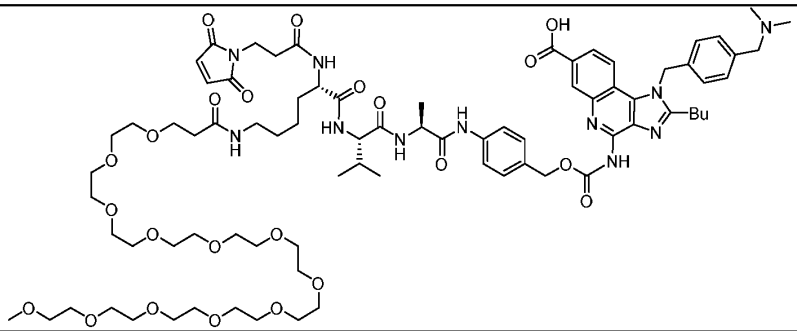
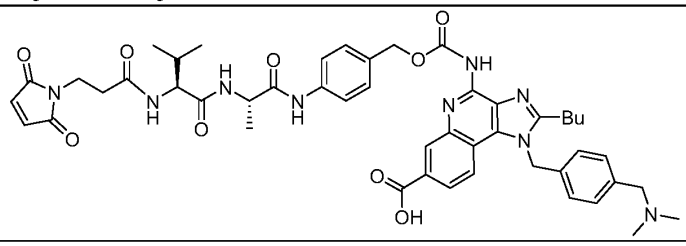
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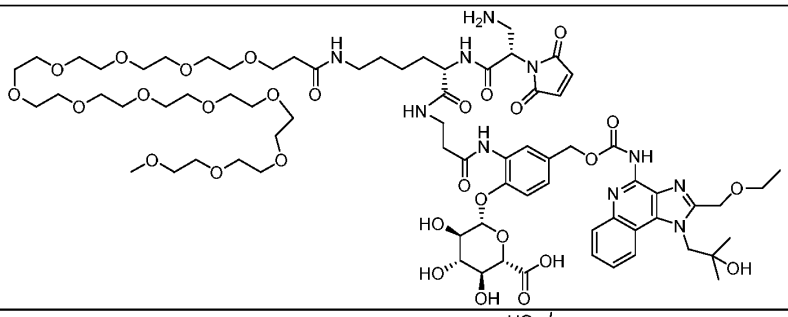
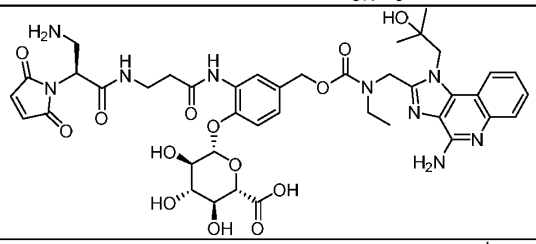
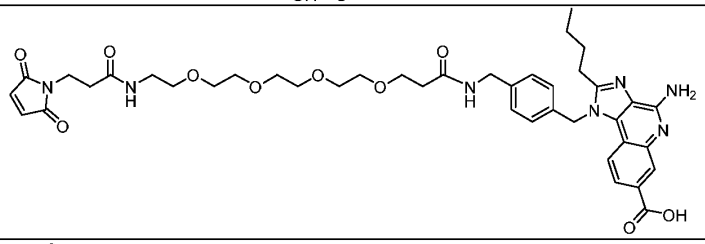
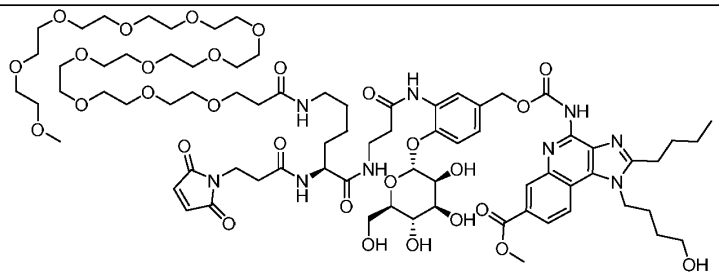
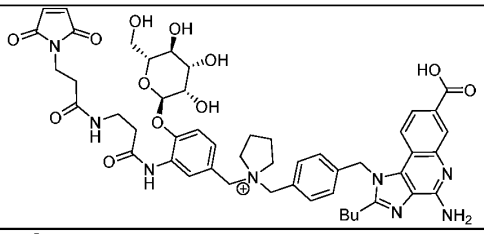
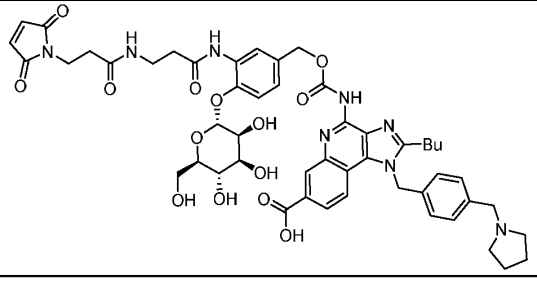
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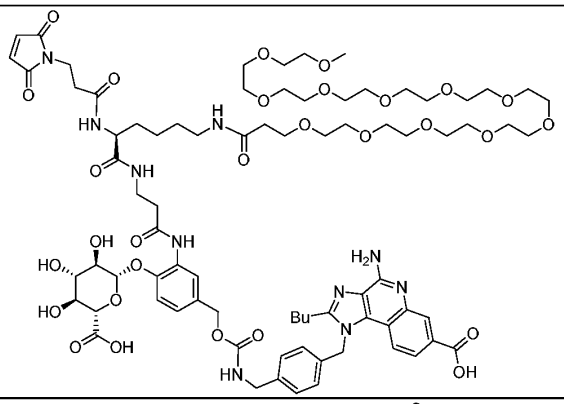
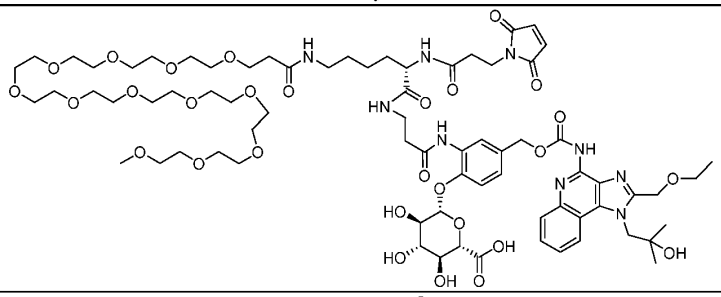
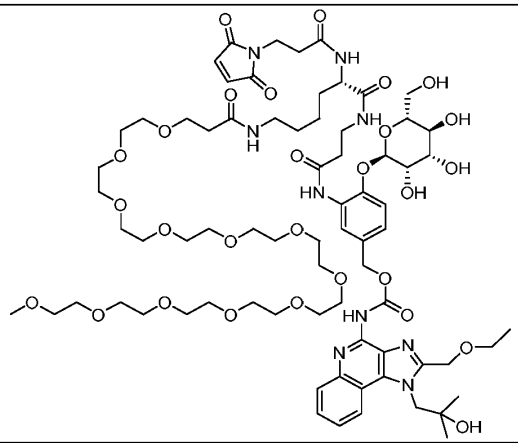
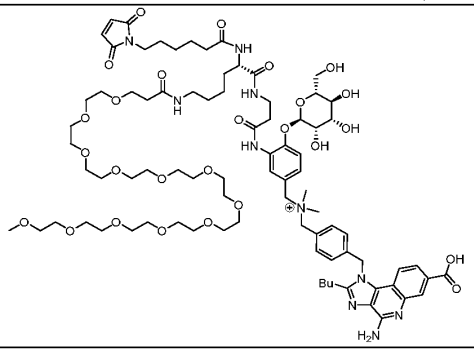
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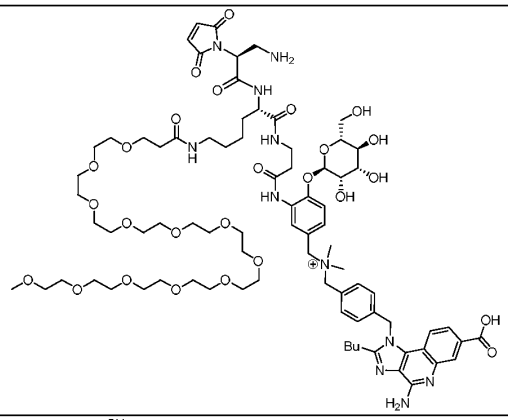
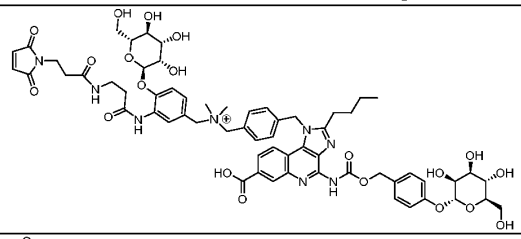
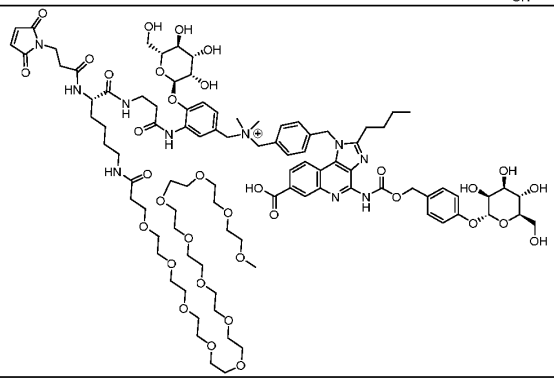
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[0512] In some embodiments, the compounds of Formula L^1-D described herein are present in the form of a salt. In some embodiments, the salt is a pharmaceutically acceptable salt.

EXAMPLES

[0513] A number of embodiments of the present disclosure are described herein. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the disclosure. Accordingly, other embodiments are within the scope of the following claims.

EXAMPLE 1

General Methods

[0514] All commercially available anhydrous solvents and reagents were used without further purification. Preparative high-performance liquid chromatography (HPLC) was carried out on a

Waters 2545 solvent delivery system configured with a Waters 2998 photodiode array (PDA) detector. Unless otherwise specified, products were purified using either Method A or Method B.

[0515] Method A: Reversed phase HPLC (RP-HPLC) using Phenomenex Synergi C12 columns (10-50 mm in diameter, 250 mm in length, 4 μm, 80 Å), eluting with 0.05% (v/v) trifluoroacetic acid (TFA) in water (solvent A) and 0.05% (v/v) trifluoroacetic acid (TFA) in acetonitrile (MeCN) (solvent B); consisted of linear gradients of solvent A to solvent B, ramping from 5 to 10% aqueous solvent B to 95% solvent B; flow rate was varied from 4.6 mL/min to 60 mL/min depending on column diameter.

[0516] Method B: Normal phase Biotage Isolera system with Biotage Sfär silica columns, eluting with either hexane or dichloromethane (DCM) as Solvent A and ethyl acetate (EtOAc) or methanol (MeOH) as solvent B. The normal phase purification methods generally consisted of linear gradients of solvent A to solvent B, ramping from 0% solvent B to 100% solvent B; flow rate was varied depending on column diameter.

[0517] LC-MS analyses were performed on either Waters Acquity SDS system (Method C) or Waters Acquity QSM system (Method D) with the following parameters:

Method C: Column = Waters CORTECS UPLC C18 1.6 μm, 2.1x50mm column; 0.1% (v/v) formic acid (FA) in water (solvent A) and 0.1% (v/v) FA in MeCN (solvent B) as mobile phases. Elution gradients are listed as follows: 3% B to 60% B over 1.7 min, 60% B to 95% B over 0.3 min, 95% B back to 3% B (initial condition) over 0.5 min and equilibrate for 0.3 min; flow rate was set at 0.5 mL/min.

Method D: Column = Waters CORTECS UPLC C18 1.6 μm, 2.1x50mm column; 0.1% (v/v) formic acid (FA) in water (solvent A) and 0.1% (v/v) FA in MeCN (solvent B) as mobile phases. Elution gradients are listed as follows: 3% B to 60% B over 1.7 min, 60% B to 97% B over 0.4 min, hold at 97% for 0.4 min, 97% B back to 3% B (initial condition) over 0.1 min and equilibrate for 0.1 min; the flow rate was set at 0.6 mL/min.

Method E: Column = Waters CORTECS UPLC C18 1.6 μm, 2.1x50mm column; 0.1% (v/v) formic acid (FA) in water (solvent A) and 0.1% (v/v) FA in MeCN (solvent B) as mobile phases. Elution gradients are listed as follows: 3% B to 60% B over 1.1 min, 60% B to 97% B over 0.4 min, hold at 97% for 1.0 min, 97% B back to 3% B (initial condition) over 0.1 min and equilibrate for 0.1 min; the flow rate was set at 0.6 mL/min.

General Procedures for the Preparation of ADCs

[0518] In some embodiments, ADCs were prepared as described previously (*Methods Enzymol.* **2012**, 502, 123-138). Briefly, conjugates were prepared by partial or full reduction of the antibody inter-chain disulfide bonds using various amounts of tris(2-carboxyethyl)phosphine

(TCEP) according to the targeted DAR (drug-to-antibody ratio). In the case of DAR4, TCEP was added at approximately 2.2 molar equivalents relative to the antibody (TCEP:antibody) to a pre-warmed (37 °C) antibody stock solution in phosphate buffered saline, (PBS,Gibco, PN 10010023) and 1 M EDTA. The reduction reaction mixture was incubated at 37°C for approximately 60 minutes. Conjugation of the partially-reduced antibody with maleimide drug-linker was carried out by adding 6 molar equivalents of the drug-linker as a DMSO stock solution. Additional DMSO was added as necessary to achieve a final reaction concentration of 10% (v/v) DMSO to keep the drug-linker remain in solution during the conjugation reaction. The conjugation reaction was allowed to proceed for 30 minutes at room temperature or until all available antibody cysteine thiols had been alkylated by drug-linker as indicated by reversed-phase HPLC (Method G). Removal of excess drug-linker was achieved by incubating the reaction mixture with 100% molar excess QuadraSil® MP resin (Millipore Sigma, PN 679526) for 30 minutes at room temperature. Buffer exchange into formulation buffer (PBS, Gibco, PN 10010023) was achieved by gel filtration chromatography using a prepacked PD-10 column (GE Life Sciences, PN 17043501) according to manufacturer's instructions. Further removal of residual drug-linker was achieved by repeated diafiltration (5-10 times) of the reaction mixture containing the ADCs in formulation buffer using a 30 kilodalton molecular weight cutoff centrifugal filter (Millipore Sigma, PN Z717185), until there was no detectable free drug-linker remaining, as indicated by HPLC analysis (Method K).

General Procedures for the Characterization of ADCs

[0519] ADCs were characterized using the following methods:

[0520] Method I: Size-exclusion chromatography (SEC) was performed with a Waters ACQUITY UPLC system and an Acquity UPLC Protein BEH SEC Column, (200 Å, 1.7µm, 4.6 x 150mm, PN: 186005225). The mobile phase used was 7.5% isopropanol in 92.5% aqueous (25 mM sodium phosphate, 350mM NaCl, pH 6.8), v/v. Elution was performed isocratically at a flow rate of 0.4 mL/min at ambient temperature.

[0521] Method J: Reversed-phase chromatography (RP-HPLC) was performed on a Waters 2695 HPLC system and an Agilent PLRP-S column (1000 Å, 8µm 50x2.1mm, PN: PL1912-1802). ADCs were treated with 10 mM DTT to reduce disulfide bonds prior to analysis. Sample elution was done using Mobile Phase A (0.05% (v/v) TFA in water) and Mobile Phase B (0.01% (v/v) TFA in MeCN) with a gradient of 25-44% B over 12.5 minutes at 80°C. The drug-to-antibody ratio (DAR) was calculated based on the integrated peak area measured at UV 280 nm.

Calculation of Molar Ratios

[0522] The average drug loading per antibody light-chain (MR_{DLC}) or antibody heavy-chain (MR_{DHC}) was calculated using the equations below:

$$MR_{DLC} = \frac{\sum(LC\%area_n \times MR_n)}{100}$$

where MR_{DLC} = average drug-to-light chain ratio

$LC\%area_n$ = % area of the *n*th loaded light chain species

% areas based on light chain peaks only

MR_n = drug-to-antibody ratio of the *n*th loaded species

AND

$$MR_{DHC} = \frac{\sum(HC\%area_n \times MR_n)}{100}$$

where MR_{DHC} = average drug-to-heavy chain ratio

$HC\%area_n$ = % area of the *n*th loaded heavy chain species

% areas based on heavy chain peaks only

MR_n = drug-to-antibody ratio of the *n*th loaded species

[0523] The average drug loading per antibody (MR_D) was calculated using the equation below:

$MR_D = 2 \times (MR_{DLC} + MR_{DHC})$

whereMR_D = average drug-to-antibody ratio

MR_{DLC} = average drug-to-light chain ratio

MR_{DHC} = average drug-to-heavy chain ratio

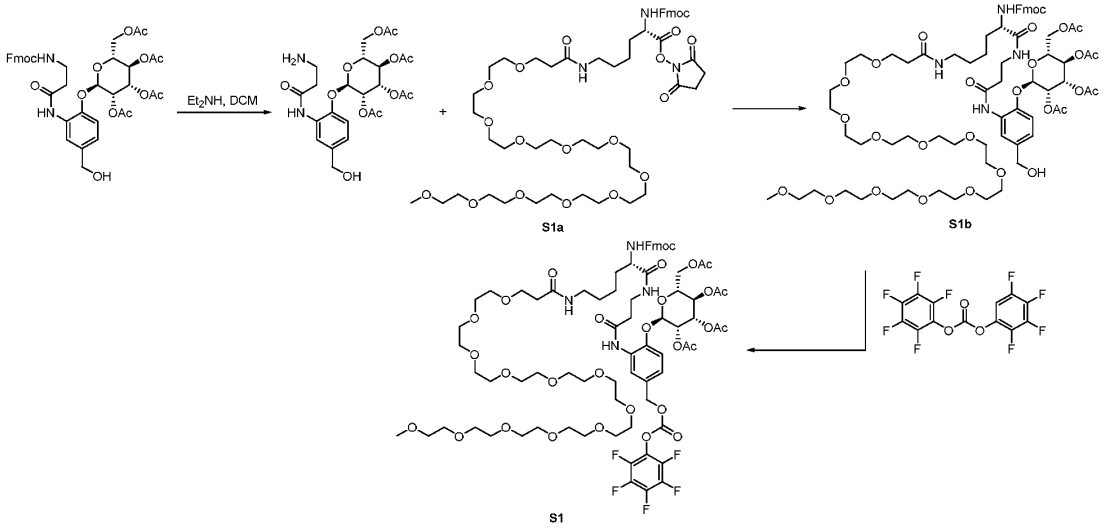
[0524] Method K: Residual unconjugated drug linker was measured on a Waters ACQUITY UPLC system using an ACQUITY UPLC BEH C18 Column (130Å, 1.7 μm, 2.1 mm X 50 mm, PN: 186002350). ADC samples were treated with 2x volumes of ice-cold MeOH to induce precipitation and pelleted by centrifugation. The supernatant, containing any residual, unconjugated drug-linker, was injected onto the system. Sample elution was done using Mobile Phase A (0.05% (v/v) TFA in Water) and Mobile Phase B (0.01% TFA (v/v) in MeCN) with a gradient of 1-95% B over 2 minutes at 50°C. Detection was performed at 215 nm and quantitation of the residual drug-linker compound was achieved using an external standard of the corresponding linker.

EXAMPLE 2

Synthesis of a PEGylated Drug Linker

[0525] Synthesis of 3-((S)-44-((S)-3-amino-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl (2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamate (S1). A general scheme for linker (S1) synthesis is provided in SCHEME 1 below.

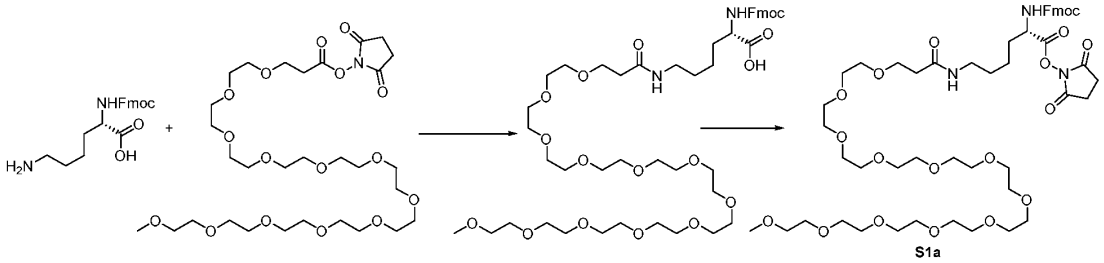
SCHEME 1



[0526] Synthesis of (9H-fluoren-9-yl)methyl (S)-(45-(((2,5-dioxocyclopentyl)oxy)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39-azapentatetracontan-44-yl)carbamate compound with methane (1:1) (S1a). A general synthesis of intermediate S1a for generating linker S1 is provided in SCHEME 2 below. Briefly, Fmoc-Lys-OH (Sigma-Aldrich, 1.34 g, 3.65 mmol) and PEG12-NHS ester (BroadPharm, 2.5 g, 3.65 mmol) were dissolved in dimethylformamide (DMF, 4 mL), followed by the addition of *N,N*-diisopropylethylamine (DIPEA, 1.27 ml, 7.29 mmol). The reaction mixture was stirred at room temperature for 6 h, after which solvents were removed *in vacuo*. The crude reaction mixture was purified by NP-Biotage (Method B) to provide Fmoc-LysPEG12-OH (2.99 g, 03.18 mmol, 87.3%) as colorless liquid. LCMS: m/z $[M+H]^+$ = 939.51 (theoretical); 939.46 (observed). HPLC retention time = 1.83 min (Method C). Fmoc-LysPEG12-OH (890 mg, 0.92 mmol) and N-hydroxysuccinimide (Sigma-Aldrich, 212 mg, 1.84 mmol) was dissolved in tetrahydrofuran (THF, (10 mL), followed by the addition of diisopropylc carbodiimide (DIC, Sigma-Aldrich, 288 µL, 1.84 mmol). After stirring for 3 h at room temperature, the solids were filtered off and solvents were removed *in*

vacuo. The crude product was purified by NP-Biotage (Method B) to give intermediate S1a (843 mg, 0.81 mmol, 88.4%) as colorless liquid. LCMS: m/z $[M+H]^+$ = 1036.52 (theoretical); 1036.66 (observed). HPLC retention time = 1.85 min (Method C).

SCHEME 2



[0527] Synthesis of (2R,3S,4S,5R,6R)-2-(2-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((perfluorophenoxy)carbonyl)oxy)methyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S1) from S1a. Fmoc-mann-PAB-OH (Wuxi AppTech, 2.2 g (2.85 mmol) was dissolved in a 5:1 (v/v) mixture of dichloromethane/diethylamine (DCM/Et_2NH, 20 mL) and the resulting reaction mixture was stirred at room temperature for 2 h. Solvents were removed after 2 h and the crude product was used directly in the next step without purification. LCMS: m/z $[M+H]^+$ = 541.20 (theoretical); 541.41 (observed). HPLC retention time = 1.50 min (Method C). NH_2-mann-PAB-OH (1.54 g, 2.85 mmol) and S1a (3.54 g, 3.42 mmol) were dissolved in DMA (20 mL), followed by the addition of *N,N*-diisopropylethylamine (DIPEA, 1.5 ml, 8.55 mmol) and the reaction mixture was stirred at room temperature for 2 h, after which solvents were removed *in vacuo*. The crude reaction mixture was purified by NP-Biotage (Method B) to provide S1b (3.21 g, 2.2 mmol, 77.1%) as colorless liquid. LCMS: m/z $[M+H]^+$ = 1461.69 (theoretical); 1461.66 (observed). HPLC retention time = 1.80 min (Method C). Fmoc-Compound S1b (460 mg, 0.315 mmol) and Bis(pentafluorophenyl) carbonate (Sigma-Aldrich, 186 mg, 0.472 mmol) were dissolved in dimethylacetamide (DMA, 2 mL) followed by the addition of DIPEA (0.164 ml, 0.944 mmol). The reaction mixture was stirred at room temperature for 6 h after which solvents were removed *in vacuo*. The crude reaction mixture was purified by NP-Biotage (Method B) to provide S1 (301 mg, 0.18 mmol, 57.2%) as colorless sticky liquid. LCMS: m/z $[M+H]^+$ = 1671.67 (theoretical); 1671.60 (observed). HPLC retention time = 2.17 min (Method C).

EXAMPLE 3

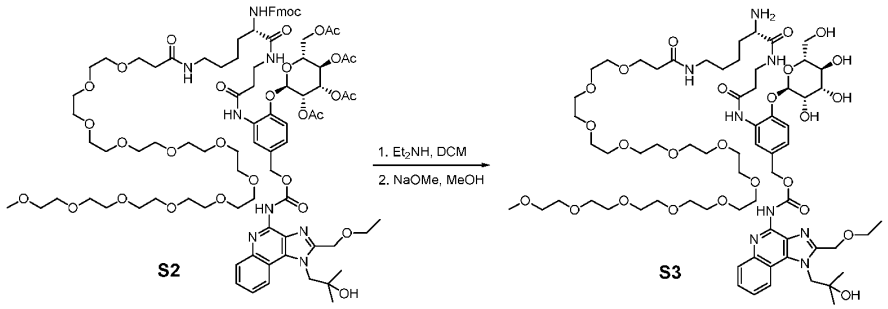
Synthesis of a drug-linker conjugate

[0528] This example covers synthesis of a complex with a toll-like receptor 7 and toll like receptor 8 (TLR7/8) agonist coupled to a linker by a C4 amine of its imidazoquinoline core and capable of coupling to a protein. The TLR7/8 agonist is unfunctionalized at its imidazoquinoline C7 position.

[0529] Synthesis of (2R,3S,4S,5R,6R)-2-(2-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S2). Intermediate S1 (49.3 mg, 0.029 mmol), resiquimod (Asta Tech, 7.1 mg, 0.023 mmol), 1-Hydroxybenzotriazole (HOBt, 1.53 mg, 0.011 mmol), and DIPEA (11.9 µl, 0.068 mmol) were dissolved in DMA and the reaction mixture was stirred at 30 °C for 14 h. After 14 h, the reaction mixture was diluted with dimethylsulfoxide (DMSO)/water and purified by RP-HPLC (Method A) to give intermediate S2 (20.1 mg, 0.011 mmol, 39.5%) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1801.84 (theoretical); 1801.77 (observed); HPLC retention time = 1.77 min (Method C).

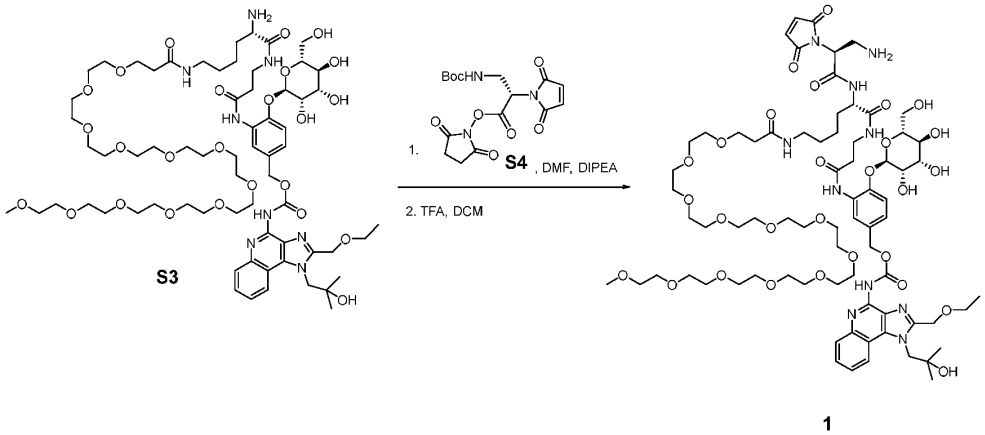
[0530] Synthesis of 3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl (2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamate (S3). A synthesis of S3 using intermediate S2 is outlined in SCHEME 3 below. Intermediate S2 (20.1 mg, 0.011 mmol) was dissolved in dichloromethane (DCM, 0.5 mL) at rom temperature (RT) followed by the addition of dimethylamine (Et_2NH, 0.25 mL). The reaction mixture was stirred at RT for 45 min. After 45 min, solvents were removed *in vacuo* and the crude reaction mixture was re-dissolved in methanol (MeOH, 0.8 mL) at 0 °C and a sodium methoxide (NaOMe) solution (0.5 M in MeOH, 0.178 mL, 0.089 mmol) was added. The resulting reaction mixture was stirred at 0 °C for 90 min, upon which, glacial acetic acid (AcOH, 6.32 uL, 0.112 mmol) was added to neutralize the reaction mixture. The reaction mixture was diluted with water/DMSO and purified by preparative RP-HPLC (Method A) to give intermediate S3 (9.7 mg, 0.006 mmol, 57.0% yield) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1411.7 (theoretical); 1411.99 (observed). HPLC retention time = 1.17 min (Method C).

SCHEME 3



[0531] Synthesis of 3-((S)-44-((S)-3-amino-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl (2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamate (1). Intermediate S4 was prepared according to the procedures as described in Lyon, et al. Nat. Biotechnol. Vol. 32, 1059-1062 (2014). Intermediate S3 (6.9 mg, 0.005 mmol) and 2,5-dioxopyrrolidin-1-yl (S)-3-((tert-butoxycarbonyl)amino)-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoate (S4, (2.07 mg, 0.006 mmol) were dissolved in anhydrous DMF (0.5 mL) and DIPEA (2.36 µL, 0.014 mmol) at room temperature. The reaction mixture was stirred at room temperature for 9 h. After 9 h, solvents were removed *in vacuo* and the crude reaction mixture was re-dissolved in DCM/TFA (10:1 (v/v), 0.5 mL total) and the reaction mixture was stirred at room temperature for another 30 min. Solvents were then removed and the crude reaction mixture was diluted with DMSO/water and purified by preparative RP-HPLC (Method A) to give Compound 1 (3.44 mg, 0.002 mmol, 45.3% yield) as TFA salt, white solid. LCMS: m/z $[M+H]^+$= 1577.77 (theoretical); 1577.83 (observed). HPLC retention time = 1.29 min (Method C).

SCHEME 4



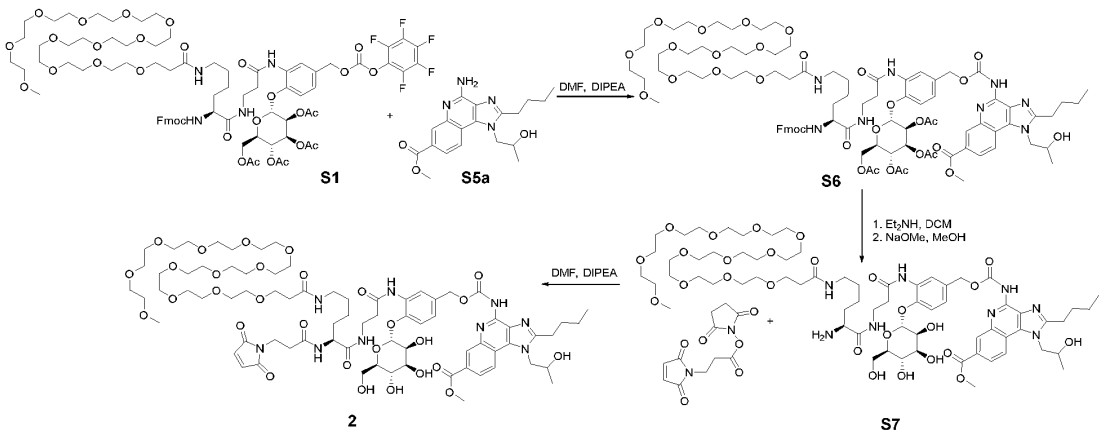
EXAMPLE 4

Synthesis of a drug-linker conjugate

[0532] This example covers synthesis of a complex with a toll-like receptor 7 and toll like receptor 8 (TLR7/8) agonist coupled to a linker by a C4 amine of its imidazoquinoline core and capable of coupling to a protein. The TLR7/8 agonist contains methyl ester functionalization at its imidazoquinoline C7 position.

Synthesis of methyl 2-butyl-4-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1-(2-hydroxypropyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (2). SCHEME 5 summarizes a synthesis of a TLR7/8 agonist, linker conjugate with a maleimide group configured to bind to basic protein residues.

SCHEME 5



[0533] Compound S5a was prepared according to the procedures as described in Larson, et al. *ACS Med.Chem. Lett.* Vol. 8, No. 11, 1148-1152 (2017).

[0534] Synthesis of (2R,3S,4S,5R,6R)-2-(2-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((2-butyl-1-(2-hydroxypropyl)-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S6). Compound S6 was synthesized using similar procedures as those used to prepare compound S2, and was obtained as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1843.85 (theoretical); 1843.94 (observed). HPLC retention time = 1.84 min (Method C).

[0535] Synthesis of methyl 4-((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-2-butyl-1-(2-hydroxypropyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (S7). Compound S7 was synthesized using similar procedures as those used to prepare compound S3, and was obtained as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1453.74 (theoretical); 1453.86 (observed). HPLC retention time = 1.41 min (Method C).

[0536] Synthesis of methyl 2-butyl-4-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1-(2-hydroxypropyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (2). Compound 2 was prepared using similar procedures as those used to prepare compound 1 by reacting compound S7 with 2,5-dioxopyrrolidin-1-yl 3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoate (mp-OSu from TCI). Compound 2 was isolated as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1604.76 (theoretical); 1604.88 (observed). HPLC retention time = 1.48 min (Method C).

EXAMPLE 5

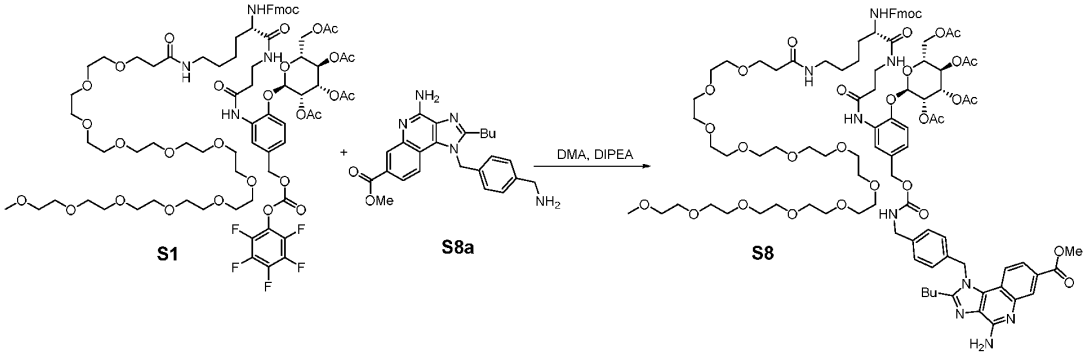
Synthesis of a drug-linker conjugate

[0537] This example covers synthesis of a complex with a toll-like receptor 7 and toll like receptor 8 (TLR7/8) agonist coupled to a linker by a C4 amine of its imidazoquinoline core and methyl ester functionalization at its imidazoquinoline C7 position, namely 4-amino-2-butyl-1-(4-(((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (3).

[0538] Synthesis of (2R,3S,4S,5R,6R)-2-(2-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)carbamoyl)oxy)methyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S8). Synthesis of intermediate S8 with compound S8a is summarized in SCHEME 6. Compound S8a was prepared according to the procedures in Larson, et al. *ACS Med.Chem. Lett.* Vol. 8, No. 11, 1148-1152 (2017).

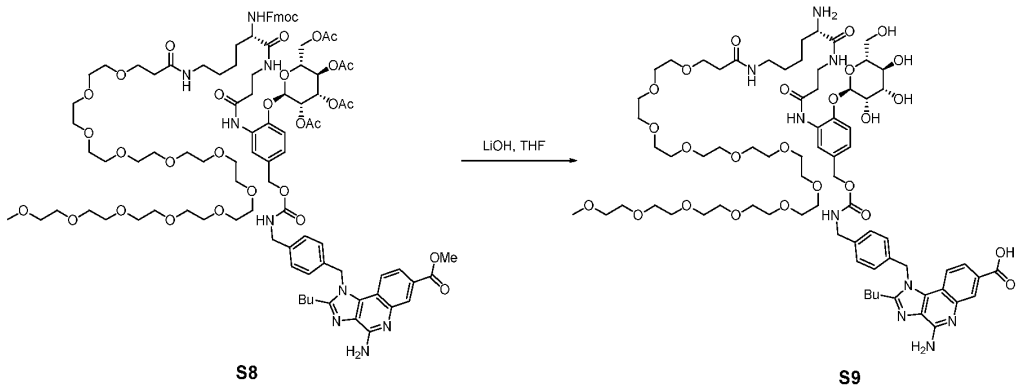
Compounds S1 (33.0 mg, 0.198 mmol), S8a (5.5 mg, 0.132 mmol) and DIPEA (6.9 µL, 0.04 mmol) were dissolved in anhydrous DMA (0.5 mL) and the reaction mixture was stirred for 5 min at room temperature. After 5 min, the reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate S8 (23.2 mg, 0.011 mmol, 87.2%) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1905.88 (theoretical); 1905.21 (observed). HPLC retention time = 1.86 min (Method C).

SCHEME 6



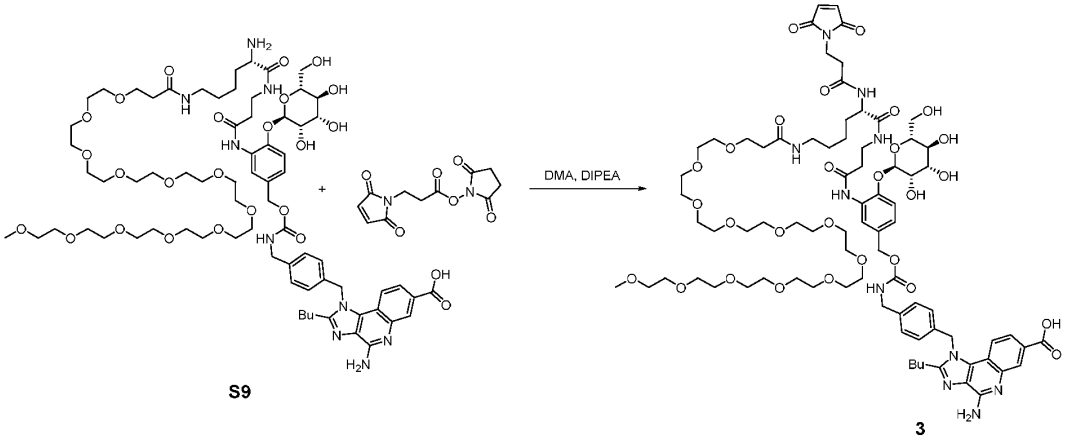
[0539] Synthesis of 4-amino-1-(4-(((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)methyl)benzyl)-2-butyl-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S9**). **SCHEME 7** outlines a synthesis of **S9** from **S8**. Intermediate **S8** (20.0 mg, 0.105 mmol) was dissolved in tetrahydrofuran (THF, 0.6 mL) and an aqueous lithium hydroxide (LiOH) solution (0.2 M, 0.525 mL, 0.105 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, upon which LCMS analysis indicated full conversion. The reaction mixture was quenched with glacial acetic acid (HOAc, 6 µL) and the solvent was removed *in vacuo*. The resulted residue was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate **S9** (11.4 mg, 0.007 mmol, 67.3%) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1500.75 (theoretical); 1500.56 (observed). HPLC retention time = 1.43 min (Method C).

SCHEME 7



[0540] Synthesis of 4-amino-2-butyl-1-(4-(((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**3**). Synthesis of compound **3** from **S9** is outlined in **SCHEME 8.** Intermediate **S9** (6.6 mg, 4.09 μmol) and mp-OSu (TCI, 1.31 mg, 4.91 μmol) were dissolved in anhydrous DMA (0.3 mL) and DIPEA (2.2 μL, 0.012 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 30 min. After 30 min, the reaction mixture was quenched with HOAc (5 μl), diluted with DMSO/water and purified by RP-HPLC (Method A) to give compound **3** (4.9 mg, 0.003 mmol, 67.9 %) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1651.78 (theoretical); 1652.49 (observed). HPLC retention time = 1.32 min (Method C).

SCHEME 8



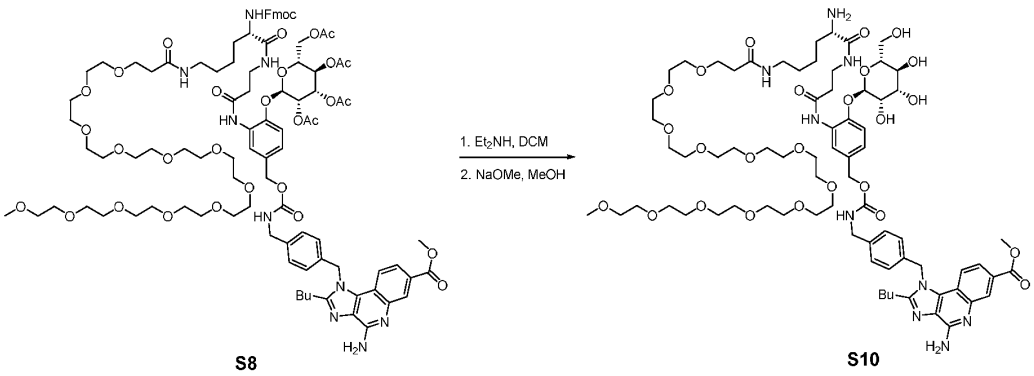
EXAMPLE 6

Synthesis of a drug, Linker Conjugate

[0541] This example covers synthesis of a complex with a toll-like receptor 7 and toll like receptor 8 (TLR7/8) agonist coupled to a linker by an N1 of its imidazoquinoline core and capable of coupling to a protein. The TLR7/8 agonist contains methyl ester functionalization at its imidazoquinoline C7 position.

[0542] Synthesis of methyl 4-amino-1-(4-(((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)methyl)benzyl)-2-butyl-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (S10). Synthesis of intermediate S10 from intermediate S8 is summarized in SCHEME 9. Intermediate S8 (19.3 mg, 11.5 μmol) was dissolved in 0.8 mL of a 4:1 (v/v) mixture of DCM and Et_2NH, and the resulting solution was stirred at room temperature for 15 min. After 15 min, solvents were removed *in vacuo* and the reaction mixture was re-dissolved in MeOH (0.5 mL), followed by the addition of sodium methoxide (NaOMe, 0.5 M solution in MeOH, 0.138 mL, 0.069 mmol). The reaction mixture was stirred at room temperature for 30 min and then quenched with HOAc (7 μL). Solvents were then removed *in vacuo*. The resulting residue was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate S10 (14.0 mg, 0.008 mmol, 69.9 %) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1514.77 (theoretical); 1514.80 (observed). HPLC retention time = 1.28 (Method C).

SCHEME 9

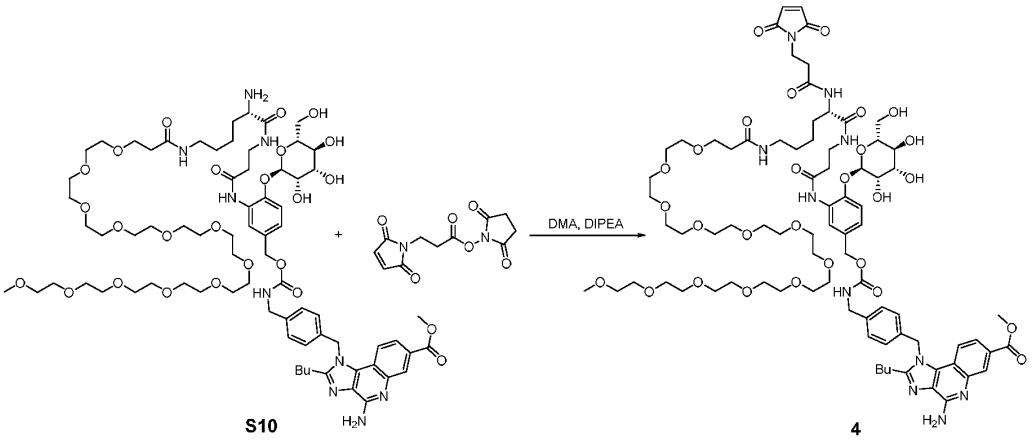


S8 S10

[0543] Synthesis of methyl 4-amino-2-butyl-1-(4-(((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (**4**). **SCHEME 10** outlines a synthesis of compound **4**

from intermediate **S10**. Intermediate **S10** (14.0 mg, 0.008 mmol) and mp-OSu (3.21 mg, 0.012 mmol) were dissolved in anhydrous DMA (0.3 mL) and DIPEA (7.0 µL, 0.04 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 15 min. After 15 min, the reaction mixture was quenched with HOAc (5 µl), diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound **4** (10.3 mg, 0.006 mmol, 72.0 %) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1665.80 (theoretical); 1666.46 (observed). HPLC retention time = 1.35 min (Method C).

SCHEME 10



EXAMPLE 7

Syntheses of two drug-linker conjugates

[0544] This example covers syntheses of complexes with TLR7/8 agonists coupled to linkers by an N1 of imidazoquinoline cores and capable of coupling to a protein. The TLR7/8 agonists contain variable functionalization at position C7 of their imidazoquinoline cores, with compound 5 containining methyl ester functionalization at this position and compound 6 containing carboxylic acid functionalization at this position.

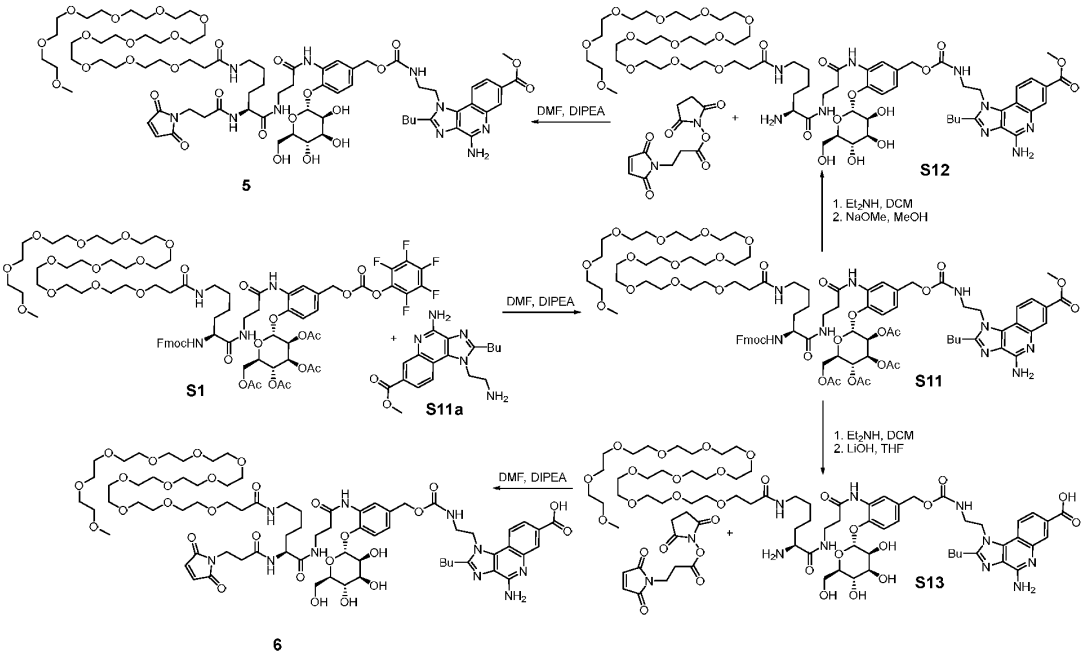
[0545] Syntheses of methyl 4-amino-2-butyl-1-(2-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)ethyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (5) and 4-amino-2-butyl-1-(2-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)ethyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (6).

[0546] These syntheses are summarized in SCHEME 11. The syntheses of compounds 5 and 6 were similar to the syntheses of compound 4 and compound 3, respectively.

[0547] The synthesis of compound 5 and compound 6 was similar to the synthesis of compound 4 and compound 3, respectively.

[0548] Compound S11a was prepared according to the procedures as described in Larson, et al. *ACS Med.*

SCHEME 11



[0549] (2R,3S,4S,5R,6R)-2-(2-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((2-(4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)ethyl)carbamoyl)oxy)methyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S11) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1828.85 (theoretical); 1828.95 (observed). HPLC retention time = 1.74 min (Method C).

[0550] Methyl 4-amino-1-(2-((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)ethyl)-2-butyl-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (S12) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1438.74 (theoretical); 1438.85 (observed). HPLC retention time = 1.33 min (Method C).

[0551] Methyl 4-amino-2-butyl-1-(2-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)ethyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (5) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1589.77 (theoretical); 1589.87 (observed). HPLC retention time = 1.39 min (Method C).

[0552] Synthesis of 4-amino-1-(2-((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)ethyl)-2-butyl-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (S13). Compound S13 was prepared using similar procedures as those used to prepare compound S10, and was isolated as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1424.72 (theoretical); 1424.83 (observed). HPLC retention time = 1.28 (Method C).
4-amino-2-butyl-1-(2-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)ethyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (6) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1575.75 (theoretical); 1576.58 (observed). HPLC retention time = 1.22 min (Method C).

EXAMPLE 8

Syntheses of two drug-linker conjugates

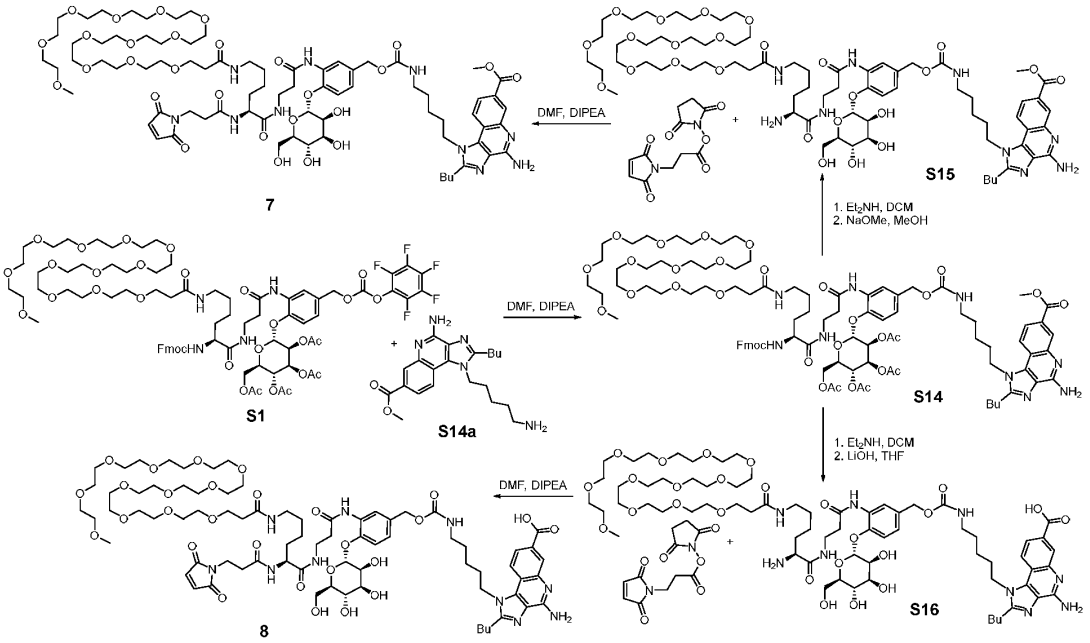
[0553] This example covers syntheses of complexes with TLR7/8 agonists coupled to linkers by an N1 of imidazoquinoline cores and capable of coupling to a protein. The TLR7/8 agonists contain variable functionalization at position C7 of their imidazoquinoline cores, with compound 7 containining methyl ester functionalization at this position and compound 8 containing carboxylic acid functionalization at this position.

[0554] Syntheses of methyl 4-amino-2-butyl-1-(5-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)pentyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (7) and 4-amino-2-butyl-1-(5-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-

(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)pentyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (8). The syntheses of compounds 7 and 8 were similar to the synthesis of compound 4 and compound 3, respectively, and are outlined in SCHEME 12 below.

[0555] The synthesis of compound 7 and compound 8 was similar to the synthesis of compound 4 and compound 3, respectively.

SCHEME 12



[0556] (2R,3S,4S,5R,6R)-2-(2-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((5-(4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)pentyl)carbamoyl)oxy)methyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**S14**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1871.90 (theoretical); 1871.74 (observed). HPLC retention time = 1.93 min (Method C).

[0557] Methyl 4-amino-1-(5-((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)pentyl)-2-butyl-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (**S15**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1480.79 (theoretical); 1481.55 (observed). HPLC retention time = 1.45 min (Method C).

[0558] Methyl 4-amino-2-butyl-1-(5-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)pentyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (**7**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1631.81 (theoretical); 1632.22 (observed). HPLC retention time = 1.47 min (Method C).

[0559] 4-amino-1-(5-((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)pentyl)-2-butyl-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S16**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1466.77 (theoretical); 1466.42 (observed). HPLC retention time = 1.17 min (Method C).

[0560] 4-amino-2-butyl-1-(5-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)pentyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**8**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1617.80 (theoretical); 1617.66 (observed). HPLC retention time = 1.28 min (Method C).

EXAMPLE 9

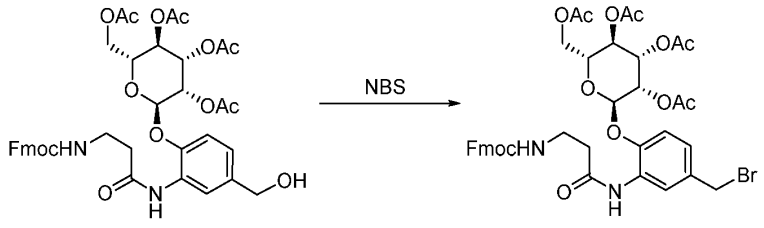
Syntheses of two drug-linker conjugates

[0561] This example covers syntheses of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with carboxylic acid functionalization at its C7 position, namely N-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (9).

[0562] Synthesis of (2R,3S,4S,5R,6R)-2-(2-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(bromomethyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S17). SCHEME 13 outlines a synthesitic scheme for intermediate S17. Fmoc-mann-PAB-OH (Wuxi AppTech, 200 mg, 0.262 mmol) and N-bromosuccinimide (NBS, Sigma-Aldrich, 70 mg, 0.393 mmol) were dissolved in DCM (8 mL) at 0 °C followed by the addition of triphenylphosphine (PPh_3, Sigma-Aldrich, 103.2 mg, 0.393 mmol). The reaction mixture was stirred at 0 °C for 10 min then warmed up to

room temperature and stirred for an additional 4 h, after which solvents were removed *in vacuo*. The crude reaction mixture was purified by NP-Biotage (Method B) to provide S17 (154 mg, 0.187 mmol, 71.1%) as white solid. LCMS: m/z [M+H]+ = 825.19 (theoretical); 825.20 (observed). HPLC retention time = 1.89 min (Method C).

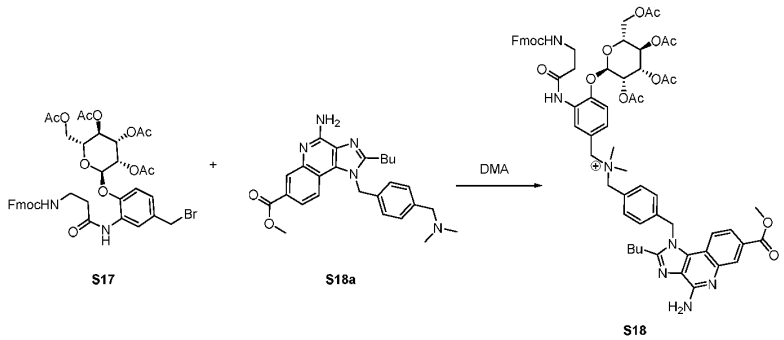
SCHEME 13



S17

[0563] Synthesis of N-(3-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(((2R,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)-1-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)phenyl)-*N,N*-dimethylmethanaminium (S18). A synthesitic route for intermediate S18 is provided in SCHEME 14 below. Compound S18a was prepared according to the procedures as described in Larson, et al. *ACS Med.Chem. Lett.* Vol. 8, No. 11, 1148-1152 (2017). Compound S17 (97.8 mg, 0.119 mmol) and S18a (44 mg, 0.099 mmol) were dissolved in DMA (1 mL). The reaction mixture was heated at 45 °C for 3 h and the reaction progress monitored by LCMS. After 3 h, the reaction mixture was diluted with DMSO /water and purified by RP-HPLC (Method A) to provide S18 (128.9 mg, 0.091 mmol, 92%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1190.51 (theoretical); 1190.75 (observed). HPLC retention time = 1.81 min (Method D).

SCHEME 14

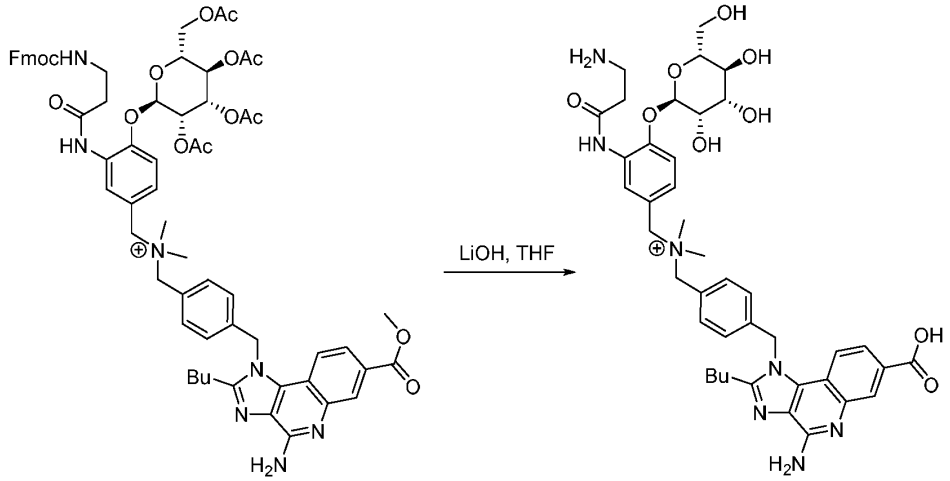


S17 **S18a** **S18**

[0564] Synthesis of N-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-aminopropanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (S19).

SCHEME 15 provides a synthetic scheme for generating intermediate S19. Intermediate S18 (87.9 mg, 0.062 mmol) was dissolved in THF (1.0 mL) and an aqueous LiOH solution (0.5 M, 1.24 mL, 0.62 mmol) was added. The reaction mixture was stirred at room temperature for 5 h, upon which LCMS indicated full conversion. The reaction mixture was quenched with HOAc (54 µl) and the THF was removed *in vacuo*. The remaining reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate S19 (50.4 mg, 0.045 mmol, 72.1%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 786.38 (theoretical); 786.53 (observed). HPLC retention time = 1.09 min (Method D).

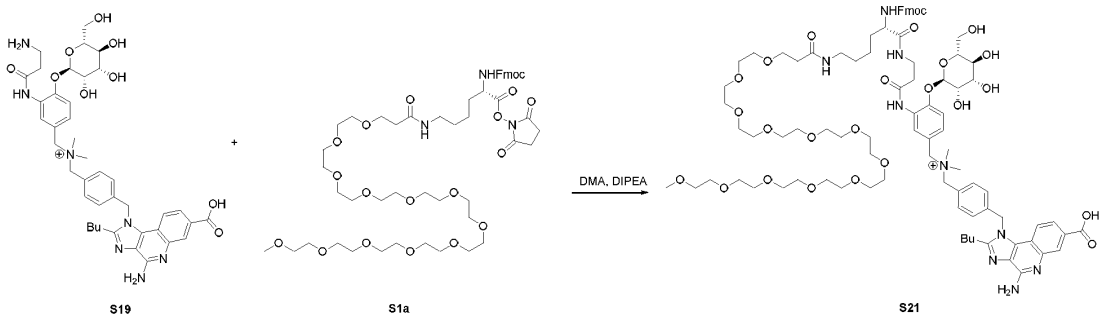
SCHEME 15



S18 S19

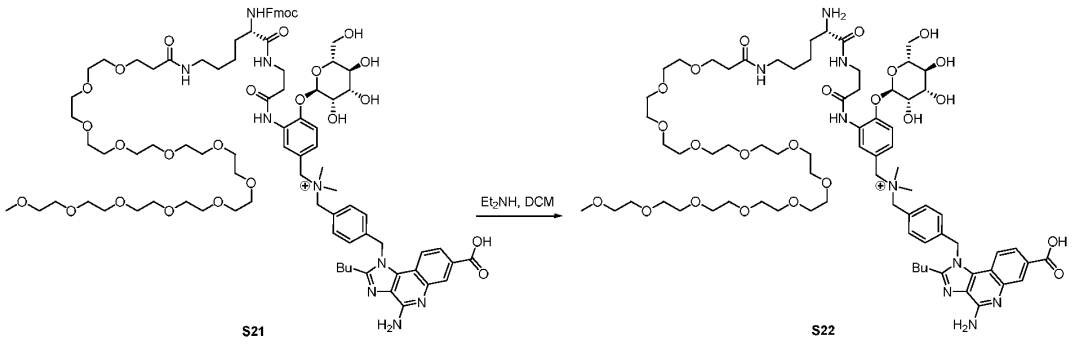
[0565] Synthesis of N-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]282uinoline-1-yl)methyl)benzyl)-1-(3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (S21). SCHEME 16 summarizes a synthetic scheme for generating intermediate S21. Intermediate S19 (23.4 mg, 0.023 mmol) and S1a (35.8 mg, 0.035 mmol) were dissolved in anhydrous DMA (0.5 mL) and DIPEA (0.024 mL, 0.138 mmol) at room temperature. The reaction mixture was stirred at room temperature for 90 min. After 90 min, the crude reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate S21 (32.1 mg, 0.017 mmol, 71.9%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1706.87 (theoretical); 1706.91 (observed). HPLC retention time = 1.71 min (Method D).

SCHEME 16



[0566] Synthesis of N-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (S22). SCHEME 17 summarizes a synthetic scheme for generating intermediate S22. Intermediate S21 (37.1, 0.022 mmol) was dissolved in 1 mL of a 4:1 (v/v) mixture of DCM/Et_2NH. The reaction mixture was stirred at room temperature for 45 min. After 45 min, solvents were removed *in vacuo* and the crude reaction mixture was diluted with DMSO/water and purified by RP-HPLC. (Method A) to give intermediate S22 (33.9 mg, 0.018 mmol, 82.9%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1484.80 (theoretical); 1484.62 (observed). HPLC retention time = 1.46 min (Method D).

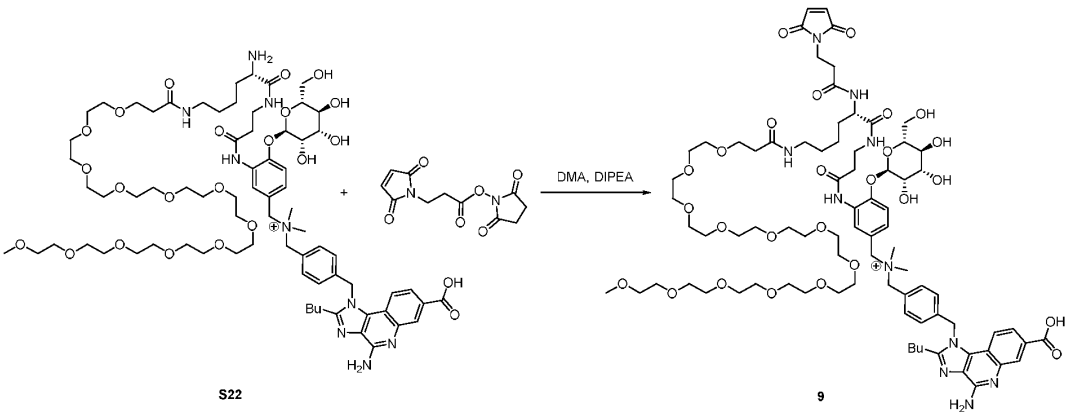
SCHEME 17



[0567] Synthesis of N-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**9**). **SCHEME 18** summarizes a synthetic scheme for generating compound 9. Intermediate **S22** (33.9 mg, 0.018 mmol) and mp-OSu (6.99 mg, 0.026 mmol) were dissolved in anhydrous DMA (0.5 mL) and DIPEA (18.3 µL, 0.105 mmol) at room

temperature. The reaction mixture was stirred at the same temperature for 30 min. After 30 min, the reaction mixture was quenched with HOAc (10 µl), diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound **9** (29.6 mg, 0.016 mmol, 90.7%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1635.83 (theoretical); 1637.38 (observed). HPLC retention time = 1.51 min (Method D).

SCHEME 18



EXAMPLE 10

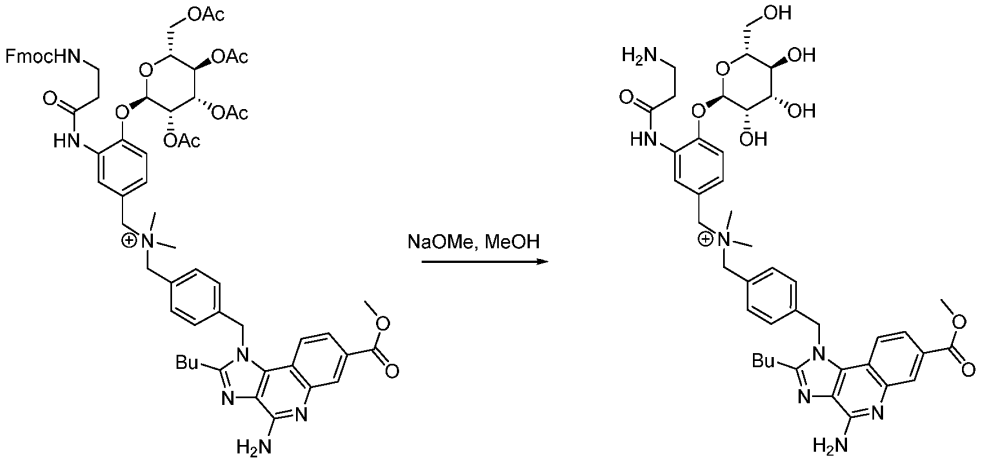
Syntheses of a drug-linker conjugate

[0568] This example covers syntheses of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with methyl ester functionalization at its C7 position, namely N-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (10).

[0569] Synthesis of N-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-aminopropanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**S23**). **SCHEME 19** outlines a synthetic scheme for generating intermediate **S23**. The intermediate **S18** (14.2 mg, 0.01 mmol) was dissolved in MeOH (0.4 mL) and cooled at 0 °C for 5 min. NaOMe solution (0.5M in MeOH, 0.12 mL, 0.06 mmol) was added. The reaction was mixture stirred at 0 °C for 30 min and then at room temperature for another 2 h. After 2 hours, the solution was neutralized with HOAc (11.6 µL) and purified by RP-HPLC (Method A) to give intermediate **S23** (7.8 mg, 0.008 mmol, 76.8 %) as TFA salt,

white solid. LCMS: m/z $[M]^+$ = 800.40 (theoretical); 800.54 (observed). HPLC retention time = 1.51 min (Method D).

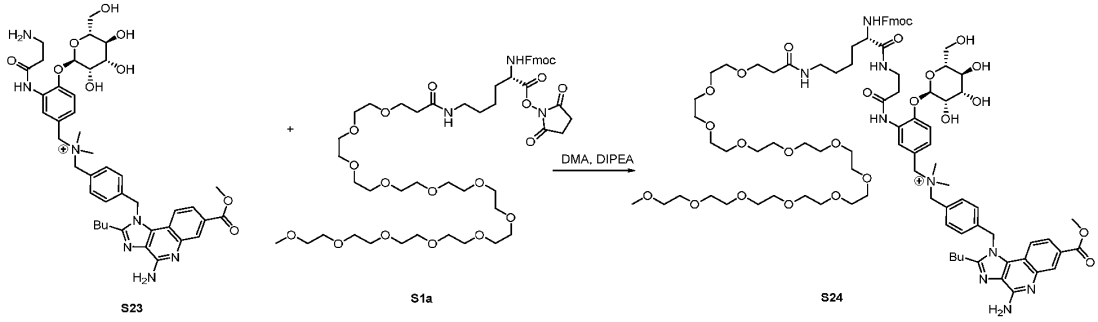
SCHEME 19



S18 S23

[0570] Synthesis of N-(3-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)-1-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)phenyl)-*N,N*-dimethylmethanaminium (S24). SCHEME 20 outlines a synthetic route for intermediate S24. Intermediates S23 (15.6 mg, 15.2 μmol) and S1a (23.6 mg, 22.8 μmol) were dissolved in anhydrous DMA (0.8 mL) and DIPEA (13.2 μL, 0.076 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min. After 30 min, the crude reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate S24 (17.2 mg, 0.012 mmol, 70.3 %) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1721.89 (theoretical); 1722.34 (observed). HPLC retention time = 1.51 min (Method D).

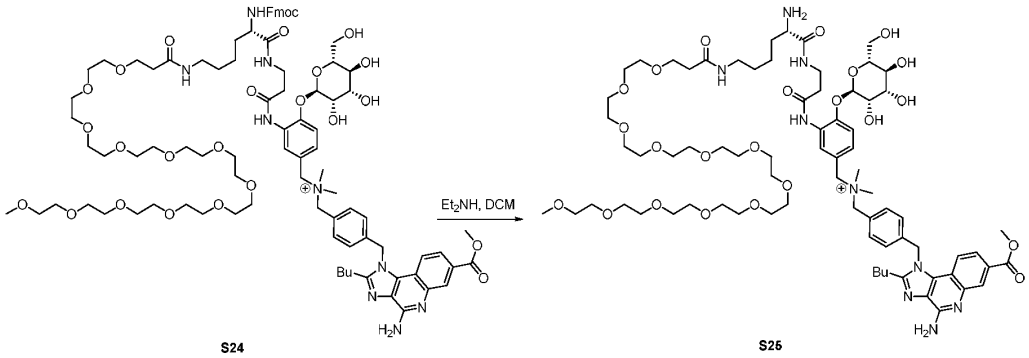
SCHEME 20



S23 S1a S24

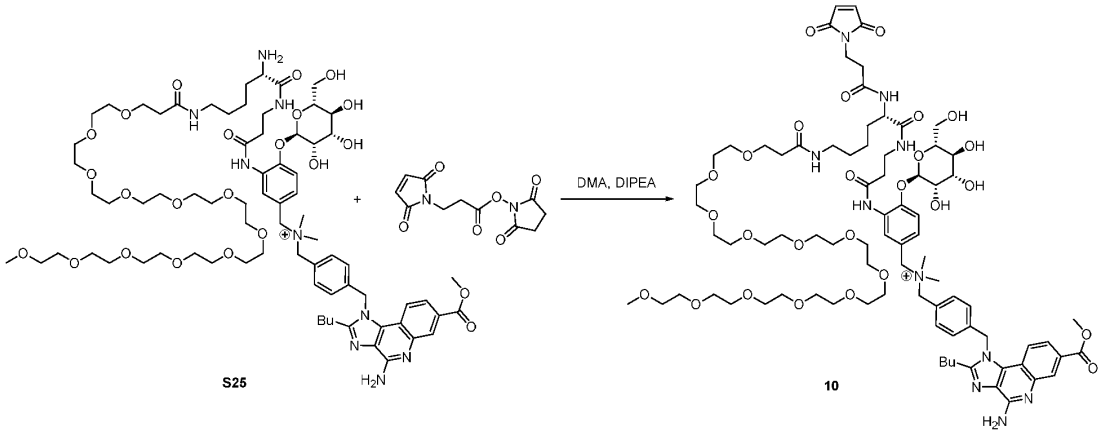
[0571] Synthesis of N-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (S25). SCHEME 21 outlines a synthetic route for generating intermediate S25. Intermediate S24 (17.2, 0.012 mmol) was dissolved in 1 mL of a 4:1(v/v) mixture of DCM/Et_2NH. The reaction mixture was stirred at room temperature for 1 h. After 1 hour, solvents were removed *in vacuo* and the crude reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate S25 (14.4 mg, 9.6 µmol, 80.1%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1498.82 (theoretical); 1499.12 (observed). HPLC retention time = 1.33 min (Method D).

SCHEME 21



[0572] Synthesis of N-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**10**). **SCHEME 22** outlines a synthesis of compound **10** from intermediate **S25**. Intermediate **S25** (9.5 mg, 0.006 mmol) and mp-OSu (2.35 mg, 8.83 µmol) were dissolved in anhydrous DMA (0.2 mL) and DIPEA (5.13 µL, 0.029 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 30 min. After 30 min, the reaction mixture was quenched with HOAc (10 µl), diluted with DMSO/water and purified by RP-HPLC (Method A) to give compound **10** (8.6 mg, 0.005 mmol, 82.8 %) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1649.8 (theoretical); 1650.2 (observed). HPLC retention time = 1.41 min (Method D).

SCHEME 22



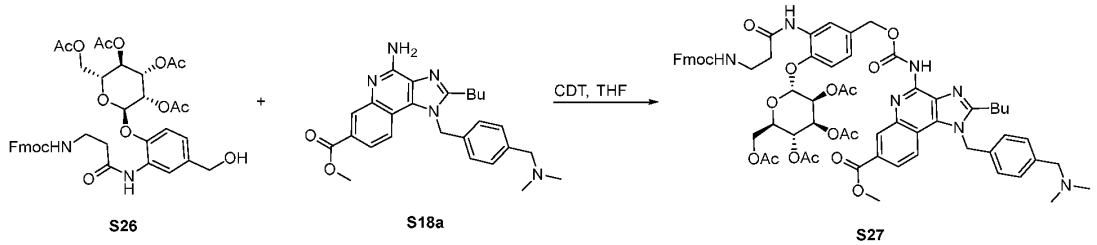
EXAMPLE 11

Syntheses of a drug-linker conjugate

[0573] This example covers syntheses of a complex comprising a linker coupled to a C4 amine of an imidazoquinoline TLR7/8 agonist with methyl ester functionalization at its C7 position and phenyl substitution at N1, namely 2-butyl-1-(4-((dimethylamino)methyl)benzyl)-4-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**11**).

[0574] Synthesis of (2R,3S,4S,5R,6R)-2-(2-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((2-butyl-1-(4-((dimethylamino)methyl)benzyl)-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]287uinoline-4-yl)carbamoyl)oxy)methyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**S27**). Intermediate **S27** was synthesized according to **SCHEME 23**. Compound **S18a** (75 mg, 0.168 mmol) was dissolved in anhydrous THF (1.5 mL) and cooled to 0 °C. 1,1'-carbonyl-do-(1,2,4-triazole) (CDT, 38.7 mg, 0.236 mmol) was added and the reaction mixture was warmed up to room temperature and stirred for 30 min. After 30 min, compound **S26** (191 mg, 0.421 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 2 h. After 2 hours, solvents were removed *in vacuo* and the crude reaction mixture was purified by normal phase HPLC (Method B, EtOAc/hexane as eluents) to give the desired product **S27** (125.7 mg, 0.136 mmol, 80.6%) as white solid. LCMS: m/z $[M+H]^+$ = 1234.49 (theoretical); 1234.91 (observed). HPLC retention time = 2.13 min (Method D).

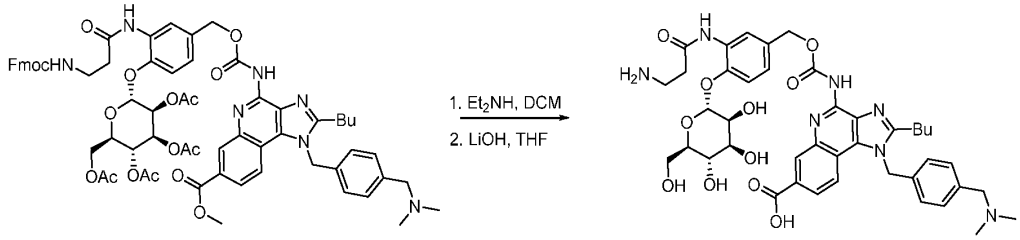
SCHEME 23



S26 S18a S27

[0575] Synthesis of 4-((((3-(3-aminopropanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S28**). Intermediate **S28** was synthesized according to **SCHEME 24**. Compound **S27** (110.0 mg, 0.082 mmol) was dissolved in a 4:1 mixture of Et_2NH and DCM (1.25 mL). The reaction was stirred at room temperature for 30 min. After 30 min, solvents were removed *in vacuo* and the residue was re-dissolved in THF (1.3 mL), followed by the addition of an aqueous LiOH solution (0.5 M, 1.3 mL, 0.653 mmol). The reaction mixture was stirred at room temperature for 6 h. After 6 h, the reaction mixture was acidified with glacial acetic acid (70 µL), THF was removed *in vacuo* and the residue was diluted with DMSO /water and purified by RP-HPLC (Method A) to provide **S28** (62.5 mg, 0.0591 mmol, 72.4%) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 830.37 (theoretical); 830.62 (observed). HPLC retention time = 1.34 min (Method D).

SCHEME 24

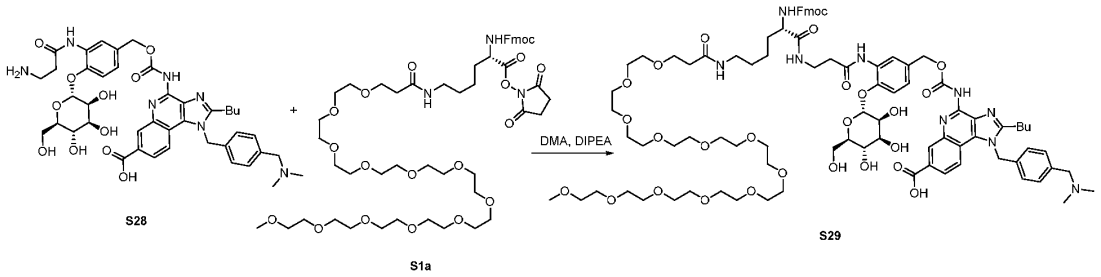


S27 S28

[0576] Synthesis of 4-((((3-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S29**). **SCHEME 25** provides a synthetic route for generating intermediate **S29**. Intermediates **S28** (20.0 mg, 0.019 mmol) and **S1a** (29.4 mg, 0.028 mmol) were dissolved in anhydrous DMA (0.6 mL) and DIPEA (16.5 µL, 0.095 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h. After 1 h, the crude

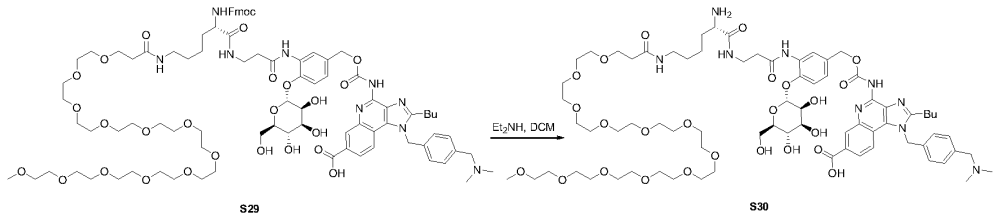
reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate **S29** (21.4 mg, 0.0122 mmol, 64.7 %) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1750.85 (theoretical); 1752.29 (observed). HPLC retention time = 1.52 min (Method D).

SCHEME 25



[0577] Synthesis of 4-((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S30**). Intermdiate **S30** was synthesized according to **SCHEME 26**. Intermediate **S29** (21.4, 0.0122 mmol) was dissolved in 1 mL of a 4:1 (v/v) mixture of DCM/Et_2NHmL. The reaction mixture was stirred at room temperature for 40 min. After 40 min, solvents were removed *in vacuo* and the crude reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate **S30** (17.4 mg, 9.92 µmol, 81.3%) as TFA salt, , white solid. LCMS: m/z $[M+H]^+$ = 1528.79 (theoretical); 1529.16 (observed). HPLC retention time = 1.36 min (Method D).

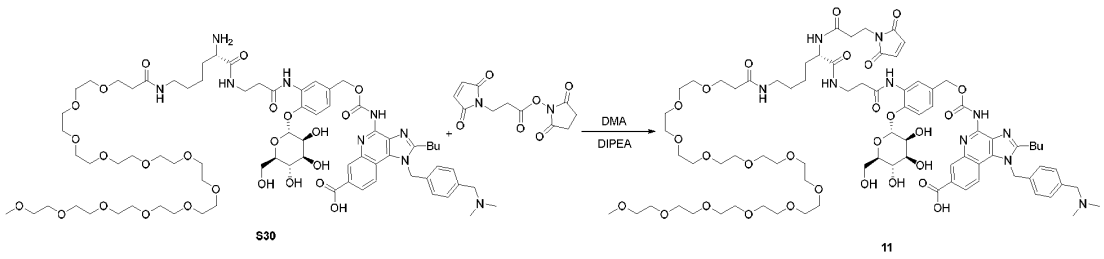
SCHEME 26



[0578] Synthesis of 2-butyl-1-(4-((dimethylamino)methyl)benzyl)-4-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**11**). Compound **11** was synthesized according to **SCHEME 27**. Intermediate **S30** (23.7 mg, 0.0144 mmol) and mp-OSu (5.76 mg, 0.0216 mmol) were dissolved in anhydrous DMA (0.5 mL) and DIPEA (12.6 µL, 0.072 mmol) at room temperature. The

reaction mixture was stirred at the same temperature for 30 min. After 30 min, the reaction mixture was quenched with HOAc (15 µl), diluted with DMSO/water and purified by RP-HPLC (Method A) to give compound **11** (21.0 mg, 0.0117 mmol, 81.1 %) as TFA salt. LCMS: m/z $[M+H]^+$ = 1679.81 (theoretical); 1680.16 (observed). HPLC retention time = 1.46 min (Method D).

SCHEME 27



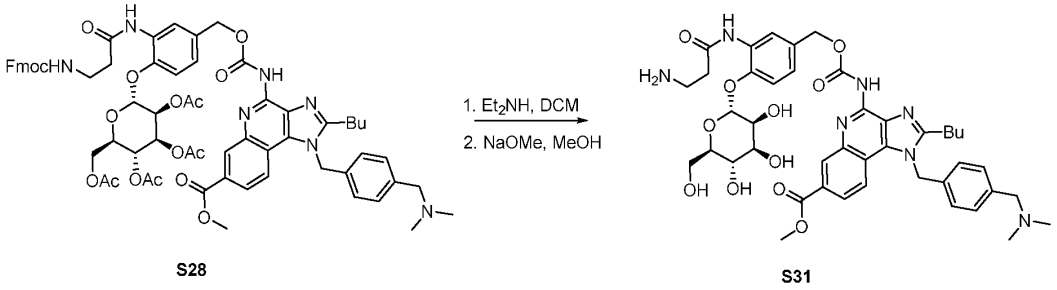
EXAMPLE 12

Syntheses of a drug-linker conjugate

[0579] This example covers syntheses of a complex comprising a linker coupled to a C4 amine of an imidazoquinoline TLR7/8 agonist with methyl ester functionalization at its C7 position and phenyl substitution at N1, namely methyl 2-butyl-1-(4-((dimethylamino)methyl)benzyl)-4-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (**12**).

[0580] Synthestis of methyl 4-((((3-(3-aminopropanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (**S31**). Intermediate **S31** was generated according to **SCHEME 28**. Intermediate **S28** (39.3 mg, 0.029 mmol) was dissolved in a 4:1 (v/v) mixture of Et_2NH and DCM (1.25 mL). The reaction mixture was stirred at room temperature for 30 min, After 30 min, solvents were removed *in vacuo* and the residue was re-dissolved in MeOH (0.4 mL) followed by the addition of a NaOMe solution (0.5 M in MeOH, 0.35 mL, 0.175 mmol). The reaction mixture was stirred at room temperature for 1 h. After 1 hour, the reaction mixture was acidified with glacial acetic acid (15 µL), THF was removed *in vacuo* and the residue was diluted with DMSO /water and purified by RP-HPLC (Method A) to provide **S31** (14.3 mg, 0.013 mmol, 45.4%) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 844.38 (theoretical); 844.62 (observed). HPLC retention time = 1.47 min (Method D).

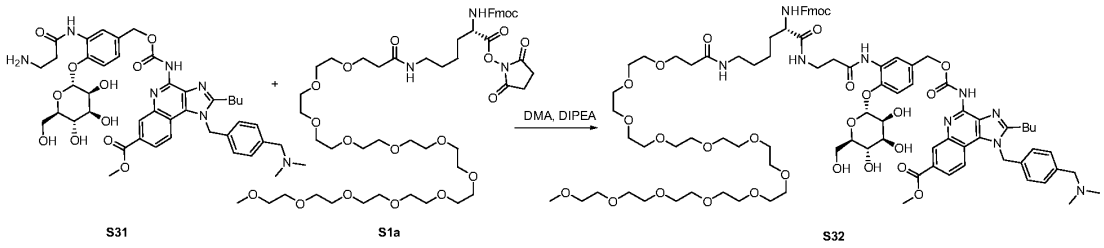
SCHEME 28



S28 S31

[0581] Synthesis of methyl 4-((((3-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (**S32**). Intermediate **S32** was generated according to **SCHEME 29**. Intermediates **S31** (14.3 mg, 0.013 mmol) and **S1a** (20.7 mg, 0.02 mmol) were dissolved in anhydrous DMA (0.6 mL) and DIPEA (13.9 µL, 0.08 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h. After 1 h, the crude reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate **S32** (16.1 mg, 9.1 µmol, 68.4 %) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1764.87 (theoretical); 1766.33 (observed). HPLC retention time = 1.84 min (Method D).

SCHEME 29

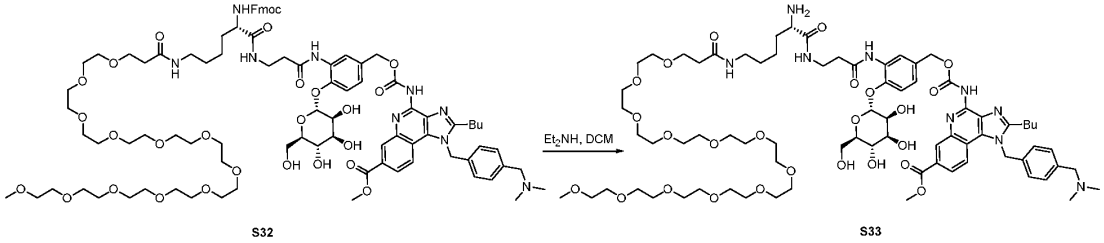


S31 S1a S32

[0582] Synthestis of methyl 4-((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (**S33**). Intermediate **S33** was synthesized according to **SCHEME 30**. Intermediate **S32** (16.1mg, 9.1 µmol) was dissolved in 1 mL of a 4:1 (v/v) mixture of DCM/Et_2NHmL. The reaction mixture was stirred at room temperature for 1 h. After 1 hour, solvents were removed *in vacuo* and the crude reaction mixture was diluted with DMSO/water, and purified by RP-HPLC (Method A) to give intermediate **S33** (10.2 mg, 6.6

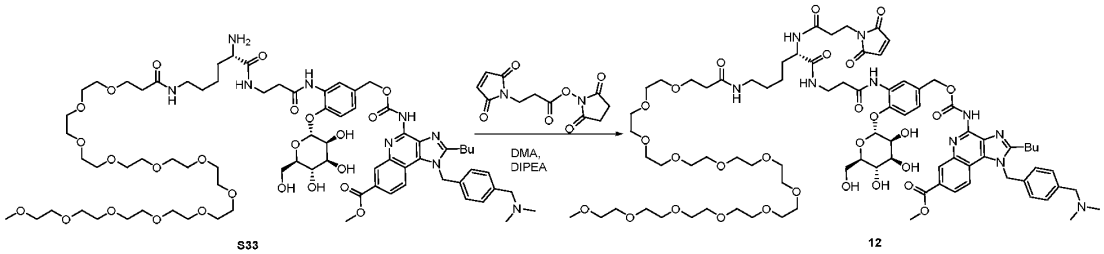
μmol, 72.2%) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1542.80 (theoretical); 1543.27 (observed). HPLC retention time = 1.56 min (Method D).

SCHEME 30



[0583] Synthesis of methyl 2-butyl-1-(4-((dimethylamino)methyl)benzyl)-4-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (**12**). Compound **12** was generated according to **SCHEME 31**. Intermediate **S33** (17.7 mg, 0.01 mmol) and mp-OSu (3.99 mg, 0.015 mmol) were dissolved in anhydrous DMA (0.5 mL) and DIPEA (10.4 μL, 0.06 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 45 min. After 45 min, the reaction mixture was quenched with HOAc (10 μL), diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound **12** (14.9 mg, 0.008 mmol, 82.5 %) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1693.8 (theoretical); 1694.4 (observed). HPLC retention time = 1.66 min (Method D).

SCHEME 31



EXAMPLE 13

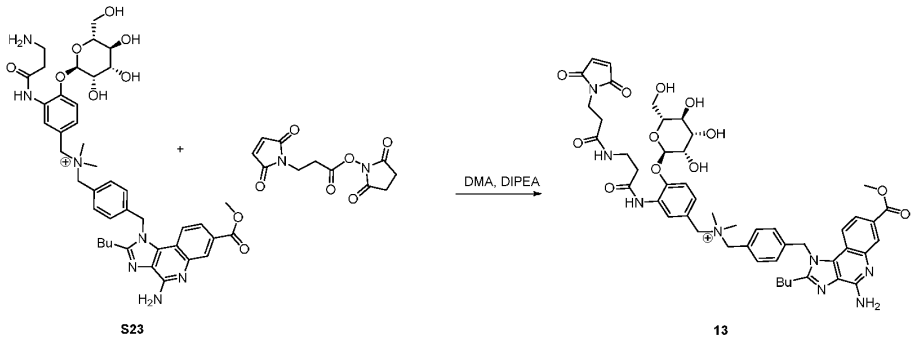
Syntheses of two drug-linker conjugates

[0584] This example covers syntheses of two complexes comprising a linker coupled to a N1 positions of imidazoquinoline TLR7/8 agonists with either carboxylic acid or methyl ester functionalization at their C7 positions, namely N-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-

yl)propanamido)propanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**13**) and N-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**14**).

[0585] Synthesis of N-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**13**). Compound **13** was synthesized according to **SCHEME 32**. Intermediate **S23** (1.9 mg, 1.85 µmol) and mp-OSu (0.64 mg, 0.002 mmol) were dissolved in anhydrous DMA (0.1 mL) and DIPEA (1.61 µLµL, 0.009 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 90 min. After 90 min, the reaction mixture was quenched with HOAc (10 µL), diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound **13** (1.8 mg, 0.002 mmol, 91.4 %) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 951.43 (theoretical); 951.62 (observed). HPLC retention time = 1.27 min (Method D).

SCHEME 32

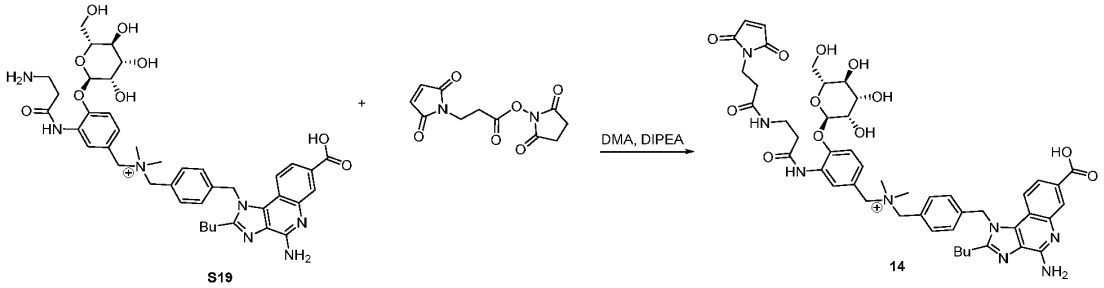


S23 **13**

[0586] N-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**14**). Synthesis of compound **14** was performed according to **SCHEME 33**. Intermediate **S19** (3.5 mg, 3.45 µmol) and mp-OSu (1.38 mg, 0.005 mmol) were dissolved in anhydrous DMA (0.2 mL) and DIPEA (3.0 µL, 0.017 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 90 min. After 90 min, the reaction mixture was quenched with HOAc (10 µL), diluted with DMSO/water, and purified by RP-

HPLC (Method A) to give compound **14** (1.7 mg, 0.002 mmol, 52.6 %) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 937.41 (theoretical); 937.58 (observed). HPLC retention time = 1.21 min (Method D).

SCHEME 33

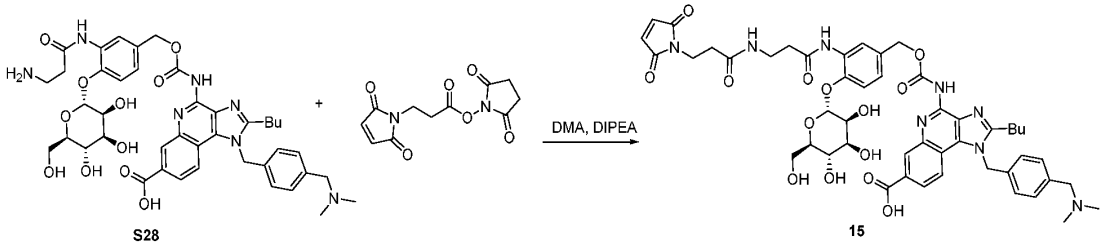


EXAMPLE 14

Syntheses of a drug-linker conjugate

[0587] This example covers synthesis of a complex comprising a linker coupled to a C4 amine of an imidazoquinoline TLR7/8 agonist with carboxylic acid functionalization at its C7 position and N1 phenyl functionalization, namely 2-butyl-1-(4-((dimethylamino)methyl)benzyl)-4-((((3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**15**). This synthesis was performed according to **SCHEME 34**. Intermediate **S28** (25.5 mg, 0.024 mmol) and mp-OSu (9.62 mg, 0.036 mmol) were dissolved in anhydrous DMA (1.5 mL) and DIPEA (21 µL, 120.5 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 30 min. After 30 min, the reaction mixture was quenched with HOAc (25 µL), diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound **15** (20.6 mg, 21.0 mmol, 87.1 %) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 981.39 (theoretical); 981.61 (observed). HPLC retention time = 1.32 min (Method D).

SCHEME 34

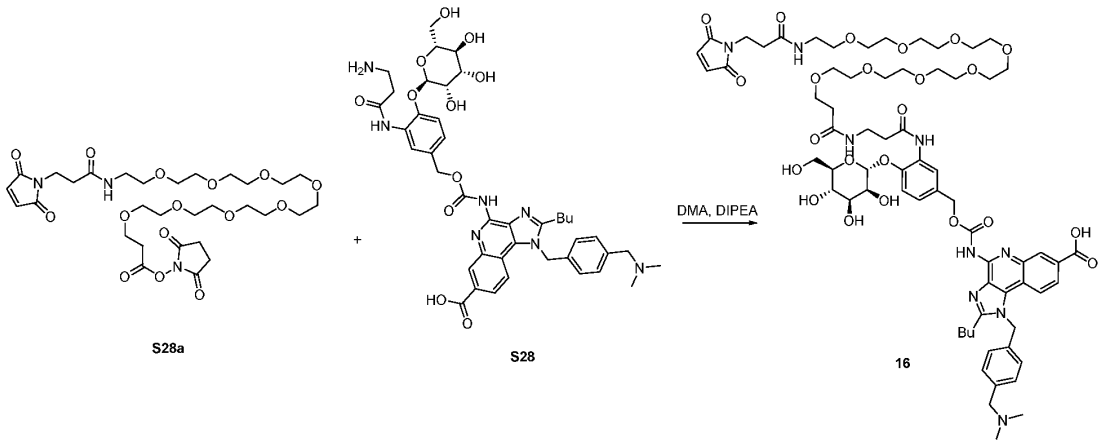


EXAMPLE 15

Syntheses of a drug-linker conjugate

[0588] This example covers synthesis of a complex comprising a linker coupled to a C4 amine of an imidazoquinoline TLR7/8 agonist with carboxylic acid functionalization at its C7 position and N1 phenyl functionalization, namely 2-butyl-1-(4-((dimethylamino)methyl)benzyl)-4-((((3-(1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,31-dioxo-7,10,13,16,19,22,25,28-octaoxa-4,32-diazapentatriacontan-35-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**16**). This synthesis is summarized in **SCHEME 35**. Intermediate **S28** (7.1 mg, 67 μmmol) and **S28a** (mp-PEG8-OSu, Broadpharm, 6.94 mg, 0.01 mmol) were dissolved in anhydrous DMA (1.3 mL) and DIPEA (7.0 μL, 0.04 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 1 h. After 1 h, the reaction mixture was quenched with HOAc (10 μL), diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound **16** (5.8 mg, 38 μmol, 56.9 %) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1404.64 (theoretical); 1405.09 (observed). HPLC retention time = 1.56 min (Method D).

SCHEME 35



EXAMPLE 16

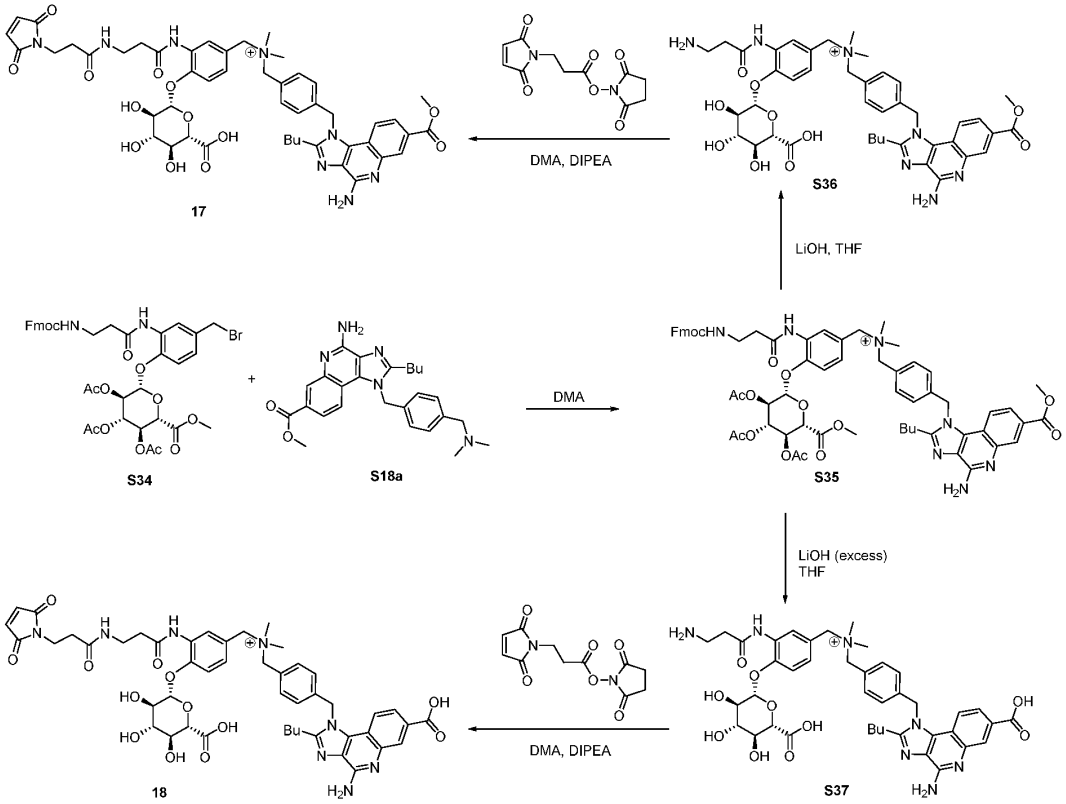
Syntheses of two drug-linker conjugates

[0589] This example covers syntheses of complexes comprising linkers coupled to a N1 positions of imidazoquinoline TLR7/8 agonists with carboxylic acid or methyl ester functionalization at their C7 positions, namely N-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-

yl)propanamido)propanamido)phenyl)-*N,N*-dimethylmethanaminium (**17**) and N-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)phenyl)-*N,N*-dimethylmethanaminium (**18**). As outlined in **SCHEME 36**, the syntheses of compounds **18** and **17** was similar to the syntheses of compounds **13** and **14**, respectively.

[0590] The synthesis of compound **18** and compound **17** was similar to the synthesis of compound **13** and compound **14**, respectively.

SCHEME 36



[0591] Compound **S34** was prepared according to the procedures as described in Burke, et al. *Mol. Cancer Ther.* Vol. 17, 1752-1760 (2018).

[0592] N-(3-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(((2S,3R,4S,5S,6S)-3,4,5-triacetoxy-6-(methoxycarbonyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)-1-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)phenyl)-*N,N*-dimethylmethanaminium (**S35**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1176.49 (theoretical); 1176.77 (observed). HPLC retention time = 1.83 min (Method D).

[0593] N-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-aminopropanamido)-4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**S36**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 814.38 (theoretical); 814.56 (observed). HPLC retention time = 1.23 min (Method D).

[0594] N-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-aminopropanamido)-4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**S37**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 800.36 (theoretical); 800.53 (observed). HPLC retention time = 1.12 min (Method D).

[0595] N-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)phenyl)-*N,N*-dimethylmethanaminium (**17**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 965.40 (theoretical); 965.42 (observed). HPLC retention time = 1.43 min (Method D).

[0596] N-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)phenyl)-*N,N*-dimethylmethanaminium (**18**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 951.39 (theoretical); 951.60 (observed). HPLC retention time = 1.31 min (Method D).

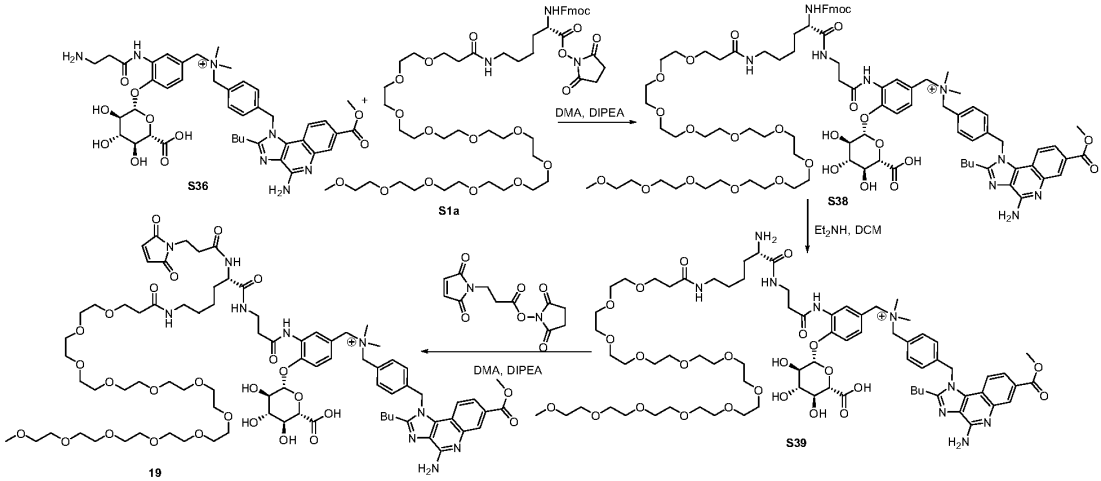
EXAMPLE 17

Syntheses of two drug-linker conjugates

[0597] This example covers syntheses of complexes comprising linkers coupled to a N1 positions of imidazoquinoline TLR7/8 agonists with carboxylic acid or methyl ester functionalization at their C7 positions, namely N-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)phenyl)-*N,N*-dimethylmethanaminium (**19**) and N-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)phenyl)-*N,N*-dimethylmethanaminium (**20**). The syntheses of

compound **20** and **19** are similar to the syntheses of compounds **9** and **10**, respectively. Syntheses of intermediates **S38** and **S39** and compound **19** are outlined in **SCHEME 37**. Synthesis of intermediates **S40** and **S41** and compound **20** are outlined in **SCHEME 38**.

SCHEME 37

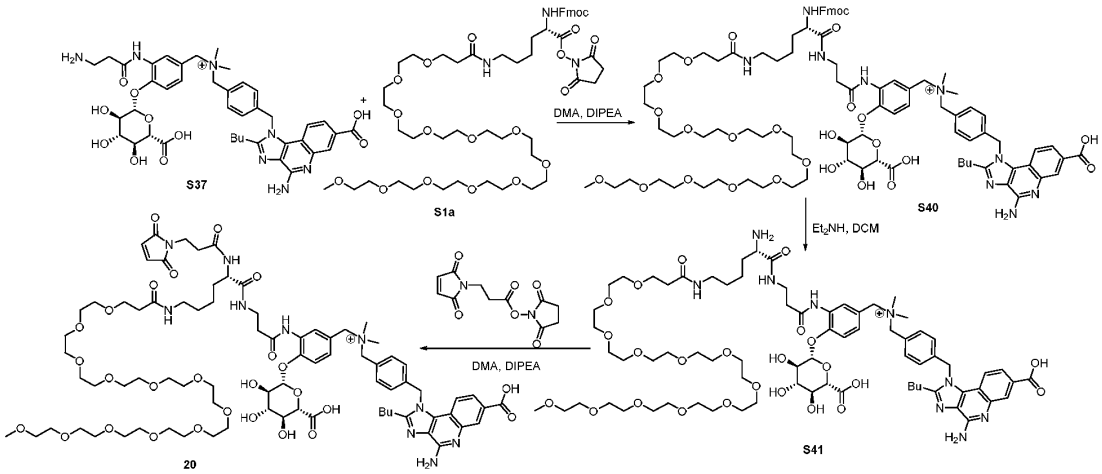


[0598] *N*-(3-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)benzyl)-1-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)phenyl)-*N,N*-dimethylmethanaminium (**S38**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1734.87 (theoretical); 1735.30 (observed). HPLC retention time = 1.73 min (Method D).

[0599] *N*-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**S39**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1511.79 (theoretical); 1513.12 (observed). HPLC retention time = 1.40 min (Method D).

[0600] *N*-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)phenyl)-*N,N*-dimethylmethanaminium (**19**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1663.82 (theoretical); 1664.24 (observed). HPLC retention time = 1.53 min (Method D).

SCHEME 38



[0601] *N*-(3-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)benzyl)-1-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)phenyl)-*N,N*-dimethylmethanaminium (**S40**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1720.85 (theoretical); 1721.22 (observed). HPLC retention time = 1.58 min (Method D).

[0602] *N*-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**S41**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1498.78 (theoretical); 1499.19 (observed). HPLC retention time = 1.37 min (Method D).

[0603] *N*-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)phenyl)-*N,N*-dimethylmethanaminium (**20**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1649.81 (theoretical); 1650.22 (observed). HPLC retention time = 1.48 min (Method D).

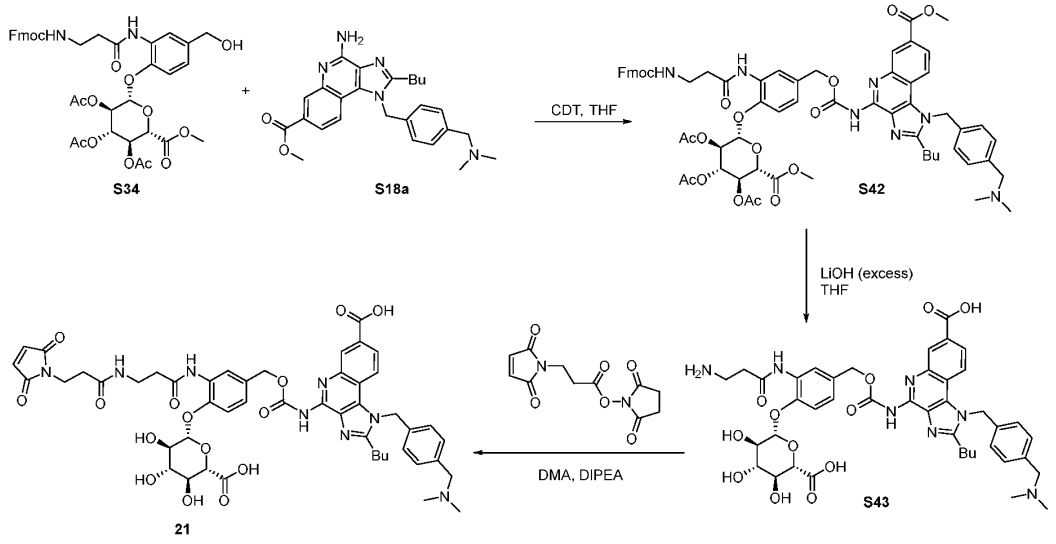
EXAMPLE 18

Syntheses of two drug-linker conjugates

[0604] This example covers synthesis of complexes comprising linkers coupled to C4 amines of imidazoquinoline TLR7/8 agonists with C7 carboxylic acid functionalization, namely

2-butyl-4-((((4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)benzyl)oxy)carbonyl)amino)-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**21**) and 2-butyl-4-((((4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)benzyl)oxy)carbonyl)amino)-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**22**). The syntheses of compounds **21** and **22** are outlined in **SCHEMES 39** and **40**, respectively. The syntheses of compounds **21** and **22** were similar to the syntheses of compounds **11** and **15**, respectively.

SCHEME 39



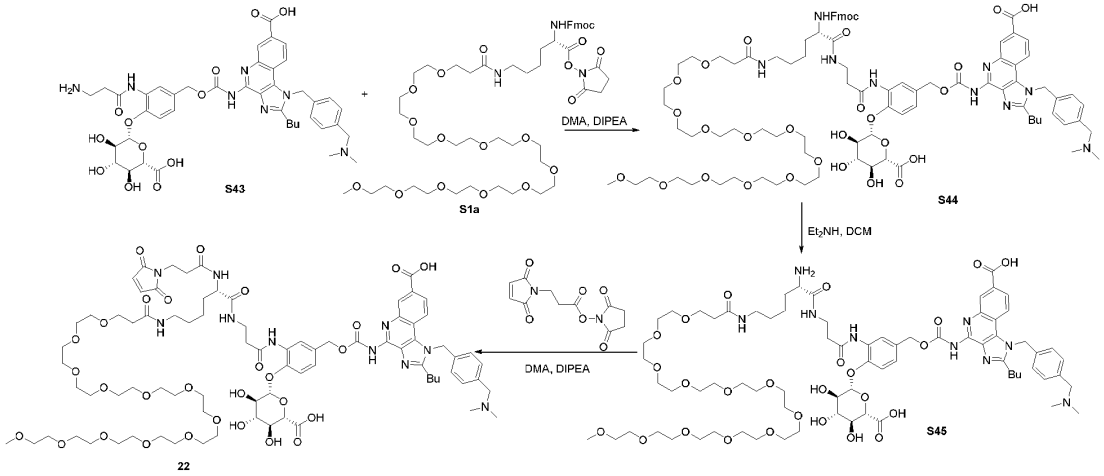
[0605] (2S,3R,4S,5S,6S)-2-(2-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((2-butyl-1-(4-((dimethylamino)methyl)benzyl)-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**S42**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1220.48 (theoretical); 1220.92 (observed). HPLC retention time = 1.70 min (Method E).

[0606] 4-((((3-(3-aminopropanamido)-4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S43**) as TFA

salt, white solid. LCMS: m/z $[M+H]^+$ = 844.34 (theoretical); 844.66 (observed). HPLC retention time = 1.30 min (Method D).

[0607] 2-butyl-4-((((4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)benzyl)oxy)carbonyl)amino)-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**21**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 995.37 (theoretical); 995.73 (observed). HPLC retention time = 1.44 min (Method D).

SCHEME 40



[0608] (2S,3S,4S,5R,6S)-6-(2-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((2-butyl-1-(4-((dimethylamino)methyl)benzyl)-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (**S44**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1764.83 (theoretical); 1766.24 (observed). HPLC retention time = 1.76 min (Method D).

[0609] 4-((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S45**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1542.76 (theoretical); 1543.22 (observed). HPLC retention time = 1.51 min (Method D).

[0610] 2-butyl-4-((((4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-

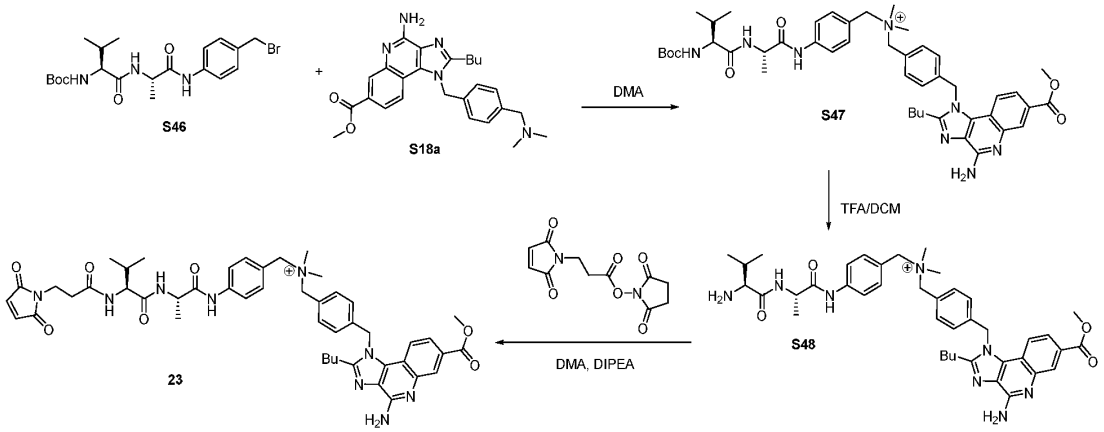
amido)benzyl)oxy)carbonyl)amino)-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**22**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1693.79 (theoretical); 1694.36 (observed). HPLC retention time = 1.61 min (Method D).

EXAMPLE 19

Synthesis of a drug-linker conjugate

[0611] This example covers synthesis of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with C7 methyl ester functionalization, namely *N*-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)propanamido)phenyl)-*N,N*-dimethylmethanaminium (**23**). This synthesis is outlined in **SCHEME 41**.

SCHEME 41



[0612] Compound S46 was prepared according to the procedures as described in WO2016040684.

[0613] *N*-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-((S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)propanamido)phenyl)-*N,N*-dimethylmethanaminium (S47). Compound S46 (16.6 mg, 0.036 mmol) and S18a (13.0 mg, 0.030 mmol) were dissolved in DMA (0.6 mL). The reaction was heated at 50 °C for 2 h and the reaction progress was monitored by LCMS. After 2 h, the reaction mixture was diluted with DMSO /water, and purified by RP-HPLC (Method A) to provide S47 (18.6 mg, 0.022 mmol, 77.6%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 821.47 (theoretical); 821.66 (observed). HPLC retention time = 1.62 min (Method D).

[0614] *N*-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-((S)-2-((S)-2-amino-3-methylbutanamido)propanamido)phenyl)-*N,N*-

dimethylmethanaminium (S48). Intermediate S47 (18.6 mg, 0.022 mmol) was dissolved in 0.6 mL of a 5:1 (v/v) mixture of DCM/TFA and stirred at room temperature for 30 min, after which the solvents were removed *in vacuo*. The crude reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to provide S48 (13.5 mg, 0.019 mmol, 82.5%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 721.42 (theoretical); 721.56 (observed). HPLC retention time = 1.26 min (Method D).

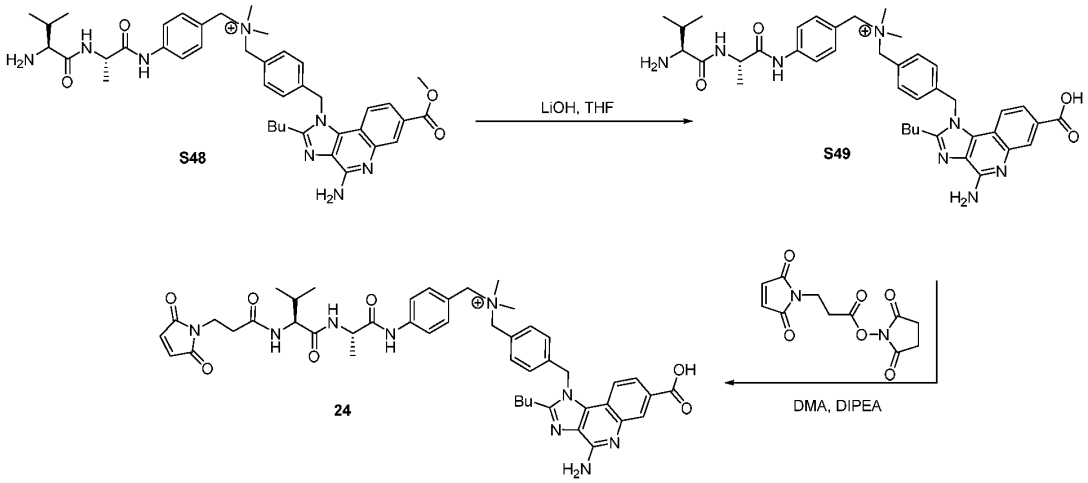
[0615] *N*-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)propanamido)phenyl)-*N,N*-dimethylmethanaminium (23). Intermediate S48 (3.20 mg, 0.004 mmol) and mp-OSu (1.53 mg, 0.006 mmol) were dissolved in anhydrous DMA (0.2 mL) and DIPEA (3.33 µL, 0.019 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 30 min. After 30 min, the reaction mixture was quenched with HOAc (5 µl), diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound 23 (1.6 mg, 0.02 mmol, 42.3%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 872.45 (theoretical); 872.64 (observed). HPLC retention time = 1.51 min (Method D).

EXAMPLE 20

Synthesis of a drug-linker conjugate

[0616] This example covers synthesis of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with C7 carboxylic acid functionalization, namely *N*-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)propanamido)phenyl)-*N,N*-dimethylmethanaminium (24). This synthesis is outlined in SCHEME 42.

SCHEME 42



[0617] Synthesis of *N*-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-((S)-2-((S)-2-amino-3-methylbutanamido)propanamido)phenyl)-*N,N*-dimethylmethanaminium (S49). Intermediate S48 (9.1 mg, 0.011 mmol) was dissolved in THF/MeOH (0.3 mL/0.05 mL) followed by the addition of an aqueous LiOH solution (0.5M, 0.109 mL, 0.054 mmol). The reaction mixture was stirred at room temperature for 90 min. After 90 min, the reaction mixture was quenched with HOAc (6.5 µL). THF was removed *in vacuo* and the crude product was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate S49 (4.6 mg, 0.006 mmol, 59.5 %) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 707.40 (theoretical); 707.55 (observed). HPLC retention time = 1.25 min (Method D).

[0618] Synthesis of *N*-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)propanamido)phenyl)-*N,N*-dimethylmethanaminium (24). Intermediate S49 (3.90 mg, 0.005 mmol) and mp-OSu (1.90 mg, 0.007 mmol) were dissolved in anhydrous DMA (0.2 mL) and DIPEA (4.13 µL, 0.024 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 30 min. After 30 min, the reaction mixture was quenched with HOAc (5 µL), diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound 24 (2.7 mg, 0.03 mmol, 66.2%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 858.43 (theoretical); 858.62 (observed). HPLC retention time = 1.48 min (Method D).

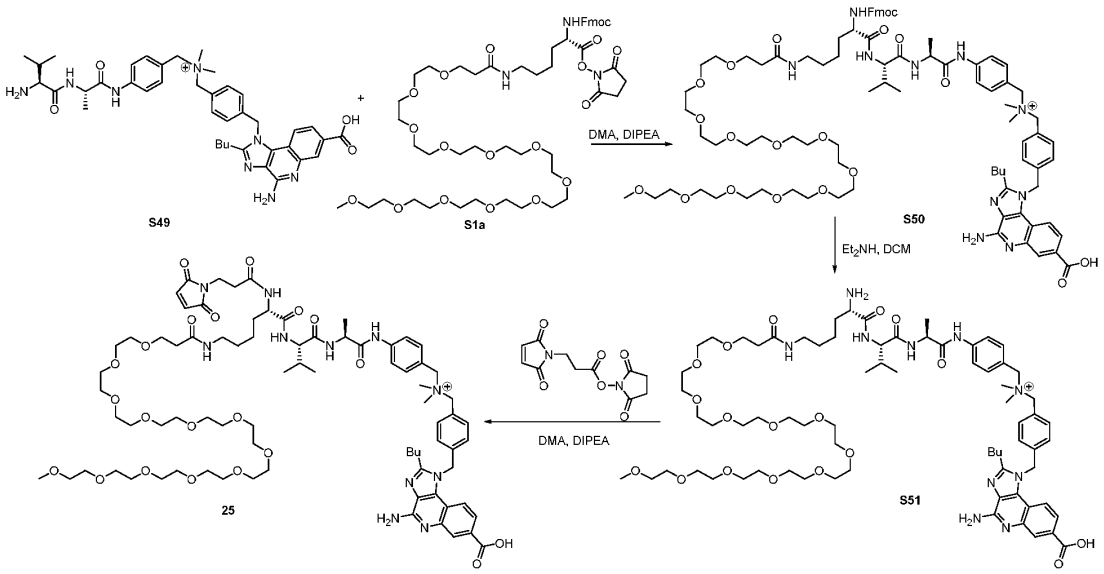
EXAMPLE 21

Synthesis of a drug-linker conjugate

[0619] This example covers synthesis of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with C7 carboxylic acid functionalization,

namely *N*-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-((44S,47S,50S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-47-isopropyl-50-methyl-38,45,48-trioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46,49-triazahenpentacontan-51-amido)phenyl)-*N,N*-dimethylmethanaminium (25). As outlined in SCHEME 43, synthesis of compound 25 was similar to the synthesis of compound 9.

SCHEME 43



[0620] *N*-(4-((44S,47S,50S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-47-isopropyl-50-methyl-38,45,48-trioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46,49-triazahenpentacontan-51-amido)benzyl)-1-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)phenyl)-*N,N*-dimethylmethanaminium (**S50**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1628.89 (theoretical); 1629.27 (observed). HPLC retention time = 1.70 min (Method D).

[0621] *N*-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-((44S,47S,50S)-44-amino-47-isopropyl-50-methyl-38,45,48-trioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46,49-triazahenpentacontan-51-amido)phenyl)-*N,N*-dimethylmethanaminium (**S51**) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1405.82 (theoretical); 1406.17 (observed). HPLC retention time = 1.28 min (Method D).

[0622] *N*-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(4-((44S,47S,50S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-47-isopropyl-50-methyl-38,45,48-trioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46,49-triazahenpentacontan-51-amido)phenyl)-*N,N*-dimethylmethanaminium (**25**) as TFA salt, white

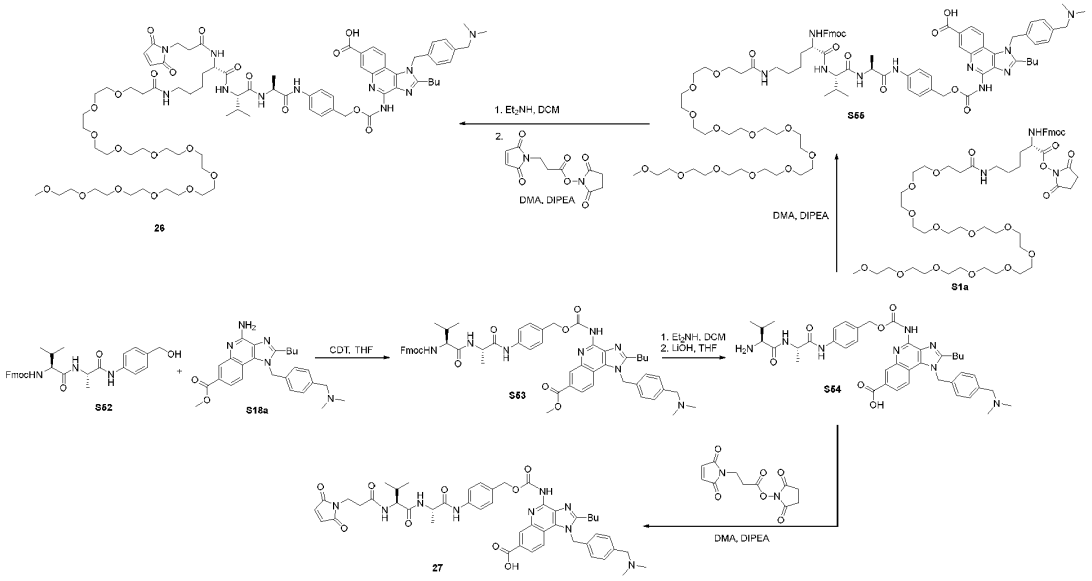
solid. LCMS: m/z $[M]^+$ = 1556.85 (theoretical); 1556.83 (observed). HPLC retention time = 1.50 min (Method D).

EXAMPLE 22

Syntheses of two drug-linker conjugates

[0623] This example covers syntheses of two complexes comprising linkers coupled to C4 amines of imidazoquinoline TLR7/8 agonists with C7 carboxylic acid functionalization, namely 2-butyl-1-(4-((dimethylamino)methyl)benzyl)-4-((((4-((44S,47S,50S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-47-isopropyl-50-methyl-38,45,48-trioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46,49-triazahenpentacontan-51-amido)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**26**) and 2-butyl-1-(4-((dimethylamino)methyl)benzyl)-4-((((4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)propanamido)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**27**). The syntheses of compounds **26** and **27** were similar to the syntheses of compounds **11** and **15**, respectively, and are outlined in **SCHEME 44**.

SCHEME 44



[0624] Compound **S52** was prepared according to the procedures as described in Wang et al. *Int. J. Mol. Sci.* Vol. 18, No. 9, 1860 (2017).

[0625] Methyl 4-((((4-((S)-2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)propanamido)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (**S53**) as TFA salt,

white solid. LCMS: m/z $[M+H]^+$ = 987.41 (theoretical); 987.51 (observed). HPLC retention time = 1.68 min (Method D).

[0626] 4-((((4-((S)-2-((S)-2-amino-3-methylbutanamido)propanamido)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S54**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 751.39 (theoretical); 751.42 (observed). HPLC retention time = 1.31 min (Method D).

[0627] 4-((((4-((44S,47S,50S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-47-isopropyl-50-methyl-38,45,48-trioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46,49-triazahenpentacontan-51-amido)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-((dimethylamino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S55**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1671.87 (theoretical); 1671.68 (observed). HPLC retention time = 1.92 min (Method D).

[0628] 2-butyl-1-(4-((dimethylamino)methyl)benzyl)-4-((((4-((44S,47S,50S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-47-isopropyl-50-methyl-38,45,48-trioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46,49-triazahenpentacontan-51-amido)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**26**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1600.83 (theoretical); 1600.57 (observed). HPLC retention time = 1.59 min (Method D).

[0629] 2-butyl-1-(4-((dimethylamino)methyl)benzyl)-4-((((4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)propanamido)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**27**) as TFA salt, white solid. LCMS: m/z $[M+Li]^+$ = 924.46 (theoretical); 924.28 (observed). HPLC retention time = 1.58 min (Method D).

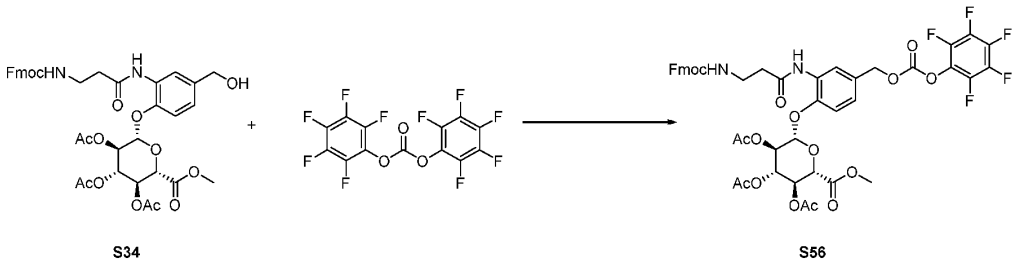
EXAMPLE 23

Synthesis of a drug-linker conjugate

[0630] This example covers synthesis of a complex comprising a PEGylated linker coupled to a C4 amine of an imidazoquinoline TLR7/8 agonist lacking C7 functionalization, namely (2S,3S,4S,5R,6S)-6-(2-((S)-44-((S)-3-amino-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (**28**).

[0631] Synthesis of (2S,3R,4S,5S,6S)-2-(2-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((perfluorophenoxy)carbonyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**S56**). Synthesis of intermediate **S56** is outlined in **SCHEME 45**. Intermediate **S34** (2.6 g, 3.47 mmol) and bis-(pentafluorophenyl) carbonate (Combi-Blocks Inc. 1.64 g, 4.16 mmol) were dissolved in DCM (30 mL), followed by the addition of DIPEA (1.21 ml, 7.94 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature and the reaction progress was monitored by LCMS. Solvent was removed and the crude product was purified by Biotage (Method B) to give **S56** as white solid (2.78 g, 2.90 mmol, 83.5%). LCMS: m/z $[M+H]^+$ = 959.2298 (theoretical); 959.0625 (observed). HPLC retention time = 1.81 min (Method C).

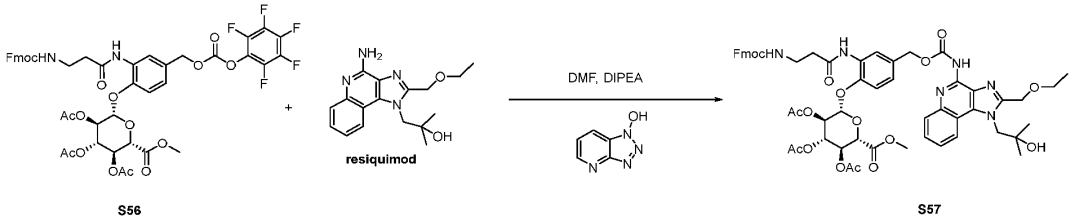
SCHEME 45



S34 S56

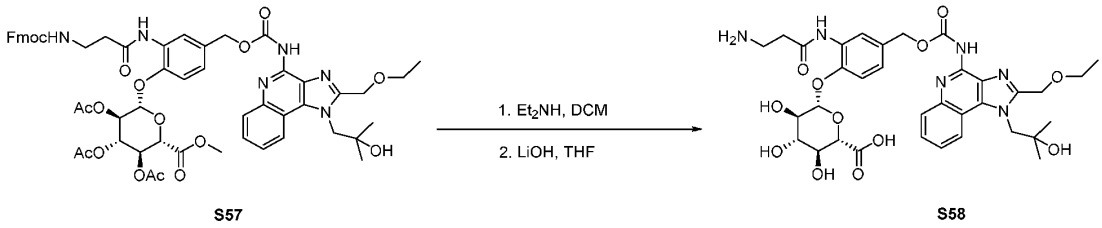
[0632] Synthesis of (2S,3R,4S,5S,6S)-2-(2-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S57). Intermediate S57 was synthesized as outlined in SCHEME 46. Resiquimod (Asta Tech, 100 mg, 0.318 mmol) and S56 (457.5 mg, 0.477 mmol) were dissolved in anhydrous DMF (3 mL) followed by the addition of DIPEA (0.166 mL, 0.954 mmol) and 1-hydroxy-7-azabenzotriazole (HOAt, 22 mg, 0.159 mmol). The reaction mixture was warmed up to 30 °C and stirred for 16 h, after which, LCMS indicated ~90% conversion of the starting material. Solvent was removed *in vacuo* and the crude reaction mixture was purified by RP-HPLC (Method A) to provide intermediate S57 (236.5 mg, 0.217 mmol, 68.3%) as TFA salt. LCMS: m/z $[M+H]^+$ = 1089.40 (theoretical); 1089.47 (observed). HPLC retention time = 1.44 min (Method C).

SCHEME 46



[0633] Synthesis of (2S,3S,4S,5R,6S)-6-(2-(3-aminopropanamido)-4-((((2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (S58). Intermediate S58 was synthesized as outlined in SCHEME 47. Intermediate S57 (473 mg, 0.474 mmol) was dissolved in DCM (5 mL) at room temperature followed by the addition of Et_2NH (1 mL). The reaction mixture was stirred at room temperature for 4 h. After 4 h, solvents were removed *in vacuo* and the crude reaction mixture was re-dissolved in THF (9 mL) at 0 °C and an aqueous LiOH solution (0.2 M, 10.9 mL, 2.172 mmol) was added. The resulting reaction mixture was stirred at 0 °C for 90 min. After 30 min, HOAc (0.124 mL, 2.172 mmol) was added to neutralize the reaction mixture. Solvents were removed *in vacuo* and the crude product was diluted with water/DMSO and purified by RP-HPLC (method A) to give intermediate S58 (292 mg, 0.308 mmol, 70.9%) as TFA salt. LCMS: m/z $[M+H]^+$ = 727.29 (theoretical); 727.24 (observed). HPLC retention time = 1.31 min (Method C).

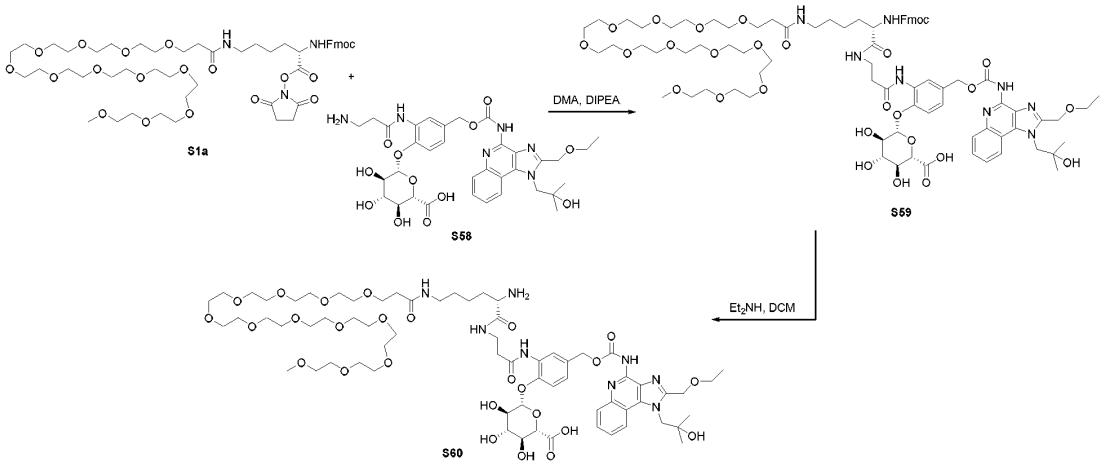
SCHEME 47



[0634] Synthesis of (2S,3S,4S,5R,6S)-6-(2-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (S60). Intermediate S60 was synthesized according to SCHEME 48. Intermediates S58 (180 mg, 0.184 mmol) and S20 (247.2 mg, 0.239 mmol) were dissolved in anhydrous DMA (0.5 mL) and DIPEA (0.127 mL, 0.734 mmol) at room temperature. The reaction mixture was stirred at room temperature for 20 min. After 20 min, the crude reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to give intermediate S59 (209 mg, 0.127 mmol, 69.1%)

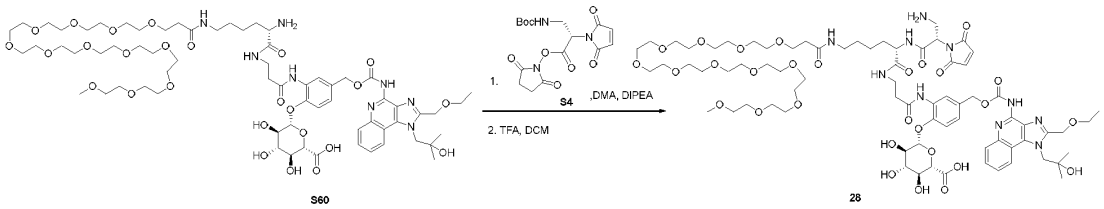
as white solid. LCMS: m/z $[M+H]^+$ = 1647.77 (theoretical); 1648.32 (observed). HPLC retention time = 1.49 min (Method C). Intermediate S59 was dissolved in DCM/Et_2NH mixture and the reaction mixture was stirred at room temperature for 30 min, upon which LCMS analysis indicated full conversion of the starting material. Solvents were removed in varuo and the crude product was dissolved with DMSO/water, and purified by RP-HPLC (Method A) to give intermediate S60 (139.4 mg, 0.097 mmol, 77.1%) as TFA salt. LCMS: m/z $[M+H]^+$ = 1425.71 (theoretical); 1425.77 (observed). HPLC retention time = 1.13 min (Method C).

SCHEME 48



[0635] Synthesis of (2S,3S,4S,5R,6S)-6-(2-((S)-44-((S)-3-amino-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (28). Compound 28 was synthesized as outlined in SCHEME 49. Intermediates S60 (47.2 mg, 0.031 mmol) and S4 (15.2 mg, 0.04 mmol) were dissolved in anhydrous DMA (0.3 mL) and DIPEA (0.016 mL, 0.092 mmol) at room temperature. The reaction was stirred at room temperature for 1 h. After 1 hour, solvent was removed *in vacuo* and the crude reaction mixture was re-dissolved in DCM/TFA (10:1 (v/v), 0.5 mL), and the reaction mixture was stirred at room temperature for 30 min. Solvent was then removed and the crude reaction mixture was diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound 28 (26.2 mg, 0.015 mmol, 50.1%) as TFA salt. LCMS: m/z $[M+H]^+$ = 1591.74 (theoretical); 1592.05 (observed). HPLC retention time = 1.16 min (Method C).

SCHEME 49

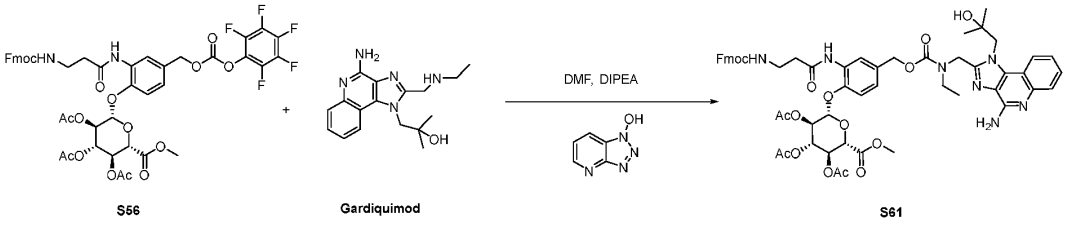


EXAMPLE 24

Synthesis of a drug-linker conjugate

[0636] This example covers synthesis of a complex comprising a linker coupled to a C2 position of an imidazoquinoline TLR7/8 agonist lacking C7 functionalization, namely (2S,3S,4S,5R,6S)-6-(4-(((((4-amino-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-2-yl)methyl)(ethyl)carbamoyl)oxy)methyl)-2-(3-((S)-3-amino-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (29).Synthesis of (2S,3R,4S,5S,6S)-2-(2-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(((((4-amino-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-2-yl)methyl)(ethyl)carbamoyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S61). SCHEME 50 outlines a synthetic scheme for intermediate S61. Gardiquimod (Sigma-Aldrich, 10.0 mg, 0.032 mmol) and S56 (34.99 mg, 0.038 mmol) were dissolved in anhydrous DMF (0.3 mL), followed by the addition of pyridine (0.06 mL) and HOAt (2.0 mg, 0.013 mmol). The reaction mixture was stirred for 3 h, upon which LCMS indicated full conversion of the starting material. The crude reaction mixture was diluted, and purified by RP-HPLC (Method A) to provide intermediate S61 (20.2 mg, 0.019 mmol, 58.2%) as TFA salt. LCMS: m/z $[M+H]^+$ = 1088.42 (theoretical); 1088.67 (observed). HPLC retention time = 1.56 min (Method D).

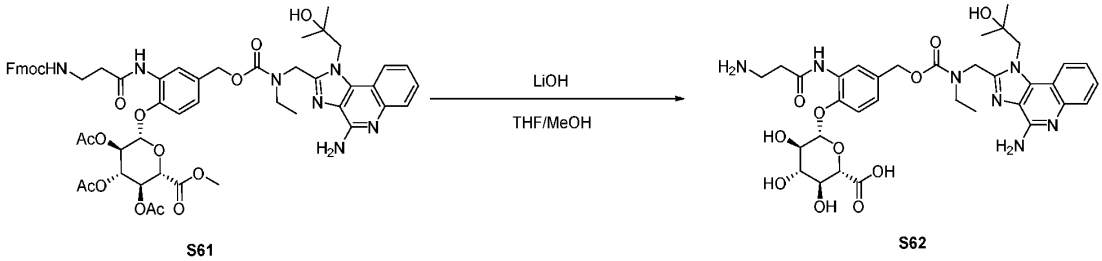
SCHEME 50



[0637] Synthesis of (2S,3S,4S,5R,6S)-6-(4-(((((4-amino-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-2-yl)methyl)(ethyl)carbamoyl)oxy)methyl)-2-(3-aminopropanamido)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (S62). SCHEME 51 outlines a synthetic scheme for generating intermediate S62. Intermediate S61

(20.2 mg, 0.019 mmol) was dissolved in 1.0 mL of a 1:1 (v/v) THF/MeOH mixture and the resulting reaction mixture was stirred at 0 °C for 5 min, followed by the addition of aqueous LiOH (0.2M, 0.928 mL). The reaction mixture was stirred at 0 °C for 30 min, and was then warmed up to room temperature and stirred for another 4 h. After 4 h, the reaction mixture was neutralized with HOAc (5 µL), diluted with water/DMSO, and purified by RP-HPLC (Method A) to give intermediate S62 (16 mg, 0.019 mmol, 100 %) as TFA salt. LCMS: m/z $[M+H]^+$ = 726.30 (theoretical); 726.49 (observed). HPLC retention time = 0.62 min (Method D).

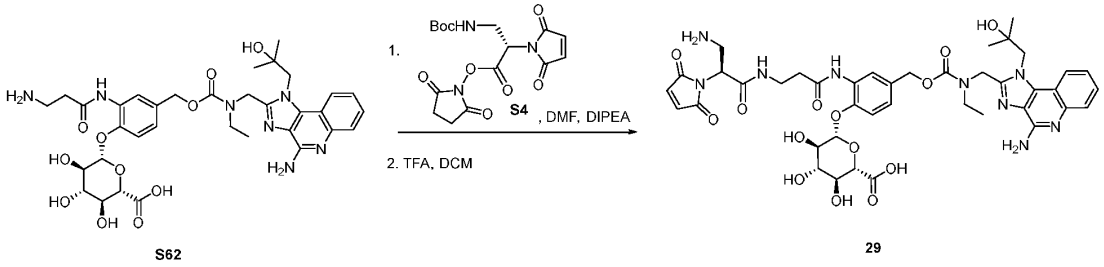
SCHEME 51



S61 S62

[0638] Synthesis of (2S,3S,4S,5R,6S)-6-(4-(((((4-amino-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-2-yl)methyl)(ethyl)carbamoyl)oxy)methyl)-2-(3-((S)-3-amino-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (29). Compound 29 was synthesized as outlined in SCHEME 52. Intermediates S62 (16.0 mg, 0.019 mmol) and S4 (7.99 mg, 0.021 mmol) were dissolved in anhydrous DMF (0.2 mL) and DIPEA (0.01 mL, 0.057 mmol) at room temperature. The reaction mixture was stirred at room temperature for 15 min. After 15min, the crude reaction mixture was neutralized with acetic acid (2 µL), diluted with DMSO/water and purified by RP-HPLC (Method A) to give the Boc-protected compound 29 (9.0 mg, 0.009 mmol, 47.6%) as TFA salt, which was used in subsequent step without further purification. LCMS: m/z $[M+H]^+$ = 992.39 (theoretical); 992.62 (observed). HPLC retention time = 1.01 min (Method D). The crude Boc-protected compound 29 (9.0 mg, 0.009 mmol) was dissolved in DCM (1 mL) and TFA (0.25 mL) and the reaction mixture was stirred at room temperature for 30 min. After 30 min, solvents were removed *in vacuo* and the crude reaction mixture was re-dissolved in DMSO and purified by RP-HPLC (Method A) to give compound 29 (4.6 mg, 0.005 mmol, 50.4%) as TFA salt. LCMS: m/z $[M+H]^+$ = 892.34 (theoretical); 892.55 (observed). HPLC retention time = 0.68 min (Method D).

SCHEME 52



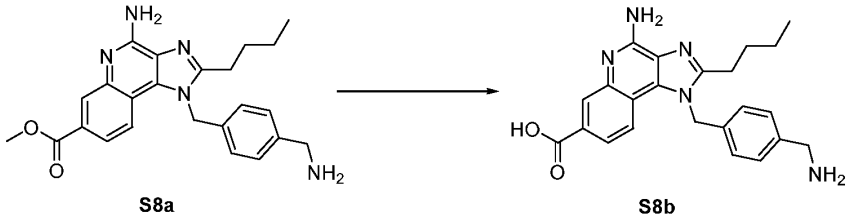
EXAMPLE 25

Synthesis of a drug-linker conjugate

[0639] This example covers synthesis of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with C7 carboxylic acid functionalization, namely 4-amino-2-butyl-1-(4-(21-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,19-dioxo-6,9,12,15-tetraoxa-2,18-diazahenicosyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (30).

[0640] Synthesis of 4-amino-1-(4-(aminomethyl)benzyl)-2-butyl-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (S8b). The synthesis of intermediate S8b is outlined in SCHEME 53. Intermediate S8a (8.3 mg, 0.02 mmol) was dissolved in THF (0.4 mL), followed by the addition of 0.5M LiOH (0.2 ml, 0.1 mmol) and the resulting mixture was stirred at room temperature for 2 h, after which the reaction was quenched with AcOH (6 µL) and solvents were removed *in vacuo*. The crude reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to provide S8b (7.5 mg, 0.012 mmol, 59.7%) as 2X TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 404.21 (theoretical); 404.26 (observed). HPLC retention time = 1.12 min (Method D).

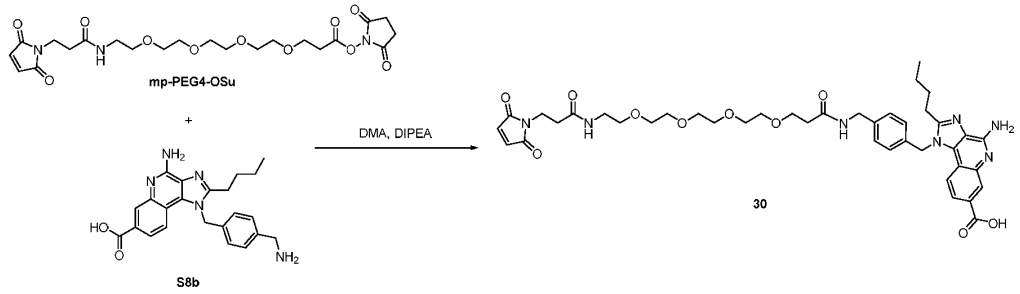
SCHEME 53



[0641] Synthesis of 4-amino-2-butyl-1-(4-(21-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,19-dioxo-6,9,12,15-tetraoxa-2,18-diazahenicosyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (30). Compound 30 was synthesized as outlined in SCHEME 54. 2,5-dioxopyrrolidin-1-yl 1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-oxo-7,10,13,16-tetraoxa-4-azanonadecan-19-oate (mp-PEG4-OSu, Broadpharm, 1.31 mg, 0.003 mmol) and S8b were dissolved in DMA (0.3 mL),

followed by the addition of DIPEA (1.85 µL, 0.011 mmol). The reaction mixture was stirred at room temperature for 30 min. After 30 min, the crude reaction mixture was neutralized with acetic acid (2 µL), diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound 30 (1.0 mg, 0.001 mmol, 58.7%) as TFA salt. LCMS: m/z $[M+H]^+$ = 802.37 (theoretical); 802.41 (observed). HPLC retention time = 1.56 min (Method C).

SCHEME 54

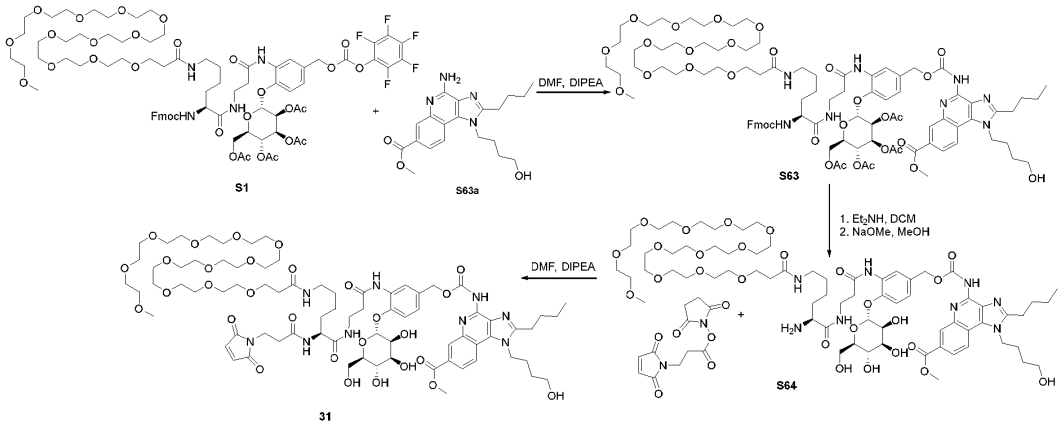


EXAMPLE 26

Synthesis of a drug-linker conjugate

[0642] This example covers synthesis of a complex comprising a linker coupled to a C4 amine of an imidazoquinoline TLR7/8 agonist with C7 methyl ester functionalization, namely methyl 2-butyl-4-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1-(4-hydroxybutyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (31). As outlined in SCHEME 55, the synthesis of compound 31 was similar to the synthesis of compound 1.

SCHEME 55



[0643] Compound **S63a** was prepared according to the procedures as described in Larson, et al. *ACS Med.Chem. Lett.* Vol. 8, No. 11, 1148-1152 (2017).

[0644] (2R,3S,4S,5R,6R)-2-(2-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((2-butyl-1-(4-hydroxybutyl)-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**S63**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1857.86 (theoretical); 1857.97 (observed). HPLC retention time = 2.02 min (Method C).

[0645] Methyl 4-((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-hydroxybutyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (**S64**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1467.75 (theoretical); 1468.94 (observed). HPLC retention time = 1.27 min (Method C).

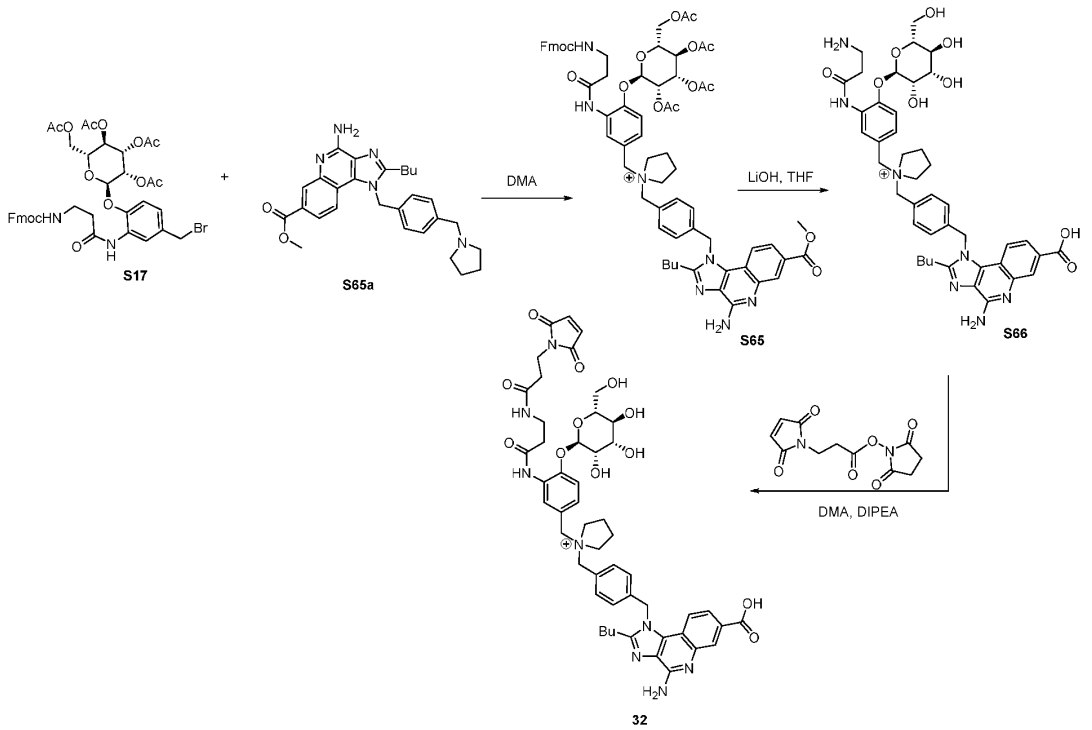
[0646] Methyl 2-butyl-4-((((3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1-(4-hydroxybutyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylate (**31**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1618.78 (theoretical); 1619.60 (observed). HPLC retention time = 1.33 min (Method C).

EXAMPLE 27

Synthesis of a drug-linker conjugate

[0647] This example covers synthesis of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with C7 carboxylic acid functionalization, namely 1-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)pyrrolidin-1-ium (32). As outlined in SCHEME 56, the synthesis of compound 32 was similar to the synthesis of compound 14.

SCHEME 56



[0648] Compound S65a was prepared according to the procedures as described in Larson, et al. *ACS Med.Chem. Lett.* Vol. 8, No. 11, 1148-1152 (2017).

[0649] 1-(3-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(((2R,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)-1-(4-((4-amino-2-butyl-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)pyrrolidin-1-ium (S65) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1216.52 (theoretical); 1216.38 (observed). HPLC retention time = 1.51 min (Method D).

[0650] 1-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-aminopropanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)pyrrolidin-1-ium (S66) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 812.40 (theoretical); 812.40 (observed). HPLC retention time = 1.16 min (Method D).

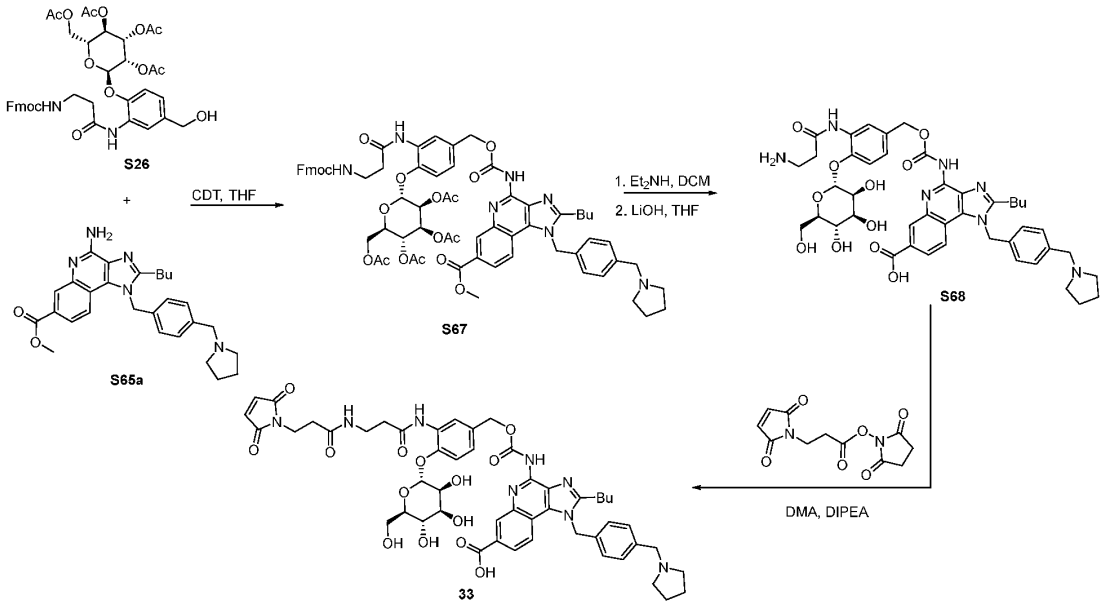
1-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)pyrrolidin-1-ium (32) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 963.43 (theoretical); 963.47 (observed). HPLC retention time = 1.29 min (Method D).

EXAMPLE 28

Synthesis of a drug-linker conjugate

[0651] This example covers synthesis of a complex comprising a linker coupled to a C4 amine of an imidazoquinoline TLR7/8 agonist with C7 carboxylic acid functionalization, namely 2-butyl-4-((((3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1-(4-(pyrrolidin-1-ylmethyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**33**). As outlined in **SCHEME 57**, the synthesis of compound **33** was similar to the synthesis of compound **15**.

SCHEME 57



[0652] (2R,3S,4S,5R,6R)-2-(2-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-((((2-butyl-7-(methoxycarbonyl)-1-(4-(pyrrolidin-1-ylmethyl)benzyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**S67**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1260.51 (theoretical); 1260.59 (observed). HPLC retention time = 2.09 min (Method D).

[0653] 4-((((3-(3-aminopropanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-2-butyl-1-(4-(pyrrolidin-1-ylmethyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S68**) as TFA salt, white solid. LCMS: m/z $[M+Na]^+$ = 878.38 (theoretical); 878.38 (observed). HPLC retention time = 1.25 min (Method D).

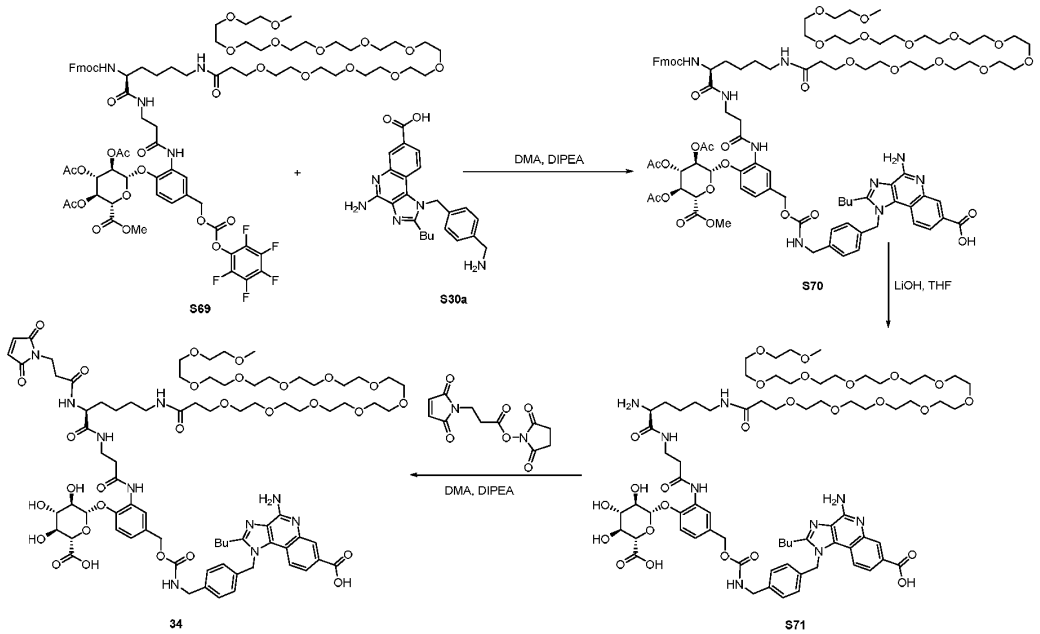
[0654] 2-butyl-4-((((3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1-(4-(pyrrolidin-1-ylmethyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**33**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1007.41 (theoretical); 1007.42 (observed). HPLC retention time = 1.38 min (Method D).

EXAMPLE 29

Synthesis of a drug-linker conjugate

[0655] This example covers synthesis of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with C7 carboxylic acid functionalization, namely 4-amino-2-butyl-1-(4-(((((4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)benzyl)oxy)carbonyl)amino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**34**). As outlined in **SCHEME 58**, the synthesis of compound **34** was similar to the synthesis of compound **3**.

SCHEME 58

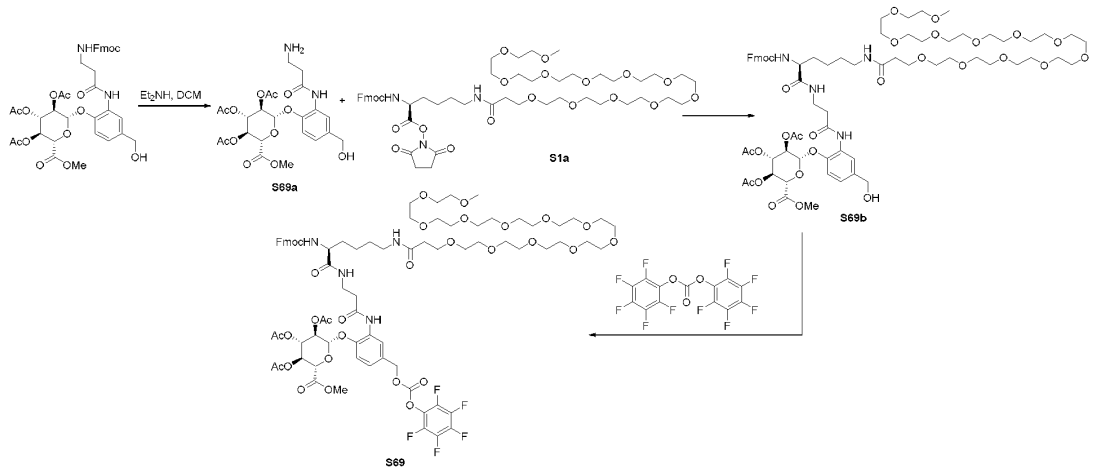


EXAMPLE 30

Synthesis of a PEGylated linker

[0656] This example covers synthesis of a PEGylated linker capable of dual binding to imidazoquinoline compounds and proteins, namely (2S,3R,4S,5S,6S)-2-(2-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((perfluorophenoxy)carbonyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**S69**). This synthesis is summarized in **SCHEME 59**.

SCHEME 59



[0657] Compound **S69** was prepared using similar procedures as those used in the synthesis of **S1**.

[0658] (2S,3R,4S,5S,6S)-2-(2-(3-aminopropanamido)-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (NH_2-Gluc-PAB-OH) (**S69a**): as light yellow solid LCMS: m/z $[M+H]^+$ = 527.19 (theoretical); 527.32 (observed). HPLC retention time = 1.58 min (Method C).

[0659] (2S,3R,4S,5S,6S)-2-(2-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (NH_2-Fmoc-LysPEG12-Gluc-OH) (**S69b**): as colorless liquid. LCMS: m/z $[M+H]^+$ = 1447.68 (theoretical); 1447.44 (observed). HPLC retention time = 1.85 min (Method C).

[0660] (2S,3R,4S,5S,6S)-2-(2-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((perfluorophenoxy)carbonyl)oxy)methyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-

pyran-3,4,5-triyl triacetate (**S69**) as colorless sticky liquid . LCMS: m/z $[M+H]^+$ = 1657.65 (theoretical); 1657.91 (observed). HPLC retention time = 2.21 min (Method C).

[0661] 1-(4-(((((3-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2S,3R,4S,5S,6S)-3,4,5-triacetoxy-6-(methoxycarbonyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)methyl)benzyl)-4-amino-2-butyl-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S70**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1877.85 (theoretical); 1877.27 (observed). HPLC retention time = 1.80 min (Method C).

[0662] 4-amino-1-(4-(((((3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)methyl)benzyl)-2-butyl-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**S71**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1514.73 (theoretical); 1515.51 (observed). HPLC retention time = 1.21 min (Method C).

[0663] 4-amino-2-butyl-1-(4-(((((4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)benzyl)oxy)carbonyl)amino)methyl)benzyl)-1H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (**34**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1665.76 (theoretical); 1666.27 (observed). HPLC retention time = 1.34 min (Method C).

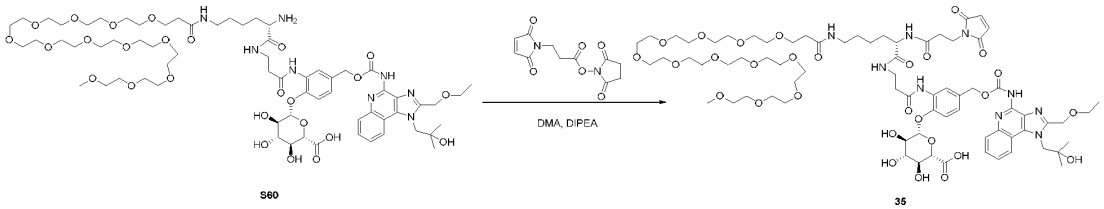
EXAMPLE 31

Synthesis of a drug-linker conjugate

[0664] This example covers synthesis of a complex comprising a linker coupled to a C4 amine of an imidazoquinoline TLR7/8 agonist with C7 carboxylic acid functionalization, namely (2S,3S,4S,5R,6S)-6-(2-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-((((2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (**35**). As outlined in **SCHEME 60**, compound **35** was generated from intermediate **S60**. Brieflt, intermediate **S60** (12.5 mg, 0.009 mmol) and mp-OSu (2.80 mg, 0.011 mmol) were dissolved in anhydrous DMA (0.5 mL) and DIPEA (1.83 µL, 0.011 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 90 min. After 90 min, the reaction mixture was quenched with HOAc (5 µL), diluted with DMSO/water, and purified by RP-HPLC (Method A)

to give compound **33** (9.1 mg, 0.006 mmol, 65.8%) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1576.73 (theoretical); 1577.11 (observed). HPLC retention time = 1.25 min (Method C).

SCHEME 60

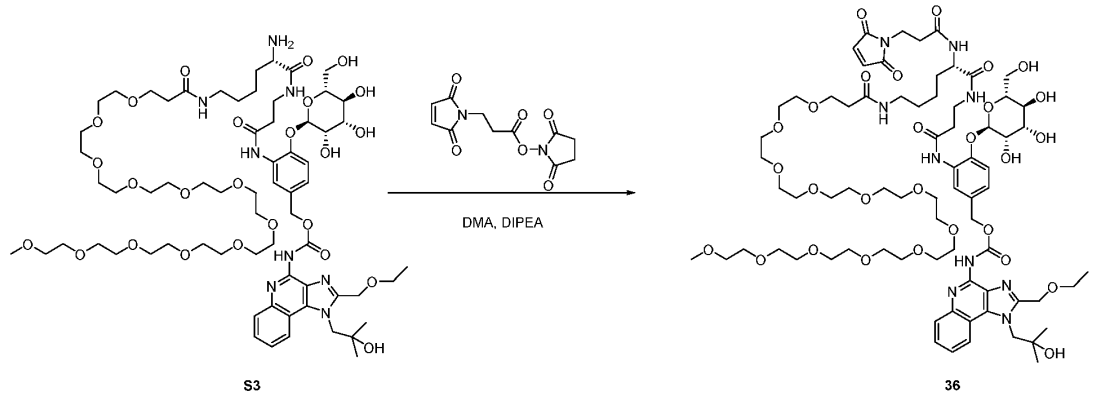


EXAMPLE 32

Synthesis of a drug-linker conjugate

[0665] This example covers synthesis of a complex comprising a linker coupled to a C4 amine of an imidazoquinoline TLR7/8 agonist lacking C7 functionalization, namely 3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl (2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamate (**36**). As outlined in **SCHEME 61**, the synthesis of compound **36** was similar to the synthesis of compound **35**.

SCHEME 61



[0666] Synthesis of 3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl (2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-*c*]quinolin-4-

yl)carbamate (**36**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1562.75 (theoretical); 1562.75 (observed). HPLC retention time = 1.23 min (Method C).

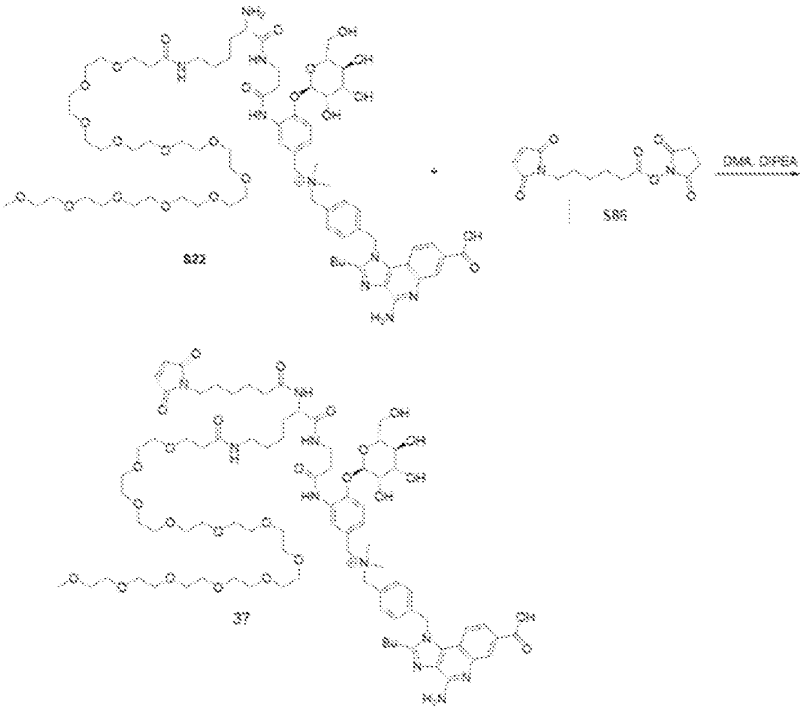
EXAMPLE 33

Synthesis of a drug-linker conjugate

[0667] This example covers synthesis of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with carboxylic acid C7 functionalization, namely *N*-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**37**).

[0668] Compound **37** was synthesized according to **SCHEME 62**. Intermediate **22** (10.3 mg, 0.0064 mmol) and **S86** (mc-OSu, AmBeed, 2.97 mg, 0.0097 mmol) were dissolved in anhydrous DMA (0.4 ml) and DIPEA (4.50 µl, 0.026 mmol) at room temperature. The reaction was stirred at the same temperature for 3h. After 3h n, the reaction mixture was quenched with HOAc (5 ul), diluted with DMSO/water and purified by RP-HPLC (Method A) to give **37** (6.7 mg, 0.004 mmol, 62.0 %) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1678.89 (theoretical); 1679.13 (observed). HPLC retention time = 1.69 min (Method D).

SCHEME 62



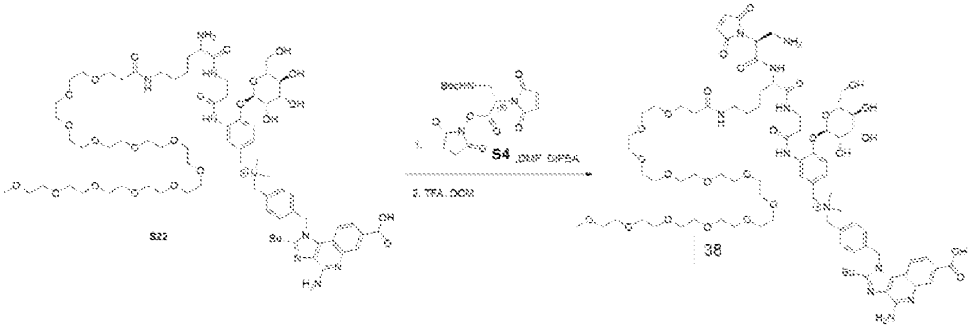
EXAMPLE 34

Synthesis of a drug-linker conjugate

[0669] This example covers synthesis of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with carboxylic acid C7 functionalization, namely *N*-(3-((S)-44-((S)-3-amino-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)-1-(4-((4-amino-2-butyl-7-carboxy-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)phenyl)-*N,N*-dimethylmethanaminium **(38).** Compound **38** synthesis was performed according to **SCHEME 63**. Intermediates **S22** (16.0 mg, 0.01 mmol) and **S4** (5.72 mg, 0.015 mmol) were dissolved in anhydrous DMA (0.4 mL) and DIPEA (0.009 mL, 0.05 mmol) at room temperature. The reaction was stirred at room temperature for 2 h. After 2 h, solvent was removed *in vacuo* and the crude reaction mixture was re-dissolved in DCM/TFA (5:1 (v/v), 0.5 mL), and the reaction mixture was stirred at room temperature for 20 min. Solvent was then removed and the crude reaction mixture was diluted with DMSO/water and purified by RP-HPLC (Method A) to give compound **38** (16.5 mg, 0.006 mmol, 61.1%) as TFA salt. LCMS:

m/z $[M+H]^+$ = 1651.85 (theoretical); 1652.10 (observed). HPLC retention time = 1.40 min (Method D).

SCHEME 63



EXAMPLE 35

Synthesis of a drug-linker conjugate

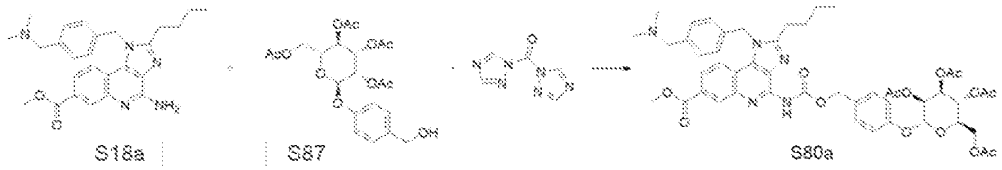
[0670] This example covers synthesis of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with carboxylic acid C7 functionalization and a hydrolysable group coupled to a C4 amine, namely *N*-(4-((2-butyl-7-carboxy-4-((((4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**40**).

[0671] Compound **S87** was prepared according to the procedures as described in *Angew. Chem. Int. Ed.* **2006**, 45, 5345 –5348.

[0672] Synthesis of (2R,3R,4S,5S,6R)-2-(acetoxymethyl)-6-(4-((((2-butyl-1-(4-((dimethylamino)methyl)benzyl)-7-(methoxycarbonyl)-1H-imidazo[4,5-*c*]quinolin-4-yl)carbamoyl)oxy)methyl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**S80a**) is outlined in **SCHEME 64**. Compound **S18a** (105 mg, 0.236 mmol) was dissolved in anhydrous THF (2.5 mL) and cooled to 0 °C. 1,1'-carbonyl-do-(1,2,4-triazole) (CDT, 54.1 mg, 0.330 mmol) was added and the reaction mixture was warmed up to room temperature and stirred for 30 min. After 30 min, compound **S87** (267.7 mg, 0.589 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 45 min. After 45 min, solvents were removed *in vacuo* and the crude reaction mixture was purified by normal phase HPLC (Method B, EtOAc/hexane as eluents) to give the desired product **S80a** (192.1 mg, 0.208 mmol, 88.0%) as

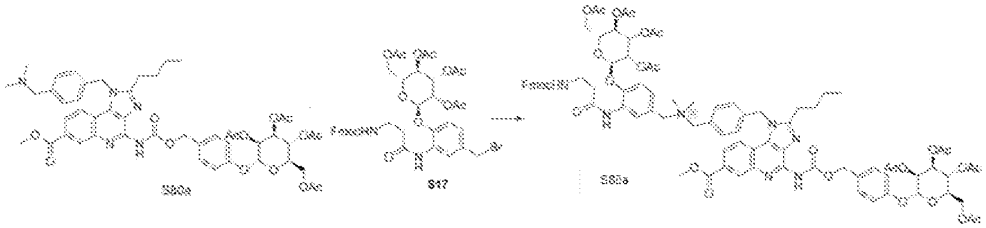
white solid. LCMS: m/z $[M+H]^+$ = 926.38 (theoretical); 926.37 (observed). HPLC retention time = 1.88 min (Method D).

SCHEME 64



[0673] Synthesis of *N*-(3-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(((2R,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)-1-(4-((2-butyl-7-(methoxycarbonyl)-4-((((4-(((2R,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)phenyl)-*N,N*-dimethylmethanaminium (S88a) is outlined in SCHEME 65. Compound S17 (252.8 mg, 0.306 mmol) and S80a (189.0 mg, 0.204 mmol) were dissolved in DMA (7.5 mL). The reaction mixture was heated at 50 °C for 90 min and the reaction progress monitored by LCMS. After 90 min, the reaction mixture was diluted with DMSO /water and purified by RP-HPLC (Method A) to provide S83a (285.1 mg, 0.171 mmol, 83.6%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1670.63 (theoretical); 1670.63 (observed). HPLC retention time = 2.34 min (Method D).

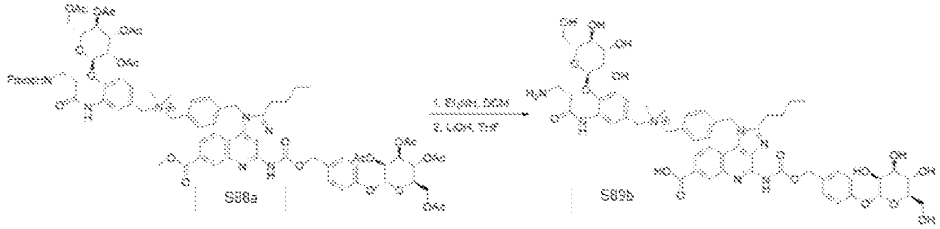
SCHEME 65



[0674] Synthesis of *N*-(3-(3-aminopropanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)-1-(4-((2-butyl-7-carboxy-4-((((4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)phenyl)-*N,N*-dimethylmethanaminium (**S89b**) is outlined in **SCHEME 66**. Intermediate **S88a** (85.0 mg, 0.051 mmol) was dissolved in dichloromethane (DCM, 3.0 mL) at rom temperature (RT) followed by the addition of dimethylamine (Et_2NH, 1.0 mL). The reaction mixture was stirred at RT for 45 min. After 45 min, solvents were removed *in vacuo* and the crude reaction mixture was re-dissolved in THF (1.0 mL) at 0 °C and a lithium hydroxide (LiOH) solution (0.5 M in MeOH, 1.0 mL, 0.509 mmol) was added. The resulting reaction mixture was stirred at 0 °C for

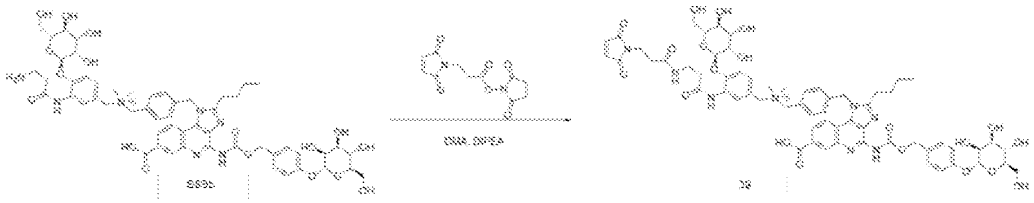
90 min, upon which, glacial acetic acid (AcOH, 60.0 uL, 1.02 mmol) was added to neutralize the reaction mixture. The reaction mixture was diluted with water/DMSO and purified by preparative RP-HPLC (Method A) to give intermediate **S89b** (39.7 mg, 0.036 mmol, 71.0%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1098.47 (theoretical); 1098.41 (observed). HPLC retention time = 1.28 min (Method D).

SCHEME 66



[0675] Synthesis of *N*-(4-((2-butyl-7-carboxy-4-((((4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium **(39)** is outlined in **SCHEME 67**. Intermediate **S89b** (40.1 mg, 0.033 mmol) and mp-OSu (13.2 mg, 0.050 mmol) were dissolved in anhydrous DMA (1.0 mL) and DIPEA (21.3 µL, 0.165 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 30 min. After 30 min, the reaction mixture was quenched with HOAc (10 µl), diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound **39** (20.6 mg, 0.017 mmol, 49.8%) as TFA salt, white solid. LCMS: m/z $[M]^+$ = 1249.49 (theoretical); 1249.51 (observed). HPLC retention time = 1.41 min (Method D).

SCHEME 67



EXAMPLE 36

Synthesis of a drug-linker conjugate

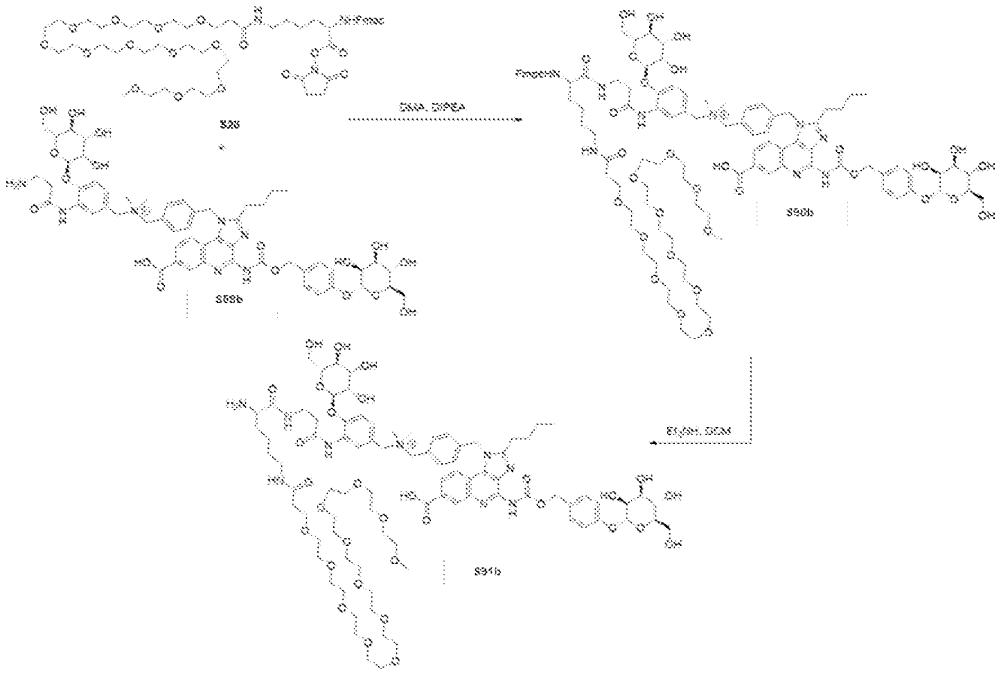
[0676] This example covers synthesis of a complex comprising a linker coupled to an N1 position of an imidazoquinoline TLR7/8 agonist with carboxylic acid C7 functionalization and a hydrolysable group coupled to a C4 amine, namely *N*-(4-((2-butyl-7-carboxy-4-((((4-

(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (40).

Synthesis of *N*-(3-((S)-44-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)-1-(4-((2-butyl-7-carboxy-4-((((4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)phenyl)-*N,N*-dimethylmethanaminium (S90b). Compound S86b was prepared using similar procedures as those used in the synthesis of S60. (**S90b**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 2019.96 (theoretical); 2019.90. (observed). HPLC retention time = 1.70 min (Method D).

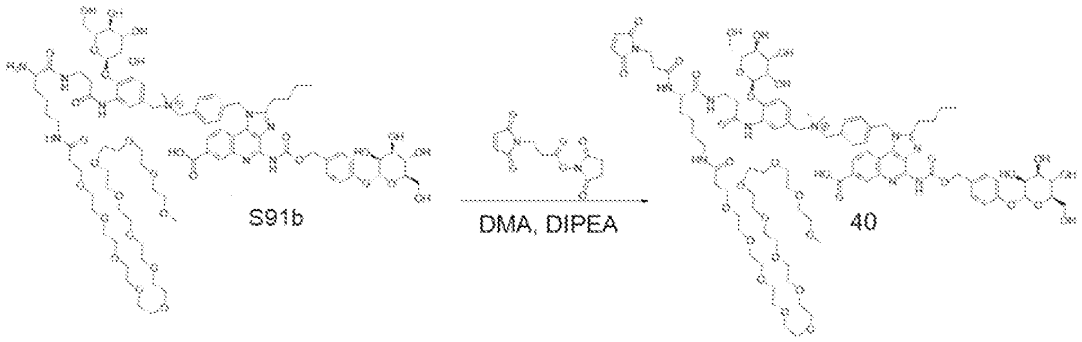
Synthesis of *N*-(3-((S)-44-amino-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)-1-(4-((2-butyl-7-carboxy-4-((((4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)phenyl)-*N,N*-dimethylmethanaminium (S91b) is outlined in SCHEME 68. (**S91b**) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1797.89 (theoretical); 1797.85. (observed). HPLC retention time = 1.47 min (Method D).

SCHEME 68



[0677] Synthesis of *N*-(4-((2-butyl-7-carboxy-4-((((4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)benzyl)oxy)carbonyl)amino)-1H-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-1-(3-((S)-44-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-38,45-dioxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39,46-diazanonatetracontan-49-amido)-4-(((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)-*N,N*-dimethylmethanaminium (**40**) is outlined in **SCHEME 69**. Intermediate **S91b** (28.2 mg, 0.016 mmol) and mp-OSu (6.26 mg, 0.024 mmol) were dissolved in anhydrous DMA (0.5 mL) and DIPEA (21.9 µL, 0.126 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 30 min. After 30 min, the reaction mixture was quenched with HOAc (10 µl), diluted with DMSO/water, and purified by RP-HPLC (Method A) to give compound **40** (21.4 mg, 0.017 mmol, 70.0%) as TFA salt, white solid. LCMS: m/z $[M+H]^+$ = 1948.92 (theoretical); 1948.83 (observed). HPLC retention time = 1.51 min (Method D).

SCHEME 69



EXAMPLE 37

Synthesis of multiple imidazoquinoline complexes

[0678] Compounds **S72a**, **S73a**, **S74a**, **S75a**, **S76a**, **S77a**, and **S78a** were prepared analogously to procedures described in U.S. Publ. No. 2017/0217960; Larson, et al. *ACS Med.Chem. Lett.* Vol. 8, No. 11, 1148-1152 (2017); and Schiaffo, et al., *J. Med. Chem.* Vol. 57, No. 2, 339-347 (2014), each of which is incorporated by reference in its entirety.

EXAMPLE 38

Biological Activity of TLR Agonists and Antibody Drug Conjugates

[0679] This example covers dose dependent human immune cell activation by small molecule TLR7/8 agonists. Primary human PBMCs were isolated from peripheral whole blood from human donors and were subjected to treatment with increasing concentrations of the agonists diluted in PBS. Cell culture supernatants were harvested 24 h after treatment and analyzed for induction of cytokines via multiplex ELISAs (Luminex).

[0680] **FIGURE 1** summarizes dose dependent interferon gamma (IFNg, top left panel), interleukin 1 beta (IL1β, top right panel), macrophage inflammatory protein 1 beta (MIP1β, bottom left panel), and tumour necrosis factor alpha (TNFα, bottom right panel) induction in primary human PBMCs by Resiquimod (a 4-imidazoquinoline compound lacking C7 functionalization) and a series of 4-imidazoquinoline compounds with C7 functionalization, namely **S5a**, **S73a**, **S74a**, **S8a**, **S63a**, **S11a**, and **S14a**. When compared to the commercially available compound resiquimod, several of the compounds displayed similar potency. Notably, the compound **S8a** exhibited the highest potency for cytokine induction **(FIGURE 1)**, eliciting cytokine responses at sub 0.1 μM concentrations.

[0681] **FIGURE 2** summarizes dose dependent cytokine induction with additional 4-imidazoquinoline methyl ester TLR agonists. Induction of interferon alpha (IFNA, top left panel), IL1β (top right panel), monocyte chemotactic protein-3 (MCP3, bottom left panel), and

TNFα (bottom right panel) responses in primary human PBMCs were measured as a function of agonist concentration to assess potency and efficacy at activating these immune cells. This series of assays utilized Reisuimod and compounds **S8a**, **S75a**, **S14a**, **S76a**, **S77a**, **S78a**, **S14a**, and **S5a**. The agonists **S18a** and **S8a** displayed some of the most potent ability to activate these cells, exhibiting activities at sub 0.1 μM concentrations, and indicating that phenylmethanamine substitution may be important for TLR activation by imidazoquinoline agonists.

[0682] To compare the effects of C7 carboxylation and carboxymethylation in imidazoquinoline TLR antagonists, PBMC cytokine responses were compared for multiple molecules of each type. **FIGURE 3** summarizes IFNa (top left panel), IL1β (top right panel), MIP1β (bottom left panel), and TNFα (bottom right panel) induction in PBMCs with multiple methyl ester imidazoquinoline TLR agonists (**S5a, S8a, S11a**) and their carboxyl counterparts (**S5b, S8b, S11b**), which were modified to include a carboxylic acid instead of a methyl ester on the C7 position. When these carboxylic acid derivatives (**S5b**, **S11b** and **S8b**) were tested for their ability to stimulate cytokine production from human peripheral blood cells, a striking phenotype was seen. Each carboxylic acid compounds exhibited markedly lower potency and activity than its corresponding parent methyl ester compound for all cytokines assessed. These results suggest that, in some cases, C7 carboxylic acids confer lower activity than C7 methyl esters, rendering them less active as small molecule innate immune agonists.

[0683] Differences in cytokine induction by C7 carboxylated and carboxymethylated antagonists are further highlighted in **FIGURES 4-5**. **FIGURE 4** provides MIP1β (left panel) and TNFα (right panel) responses generated with Resiquimod and compounds **S8a**, **S5a**, **S11a** **S8b**, and **S11b**. **S8a** and **S11a** elicited similar MIP1β responses as Resiquimod, while **S8b** and **S11b** exhibit lower activities than their methyl ester counterparts. **FIGURE 5** provides a comparison of interleukin 12 subunit beta (IL12p40, left panel) and IL1β (right panel) responses generated with the C7 carboxymethyl compound **S18a** and its C7 carboxyl analogue **S18b**. The carboxylic acid derivative **S18a** affected lower responses of both cytokines as compared to its methyl ester analogue **S18b**.

[0684] As one possibility for the reduced activity of the carboxylic acid derivative TLR7/8 agonists (as compared to the corresponding methyl ester compounds) may be due to lower permeability, it was hypothesized that conjugating these molecules to antibodies to improve cellular uptake could render these compounds more active. Cells were stimulated with the various TLR7/8 agonist-antiody conjugates at different concentrations, and resulting superntants were harvested and analyzed using a multiplex analyte kit (Luminex).

[0685] Immune cells were treated with 5 μg/mL of an immune-targeting antibody, TLR agonist compounds, and antibody conjugated with different TLR agonist compounds (to thereby form ADCs with average drug:antibody ratios of about 8). **FIGURE 6** summarizes MIP1β (left panel) and TNFα (right panel) responses generated by untreated immune cells, a TLR agonist coupled to a non-targeting antibody ('Non-targeted'), and TLR agonist compounds conjugated with immune-targeted antibodies. Targeted compound 1 corresponds to Resiquimod coupled to an immunostimulatory antibody by a cleavable linker. Targeted compounds 2, 4, 5, and 7 correspond to C7 carboxymethylated imidazoquinoline compounds coupled to immunostimulatory antibodies by cleavable linkers. Targeted compounds 3 and 6 correspond to C7 carboxylated imidazoquinoline compounds coupled to immunostimulatory antibodies by cleavable linkers. **FIGURE 7** provides dose-dependent IL12p40 (left panel) and IL1β (right panel) responses generated with non-targeted (i.e., coupled to an isotype antibody) and immune-targeting antibody conjugated compounds, with 'cmpd 9' corresponding to a C7 carboxylated imidazoquinoline compound and 'cmpd10' corresponding to its C7 carboxymethyl analogue. **FIGURE 8** provides dose-dependent interleukin 6 (IL6, left panel) and TNFα (right panel) responses with ADCs comprising immune cell targeting antibodies coupled to either C7 carboxylated (cmpd 3, 8, 9) or C7 carboxymethylated (cmpd 4, 7, 10) imidazoquinoline compounds.

[0686] Unlike unconjugated C7 carboxylated imidazoquinoline compounds, which were unable to activate immune cells (**FIGURES 4** and **5**), ADCs comprising these compounds (**S8b**, **S11b** and **S18b**) were just as, if not more potent at activating immune cells than their methyl ester analogues (**FIGURES 6, 7, and 8**). For example, in **FIGURE 8**, the C7 carboxylated compounds (indicated with dashed lines) generated much stronger responses than their C7 carboxymethyl counterparts (solid lines). Importantly the non targeting conjugated molecules did not show ability to drive activation suggesting the conjugates had immunospecificity. These results suggest that the C7 carboxylated compounds may have strong TLR7 agonistic activity but low uptake, such that conjugation to a targeting antibody could be a way to deliver these impermeable agonists to affect immune stimulating activity.

[0687] To determine if any of these differences in activity potentially resulted from increases in aggregation as a subsequent result of changes in charge, SEC analysis was performed. Immune-targeted ADCs containing either **S18a** (methyl ester) or **S18b** (carboxylic acid) were incubated with both human or mouse plasma and assessed for the formation of high molecular weight species (HMW) over time. While the conjugates did form more aggregates over time than naked monoclonal antibody (mAB) (**FIGURE 9**), there was no significant difference in the amounts of

aggregation between the methyl ester and carboxylic acid containing ADCs. Therefore, it does not appear that the differences their activity is due to physical changes in the antibody drug conjugate species.

EXAMPLE 39

In vivo Activity of Antibody Drug Conjugates with TLR7/8 Agonists

[0688] This example covers *in vivo* assessments of anti-tumor activity of ADCs with TLR7/8 agonists. An *in vivo* syngeneic system was used to assess the ability of the ADCs having TLR 7/8 agonists as the payload to induce immune responses and drive an anti-tumor immune response using a subcutaneous, heterotopic mouse colon carcinoma model (a CT26 system). Female Balb/c mice were implanted with $1x10^5$ CT26 cells sub-cutaneously in the flank on day 0. When mean tumor size of 100 mm^3 (measured using the formula: Volume (mm^3) = 0.5 * Length * $Width^2$ where length is the longer dimension) was reached, the mice were randomized into treatment groups of 6 mice per group. Animals were then treated intraperitoneally with the indicated treatment every 7 days, for 3 doses total. Stock concentrations of the ADCs were diluted to the appropriate concentration and injected into animals in 100 μL volumes. Tumor length and width and mouse weights were measured throughout the study and tumor volume was calculated using the formula above. Animals were followed until tumor volume reached ~ 1000 mm^3, when animals were then euthanized.

[0689] **FIGURE 10** summarizes tumor volume (top panel) and percent survival in 5 treatment groups. As shown, animals were treated with the immune-targeted ADC containing the the TLR7/8 agonist **S5a** (cmpd 4), some tumor growth delay and survival benefit was seen with 1/6 of the mice surviving at the end of the study. This effect was enhanced with the immune-targeted ADC over the non-targeted control conjugate. When the corresponding acid derivative (**S5b**, cmpd 3) was used as a payload on the same antibodies, greatly enhanced anti-tumor efficacy was seen with profound tumor growth delay and survival at study end of up to 50% of the animals (**FIGURE 10**).

[0690] To confirm these results and assess if ADCs containing acid derivatives of different TLR7/8 agonists induce similar increase in anti-tumor activity and potency, another CT26 syngeneic experiment was performed similar to the one described in **FIGURE 10**, with results summarized in **FIGURE 11**. In this figure, the top panel summarizes tumor volume while the bottom panel provides percent survival across 6 treatment groups. Again, it was clear that the immune-targeted ADCs containing the methyl ester derivative of the TLR 7/8 agonist (compound S14a, cmpd 7) afforded some tumor growth delay over the untreated group, though no animals

ultimately survived. However, conjugation of the acid derivative S14b (cmpd 8) appended to the immune-targeting antibody, greatly increased tumor growth delay and survival of the mice bearing these tumors was seen (**FIGURE 11**). Again, these data support the conclusion that modification of the C7 position to carboxylic acid increases the potency and anti-tumor efficacy of a TLR7/8 immune-targeted ADC.

[0691] The activity of several conjugated TLR7/8 molecules in both methyl ester and carboxylic acid forms were also assessed in another colon tumor model, MC38. Results of this analysis are summarized in **FIGURE 12**, wich the top panel summarizing tumor volume and the bottom panel providing percent survival across 9 treatment groups. For immune-targeted ADCs containing **S8a** (cmpd 4, methyl ester) or **S8b** (cmpd 3, carboxylic acid), in this tumor model, there was a slight increased survival advantage with the acid derivative (**FIGURE 12**, ♦ vs. hexagon). However, the increase in anti-tumor activity of the carboxylic acid version of the ADC was much more pronounced in this model for the **S18a** (methyl ester) or **S18b** (carboxylic acid) TLR7/8 agonist. Here we see a distinct tumor growth delay and overall survival benefit with ADC containing **S18b** over the ADC containing **S18a** (**FIGURE 12**, ▼vs. * or star).

[0692] The activity of this most active conjugate (ADC containing S18b) was further assessed in the CT26 colon tumor model; where potent tumor growth delay and a long-term overall survival benefit were also observed. **FIGURE 13** summarizes the results of this analysis, with the top panel summarizing tumor volume and the bottom panel providing percent survival for untreated, immune-targeted ADC with cmpd 9-treated, and non targeted ADC with cmpd 9-treated mice.

[0693] The difference in anti-tumor activity of the anti-immune **S18a** and **S18b** conjugates was also assessed in the Renca kidney model. In this model, mice bearing Renca tumors were treated q7dx3 when tumors reached ~ 100 mm^3 as indicated, and followed for mean group tumor growth (**FIGURE 14**, top) and survival (**FIGURE 14**, bottom) over time. Again, very clearly it was demonstrated that the conjugated **S18a** (a C7 carboxymethyl imidazoquinoline compound) provided some tumor growth benefit though no real survival benefit. However, the ADC containing **S18b** (a C7 carboxyl imidazoquinoline compound) had very good tumor growth delay and superior overall survival advantage (**FIGURE 14**).

EXAMPLE 40

Effects of C4 and N1 conjugation on imidazoquinoline compound activity

[0694] While certain studies disclosed herein utilized conjugates where the linkage of the TLR7/8 agonist drug to a linker was at the N1 position of the imidazoquinoline core, the payloads can also be conjugated to a linker at the C4 amino group as an alternative linkage site. To compare

the activity of imidazoquinoline compounds made from the same drug and linker, but linked at these two different positions, imidazoquinoline compounds with N1- or C4- coupled linkers were conjugated to an immune-targeted antibody. These ADCs were administered to non-tumor bearing mice and systemic immune activation was assessed through induction of plasma cytokines. immune-targeted ADCs with S18b linked via the N1 or C4 position were administered to non-tumor bearing Balb/c mice intraperitoneally at 2 mg/kg. Blood was isolated 3/6/24 h post dose and plasma was analyzed for cytokine induction via multiple cytokine analysis.

[0695] **FIGURE 15** provides MIP1b (top panel) and TNFα (bottom panel) responses generated with N1- (cmpd 9) and C4- (cmpd 11) linked compounds conjugated to targeting antibodies, as well as for the non-conjugated TLR agonist. For the majority of cytokines assessed (MCP1, IP10, MIP1a, MIP1b, RANTES), changing the linkage site of the drug to the linker from N1 to C4 greatly reduced the systemic cytokine induction by an average of 4.8-fold (**FIGURE 15**). Interestingly no changes in IL6 or TNFα levels were seen between these conjugates (**FIGURE 15**, bottom). The results from this study suggested that changing the linkage site of the linker to the TLR7/8 carboxylic acid drugs can greatly affect their potency and systemic cytokine induction.

[0696] This study was repeated, again in non-tumor bearing animals, with non-targeting ADCs containing TLR7/8 agonists with linkers attached at either the N1 or C4 positions (compounds 9 and 11, respectively). **FIGURE 16** provides MIP1b (top panel) and TNFα (bottom panel) responses generated with N1- (cmpd 9) and C4- (cmpd 11) linked compounds conjugated to non-targeting antibodies, as well as for the non-conjugated TLR agonist. As outlined in **FIGURE 16**, in this follow up study a very similar decrease in systemic cytokines seen by linking the linker at the C4 position vs. the N1 position of the imidazoquinoline core was seen, such that there was greatly diminished systemic cytokines and non-specific uptake of a non-targeted mAB with the TLR7/8 payload when conjugate at the C4 position.

[0697] Interestingly, in this experiment, a clear benefit of the C4-linked conjugates was observed for all cytokines monitored (shown here by MIP1β and TNFα) as opposed to the previous experiment where the majority of cytokines showed benefit but IL6 and TNFa did not. This may be due to different antibodies being used in the two studies, where the study described in **FIGURE 15** used a targeted mAB and the study described in **FIGURE 16** used a non-binding control.

[0698] In addition to analyzing this response in non-tumor bearing animals simply on systemic immune activation, the C4/N1-linked TLR7/8 drug antibody conjugates were also administered to CT26-tumor bearing animals to determine how the linkage site affects cytokine response and anti-tumor response. The results are shown in **FIGURE 17**, which provides MIP1b (top panel)

and TNFα (bottom panel) responses generated with N1- (cmpd 9) and C4- (cmpd 11) linked compounds conjugated to immune-targeting and non-targeting antibodies, as well as for untreated cells. It was again demonstrated that for the majority of cytokines evaluated there was a reduced systemic activation seen when the TLR7/8 carboxylic acid drug payload was linked at the C4 position. This was true for targeted and non-targeted control conjugates. As noted above this benefit of the C4 linkage was greater for all the cytokines for the control conjugate but less universal for the targeted antibody conjugate, where N1 and C4 were equivalent for TNFα but showed benefit for MIP1β.

[0699] In addition to assessing cytokine induction, the test subjects were also followed for tumor growth and survival over time. The data from these analyses are summarized in **FIGURE 18**, which provides tumor volume (top panel) and survival (bottom panel) as functions of days post tumor implant. While the N1 linked conjugates of the MAb control provided substantial benefits in tumor growth reduction and survival over time, (even better than conjugates of the targeted MAb), the C4 linked control MAb conjugate did not provide the same benefits. These data provide support for the hypothesis that a TLR7/8 payload linked at the N1 position to a non-targeted mAB drives non-specific uptake and activity, which can be significantly diminished by changing the linkage site to C4. In contrast, both the C4-linked and N1-linked antibody conjugates of a targeted MAb demonstrated similar anti-tumor activity, suggesting that the linkage position does not have significant impact on the anti-tumor activity of immune-targeted conjugates. These data suggest that changing the linkage site of these TLR7/8 antibody conjugates from N1 to C4 can greatly reduce non-specific/off target activity and systemic cytokine induction, while not affecting anti-tumor responses for targeted conjugates.

[0700] The comparison of the anti-tumor activity and non-specific cytokine induction between conjugates with N1 or C4 linkage was repeated in a disparate tumor model. Renca is a syngeneic kidney carcinoma model with a distinct microenvironment than CT26 (Mosely, S. et al. *Cancer Immunol. Res.*, 2017, 5:29-14), and is often resistant to treatments effective in CT26; and thus could have a different response to treatment.

[0701] **FIGURE 19** summarizes cytokine responses induced with C4- and N1- conjugates of immune-targeted and non-targeted antibodies, with the top panel providing MIP1β and the bottom panel providing TNFα levels at various times following dosing. In the Renca-bearing animals, similar systemic cytokine induction was observed in response to treatment with both of the C4- or N1-linked conjugates of targeted MAb and non-targeted MAb treatments, as was seen in the CT26 model (**FIGURE 17**). Similar to the CT26 model, conjugates (of both targeted and non-

targeted monoclonal antibodies (MAb)) with the C4 linkage afforded lower systemic cytokine induction than those with N1 linkage.

[0702] However, unlike in the CT26 model, where there was no significant difference in efficacy between the C4 and N1 linked conjugates of compound S18b with a immune-targeted MAb (**FIGURE 18**), in the Renca model there was a clear increase in anti-tumor efficacy when the S18b was linked at the N1 position. As summarized in **FIGURE 20**, which shows tumor volume (top panel) and survival rates (bottom panel) following tumor implantation (x-axes in units of days), the N1-linked isotype showed superior, non-specific anti-tumor activity in the CT26 model, in the Renca model there was good immunological specificity of both the N1- and C4-linked conjugates. In this model it appeared that the N1-linked conjugate demonstrated superior anti-tumor activity accompanied by higher systemic cytokines.

[0703] In order to ascertain whether the difference in activity of the N1 vs. C4 linked conjugates seen in the Renca model was due to variable potency, a dose range experiment was performed. The N1 and C4 linked targeted (ADC) and non-targeted conjugates were administered in a wide dose range (0.001 to 10 μg/mL) to exogenously derived human immune cells. Cells were stimulated with various TLR/7/8 agonists at different concentrations. Supernatants were harvested and analyzed using a multiplex analyte kit (Luminex).

[0704] **FIGURE 21** shows MIP1b (top panel) and TNFα (bottom panel) responses affected by immune-targeted and non-targeted imidazoquinoline-conjugated ADCs with either C4- or N1-linkages. Activation of the immune cells was observed as evidenced by cytokine induction over the entire dose range. In this experiment, it was noted that there was no activity of either of the non-targeted conjugates, but that both of the targeted conjugates were active at inducing immune cell activation. However, it was noted that the C4 linked conjugate with a targeted antibody appeared to lose some potency with a ~ 4x loss in EC50.

[0705] To further understand if this difference observed in cell culture translates to *in vivo* models, Renca-bearing animals were treated with a 2 mg/kg dose of conjugates made with compound 9 or increasing doses of the conjugate with a C4-linked payload (Compound 11) and a targeted MAb. The results of these analyses are shown in **FIGURE 22**, which provides tumor volume (top) and survival rates (bottom) for non-targeted (left) and immune-targeted (right) ADCs. Increasing the concentration of the C4-linked ADC enabled the recapitulation of the anti-tumor activity seen with the N1-linked conjugate, and the increase in the dose of the C4-linked conjugate required to restore similar activity suggests an approximately 4x loss of potency of the C4-linked conjugate. Again, in this tumor model, there was very little activity of the conjugates

made with the non-targeted control, suggesting good immunological specificity here that was not seen in the CT26 model (**FIGURE 22**, left).

[0706] In addition to evaluating anti-tumor activity, the ability to induce systemic cytokine production as effected by imidazoquinoline-antibody conjugates was evaluated at different doses. **FIGURE 23** shows MIP1b (top panel) and TNFα (bottom panel) responses induced with various doses of targeted and non-targeted antibodies conjugated to N1- and C4-linked imidazoquinoline compounds. Again, at the same dose of 2 mg/kg, the C4-linked conjugate demonstrated markedly lower cytokine induction when conjugated to a targeted MAb, compared to the corresponding N1-linked conjugate. However, when the dose of the C4-linked conjugate was increased four-fold to 8 mg/kg, systemic cytokine levels in response to this immunostimulatory drug conjugate were similar to those seen with 2 mg/kg of the N1-linked conjugate (**FIGURE 22**, circles vs. triangles). Interestingly though, when on the non-targeted control antibody even at 8 mg/kg of the C4 lower systemic cytokine levels were seen than with the N1 conjugate. These data suggest that while changing the linkage from N1 to C4 leads to a 4x decrease in potency, as observed in both *in vitro* model (**FIGURE 21**) and *in vivo* model (**FIGURE 22**) when these conjugates are targeted to immune cells, the non-specific activity observed with the N1-linked conjugate is still greater than that observed with the C4-linked conjugate. This further suggests a potential better safety margin for a C4-linked conjugate.

EXAMPLE 41

Assessment of TLR7 and TLR8 selectivity for small molecule TLR7/8 agonists

[0707] This example covers toll-like receptor 7 (TLR7) and toll-like receptor 8 (TLR8) selectivity of imidazoquinoline agonists. Assessment of TLR7 and TLR8 selectivity for the free TLR7/8 agonists was performed using HEK Blue hTLR7 and hTLR8 cells over a large dose range of compounds. **FIGURE 24** provides human toll-like receptor 7 (hTLR7, panel A) and human toll-like receptor 8 (hTLR8, panel B) activities for resiquimod ('R848'), **S5a**, **S8a**, **S18a**, **S72a**, **S75a**, **S76a**, **S77a**, and **S78a**. Activities were determined based on calculated EC50 (in μM) in each cell line, and are summarized in **TABLE 4** below, with columns providing targets and rows providing compounds. Compounds ranged in both potency for each cell line and also in their TLR7 vs TLR8 skewing.

TABLE 4

	hTLR7	**hTLR8**	**TLR7/TLR8**
Resiquimod	1.59	11.38	0.14

S5a	0.59	5.08	0.12
S8a	1.32	6.19	0.21
S14a	2.53	8.84	0.28
S18a	0.44	10.27	0.04
S76a	3.44	N/A	N/A
S77a	2.82	N/A	N/A
S78a	3.78	N/A	N/A

[0708] To assess the selectivity of the agonists *in vivo*, free molecule and conjugated drug were administered to C57BL/6 mice bearing subcutaneous MC38 tumors, which have non-functional TLR8 and only rely on TLR7 to drive activity against agonists, and TLR7 knockout animals that do not have either receptor. **FIGURE 25** summarizes tumor volume as a function of time post tumor implantation for C57BL/6 (top left) and TLR7 knockout C57BL/6 (top right) mice, as well as IL6 responses in both groups (bottom). Activity measured via systemic cytokine induction (**FIGURE 25**, bottom) demonstrated that the large IL6 induction seen with free agonist was abrogated in TLR7 knockout animals. Similar loss of systemic cytokine induction was also seen in response to the ADC, though to a lesser extent, demonstrating that the targeted drug conjugate responses are TLR7 and TLR8 specific as well. This loss of response to the TLR7/8 free agonist and conjugated drug translated into loss of anti-tumor activity in the TLR7-/- mice compared to wild type mice (**FIGURE 25**, top left and top right).

EXAMPLE 42

Effects of drug linker site and type on tumor treatment efficacy

[0709] Balb/c mice bearing Renca tumors were treated with non-targeted or targeted **S18a** payload linked via different linker sites and with or without a PEG group in the linker (Compounds **9**, **11**, **14**, and **15**). **FIGURE 26** provides tumor volumes as a function of days post tumor implantation for mice treated with various immune-targeted (top) and untargeted (bottom) ADCs. As previously demonstrated, the non-targeted conjugates demonstrated little to no activity. The targeted payload demonstrated the greatest potency when linked via the N1 position (Copounds **9** and **14**) and when linked via a PEG group, as described herein (Compound **9**).

[0710] Balb/c mice bearing Renca tumors were treated with targeted **S18a** payload linked on the N1 site (Compound **9**) or the C4 site via different linkers. **FIGURE 27** summarizes tumor volume as a function of days post tumor implantation for the various treatment groups. While the

N1 linkage site demonstrated superior potency, all C4 linked molecules demonstrated similar anti-tumor activity.

EXAMPLE 43

Anti-tumor activity of immune and tumor targeted TLR7/8 agonists

[0711] This example covers TLR7 and TLR8 (TLR7/8) agonists targeted to both the tumor and immune cells. To determine the difference in targeting intra-tumoral immune cells only as compared to immune and tumor cells a TLR7/8 agonist was conjugated to an immune targeting or a tumor and immune targeting antiody. 4T1 syngeneic breast tumors were left untreated or treated, starting at 100 mm^3, with a naked PDL1 targeted antibody, a PDL1 targeted TLR7/8 agonist IDC, the cognate isotype non-targeted IDC or a TLR7/8 agonist IDC against intra-tumoral immune cells. The tumors were followed over time for growth.

[0712] Tumor sizes at day 23 post tumor implant in each group are shown in **FIGURE 28**. Most antibody treated animals had succumbed to tumor burden and/or treatment (likely as a result of the human IgG1 backbone and anti-drug antibodies formed; Oncoimmunology. 2016 Feb; 5(2): e1075114.) by day 23. The animals treated with the ADC version of this mAb fared much better showing greatly decreased tumor size and tumor growth delay. This was greater than what was seen with the non-targeted isotype control and similar to the immune targeted IDC. The data deomstrate that conjugated TLR7/8 agonists can have activity when delivered on an immune target or a tumor/immune target.

EXAMPLE 44

Human immune cell activation by TLR7/8 agonists

[0713] Several small molecule TLR7/8 agonists were assessed for their ability to activate human immune cells in a dose dependent manner. Primary human PBMCs were isolated from peripheral whole blood from human donors and were subjected to treatment with increasing concentrations of the agonists diluted in PBS. 24 h after treatment cell culture supernatants were harvested and analyzed for induction of cytokines via multiplex ELISAs (Luminex).

[0714] **FIGURE 29** provides IL6 (top left), IL1b (top right), MIP1b (bottom left), and TNFα (bottom right) responses in PBMCs generated with compounds **8a**, **S85a**, and **S83a**. Compound **S83a**, which resembles compound **S18a** but with an ethyl linkage to the dimethyl nitrogen off the benzyl position at the N1 position, displays slightly enhanced potency to activate human PBMS when several different cytokines were evaluated. This suggests it has enhanced TLR7 and TLR8 potency. Compound **S85a** which is also similar to compound **S18a** but with a cyclohexyl group however displayed slightly decreased potency, in terms of half maximal effective concentration

as well as decreased maximal cytokine level induced, creating an overall decreased ability to activate human PBMCs.

[0715] **FIGURE 30** summarizes human immune cell activation by additional small molecules (compounds **S18a, S65a, S81a, S82a, S83a,** and **S84a**) screened in the human PBMC assay, with the top left panel summarizing IL6 responses, the top right panel summarizing TNFα responses, the bottom left panel summarizing MCP1 responses, and the bottom right panel summarizing IP10 responses. The compounds demonstrated a wide range of potencies and activities. Compound **S83a**, which carries *N,N*-diethyl group, routinely demonstrated the highest maximal cytokine and potency to induce cytokine of all compounds tested. The other two most potent compounds across the range of cytokines evaluated were **S18a** and **S65a**. Compound **S65a** did demonstrate enhanced potency to induce MCP1 and IP10 compared to compounds **S18a**, suggesting the cycloalkyl group off the terminal nitrogen increases the TLR7 potency. The remaining compounds all demonstrated decreasing levels of activity with compound **S81a** having greater activity than compound **S82a**, and compound **S82b** having greater activity than compound **S84a**. Compound **S81a** induced the same maximal level of IL6, MCP1 and IP10 as the other compounds, but was not able to reach the same maximum level of IL10 (not shown), IL1b (not shown) or TNFa. Coupled with the strong, very potent ability to drive induction of MCP1 and IP10 suggests that compound **S81a** has a TLR7 vs TLR8 skewed binding profile.

EXAMPLE 45

Imidazoquinoline compound specificity for TLR7/8

[0716] To assess if the small molecule and conjugated agonist are specific for the toll like 7 and/or 8 receptors, various small molecules and ADCs were tested on TLR7 receptor knockout animals. As TLR8 is normally nonfunctional in mice, in TLR7-/- mice there is a total loss of ability to respond to compounds that work through these receptors. To assess whether compounds are TLR7/8 specific, MC38 tumors were implanted into either wild type C57Bl/6 mice or cognate TLR7-/- mice. When tumors reached ~ 50 mm^3 mice animals were treated q7dx3 with vehicle (PBS), 1 mg/kg of the free small molecule **S18a**, the isotype/non-targeted ADC with cmpd 9 or with an immune cell targeted version of the cmpd 9 IDC.

[0717] Tumor growth over time is summarizes in **FIGURE 31**, in which the top left panel summarizes tumor growth in C57Bl/6 mice, the bottom left panel summarizes tumor growth in TLR7-/- mice, and the right panel summarizes tumor volumes on Day 36 for all mice. In the wild type B6 mice there was good MC38 tumor growth delay with the TLR7/8 agonist small molecule and delay and cures in the targeted ADC treated animals, with only minimal responses seen with

a non targeted ADC control. However, in the animals that lack TLR7 and have nonfunctional TLR8 there was no anti-tumor response seen in response to any treatment. Cytokines from the plasma of these animals were also evaluated post dose and showed no evidence of induction of any cytokine response. These results clearly demonstrate that these agonists and linked molecules work exclusively through engagement of TLR7 and TLR8 receptors to drive anti-tumor immunity.

[0718] To determine the anti-tumor activity of a TLR7/8 agonist conjugate on additional targeting antibodies the anti-tumor activity in a Renca renal syngeneic model that exogenously expresses a tumor antigen was also evaluated. For this experiment the **cmpd 9** linker was conjugated to an antibody targeting the exogenously expressed tumor antigen on either a mIgG2a Fc null backbone or wildtype backbone. Animals were treated Q7dx3 with these therapies when their tumors were 100 mm^3 and followed for tumor growth over time.

[0719] To determine how changing the loading effects the efficacy of the TLR7/8 agonist IDCs, immune targeted IDCs containing either **cmpd 9** or **cmpd 14** linked agonist were conjugated with a drug antibody ratio (DAR) of 2, 4 or 10. These were administered at varying doses Q7dx3 to mice bearing Renca tumors that were ~100 mm^3 in size and tumor size was followed over time.

[0720] **FIGURE 32** summarizes the results of these analyses. Notably, all treatments seemed to drive very similar anti-tumor activity that were not statistically different from one another. This is interesting since no IDCs seem to have diminished activity despite delivering lower quantities of drug (denoted in nmol/kg doses) demonstrating the strong potency of these treatments. Furthermore, the DAR2 IDC at the lowest dose tested, which was 4x lower dose than that given with the higher doses of the higher DAR species, showed the same activity; these data perhaps suggests that the lower loaded IDC may show enhanced potency.

EXAMPLE 46

EphA2-Targeted TLR Agonist Cancer Treatment Efficacies

[0721] This example covers cancer treatment with EphA2 targeted TLR agonists. EphA2 is a murine tumor antigen that has been found to be overexpressed in several mouse carcinoma cell lines, including CT26, MCA205, 4T1, and Renca cells (Rios-Doria, J. et al. *Cancer research* 2017; 77:2686-2698.) and can be targeted by murine cross-reactive antibodies. Balb/c mice were implanted with Renca tumor cells and when cells reached 100 mm^3 they were treated Q7dx3 treatments with 2.4 mg/kg of the indicated IDC, either non targeting isotype or an EphA2 targeting mAb.

[0722] **FIGURE 33** tracks Renca tumor volumes in untreated, tumor (EphA2) targeted TLR7/8 agonist treated, and non-targeted TLR7/8 agonist treated mice. When Renca tumor growth was followed over time post treatment with EphA2 targeted TLR7/8 IDC, a marked tumor growth delay was noted. Additionally, the tumor-targeted TLR treatment resulted in 50% durable complete tumor cures in the treated animals. Notably, this anti-tumor activity was not seen in animals treated with a non-targeted isotype control TLR7/8 IDC demonstrating specificity of the treatment in this tumor model.

[0723] To determine whether EphA2 delivered TLR7/8 agonist to drive anti-tumor activity in the Renca model, Renca tumor-bearing mice were treated with the alternate TLR7/8 drug linker cmpd 11, which is similar to the TLR7/8 agonist used in **FIGURE 33**, but is antibody linked through its C4 position. The results of this analysis are summarized in **FIGURE 34**, which provides tumor volumes in untreated, non-targeted TLR7/8 agonist treated ("Isotype"), and tumor (EphA2) targeted TLR7/8 agonist treated mice. This drug linker generally shows ~4x decrease in potency. Nonetheless, when dosed at a similar dose of 2 mg/kg, it was still able to drive anti-tumor activity with substantial tumor growth delayed noted for several of the animals when delivered via EphA2.

[0724] To determine if this tumor-targeted TLR7/8 IDC would have activity in other tumor models, Balb/c mice containing CT26 murine colon carcinoma tumors were treated with tumor (EphA2) targeted TLR7/8 agonist and non-targeted TLR7/8 agonist complexes. The results of this analysis are provided in **FIGURE 35**. EphA2 targeted TLR7/8 IDC exhibited substantial anti-tumor activity and growth delay with 83% of the animals reaching durable complete tumor cures. In this model, the non-targeted isotype control TLR7/8 IDC also resulted in some tumor growth delaying, though it was decreased vs the targeted molecule and did not drive any curative activity.

[0725] As summarized in **FIGURE 36**, this mouse model was also subjected to treatment with a similar dose of the less potent TLR7/8 drug linker cmpd 11. As seen in the Renca tumor model, the EphA2 targeted cmpd 11 TLR7/8 agonist IDC was also able to drive substantial anti-tumor activity in a subset of animals with 50% of the animals achieving full cures and all animals benefiting from tumor growth delay. Conversely, non-targeted, isotype conjugated TLR7/8 agonist demonstrated greatly decreased anti-tumor activity with only one out of the eight animals showing any response to treatment. These data support that tumor targeting of TLR7/8 agonists, with varying drug linkers, can drive specific, potent anti-tumor activity across a range of tumor models.

[0726] Activity in an additional EphA2-expressing model, the breast carcinoma model 4T1, was also assessed. The results of this analysis are provided in **FIGURE 37**, with tumor volumes

summarized for untreated, bare EphA2-targeted antibody treated, and TLR7/8 agonist EphA2-targeted antibody conjugate treated mice. For this model, animals were treated with a 3 mg/kg dose of the EphA2 antibody alone (to determine if the mAb alone can drive activity in this model) or the targeted TLR7/8 IDC. No tumor growth delay or activity was seen with the antibody alone suggesting that treatment with this antibody does not drive any of the anti-tumor activity seen. However, use of the EphA2 targeted TLR7/8 IDC did result in some tumor growth delay. The response to the tumor targeted TLR7/8 IDC in this model was muted compared to that seen in CT26 or Renca, likely concomitant with the differing baseline TMEs between the models.

[0727] In addition to assessing how tumors respond to either immune targeted or tumor targeted TLR7/8 agonist delivered via IDC, tumor volume responses with agonist directly delivered to both tumor and immune cells were assessed. This analysis leveraged a target that is known to be expressed on both cell types in the intratumoral microenvironment. Specifically, Balb/c mice were implanted with CT26 syngeneic colon carcinoma cells and when tumors reached 100 mm^3 tumor were either left untreated or were treated with the antibody alone, a non-targeted, isotype antibody conjugated to the TLR7/8 agonist drug linker cmpd 11 or drug linker conjugated to the tumor/immune targeted mAb. Animals were dosed with 2 mg/kg every 7 days for 3 doses total and followed over time for tumor growth and response. The results of these analyses are summarized in **FIGURE 38**. Although no cures were observed with the IDC, 2/8 of the naked antibody treated animals were fully cured. Median tumor volumes per group demonstrate an advantage with the TLR7/8 containing IDC vs the naked tumor/immune targeted mAb in terms of tumor growth delay.

EXAMPLE 47

Targeted ADC Tumor Cell Stimulation

[0728] This example covers PDL1 targeted ADC activity against tumor cells. To determine whether tumor cells respond to stimulation by PDL1 targeting ADCs with TLR7/8 agonist payloads, tumor cell lines from various indications were stimulated with multiple ADCs over pg to μg concentration ranges. **FIGURES 39A-F** provide cell survival for Hodgkin's lymphoma (CellBank L540CY), breast carcinoma (CellBank MDAMB231), pancreatic carcinoma (CellBank BXPC3), lung carcinoma (CellBank EBC1), anaplastic large-cell lymphoma (CellBank DEL), and CD30-positive anaplastic large T-cell lymphoma (CellBank KARPAS299) tumors, respectively. Each tumor cell line was contacted with a vedotin payload targeted to PDL1 (SEQ ID NO: 3 and 5); compound 14 coupled to a non-targeting antibody; compound 14 targeted to PDL1 (Atezolizumab); compound 14 targeted to PDL1 (SEQ ID NO: 3 and 5); and compound 14

coupled to the non-targeting antibody. As a control, each cell line was stimulated by an ADC targeting the vedotin payload to a highly expressed tumor antigen.

[0729] Several tumor cell lines demonstrated cytotoxicity in response to a PDL1 targeted vedotin conjugate, generally corresponding to the levels of PDL1 expressed by the various tumor cells. In particular, the two anaplastic large-cell lymphoma cell lines exhibited nearly complete treatment with PDL1-targeted vedotin payloads. However, PDL1-targeting ADCs with TLR7/8 agonist payloads did not induce any appreciable amount of cell death. Notably, TLR7/8-treated cells also did not demonstrate any cell growth – contrary to some published reports. These data demonstrate that some PDL1 TLR7/8 agonist containing ADCs do not exhibit direct cytotoxic effects on tumor cells.

EXAMPLE 48

ADC Stimulated Cytokine Induction

[0730] To determine whether tumor cells respond to PDL1 targeted TLR7/8 agonist ADCs, tumor cell lines from various indications were assessed for cytokine induction following ADC stimulation. Several tumor cell lines are known to induce cytokine release in response to other immune agonists such as Sting agonists. Accordingly, cytokine induction can serve as a marker for ADC-mediated tumor cell immunomodulation. In this example, four cancer cell lines were assessed for induction of 12 different cytokines.

[0731] **FIGURES 40A-D** summarize interleukin-6 (IL-6) induction in pancreatic carcinoma (CellBank BXPC3), human lung squamous cell carcinoma (EBC1), and anaplastic large-cell lymphoma (CellBank DEL and KARPS299) tumor cells following incubation with the ADCs outlined in **EXAMPLE 46**. Tumor antigen targeted vedotin elicited IL-6 induction in each of the tumor cell lines, as well as additional cell line-specific responses (e.g., TNFα and IP10 induction, data not shown). Dose dependent cytokine induction was also seen in response to the PDL1 targeted vedotin, but to a lesser extent than for the tumor antigen targeted vedotin. These responses were generally concomitant with PDL1 expression levels of the various cell lines (i.e. Karpas and DEL expressed higher levels of PDL1 and exhibited greater IL-6 induction than BXPC3 and EBC1). However, the TLR7/8 agonist containing ADCs did not induce induction for any of the 12 cytokines assessed. These data suggest that PDL1 containing tumor cells likely do not contain the TLR7 or TLR8 receptors necessary for response to certain imidazoquinoline agonists.

EXAMPLE 49

ADC-Mediated Immune Activation

[0732] This example covers immune activation by PDL1 TLR7/8 agonist containing ADCs. Un-activated "M0" macrophages, pro-inflammatory "M1" macrophages, and anti-inflammatory "M2" macrophages, were created by incubating isolated monocytes with MCSF, IFNG or IL10, respectively. These macrophages were then assessed for cytokine production following incubation with various ADCs.

[0733] **FIGURES 41A-C** summarize IL-6 production by the M0 (**FIGURE 41A**), M1 (**FIGURE 41B**), and M2 (**FIGURE 41C**) macrophage populations treated with a non-targeting antibody coupled to compound 9, a non-targeting antibody coupled to compound 14, TAM-antigen targeted compound 9, PDL1-targeted (SEQ ID NO: 3 and 5), compound 14, and naked PDL1 antibody (SEQ ID NO: 3 and 5). As a further control, cytokine production was measured for untreated macrophage populations. Treatment of these macrophages with the relatively ubiquitous and highly internalizing TAM-antigen was able to induce cytokine production from all three macrophage populations in a dose dependent manner. However, activation of the immune cells were more restricted with a PDL1 targeted TLR7/8 agonist. This ADC only appreciably induced re-activation of the M1 subset of macrophages and to a lesser extent the M0 macrophages. These activation data correlate with PDL1 expression levels, and suggest that a 'threshold' PDL1 expression level may be required to deliver sufficient TLR7/8 agonist payload to induce immune cell activation.

EXAMPLE 50

ADC Activity Within Tumor Microenvironments

[0734] This example covers influences from tumor microenvironments on ADC stimulation. To assess how PDL1 TLR7/8 agonist ADCs affect immune cells in a tumor-like environment, a tumor and immune co-culture system was used, whereby either Karpas299 or EBC-1 tumor cells were co-incubated with primary immune PBMCs and then treated with various ADC treatments and assessed for immune activation 72 hours post treatment. **FIGURES 42-A-F** summarize immune activation responses in tumor and immune cell co-cultures following treatment with various ADCs. CD69 (**FIGURES 42A-B**), IFN-γ (**FIGURES 42C-D**), and CD66 (**FIGURES 42E-F**) expression were measured following incubation of the tumor cells with PDL1 (SEQ ID NO: 3 and 5) targeted compound 14, non-targeted compound 9, and naked PDL1 (SEQ ID NO:3 and 5) antibodies. In the higher PDL1 expressing tumor cells, Karpas299, a clear dose dependent relationship to activate an immune response was seen in response to the PDL1 targeted TLR7/8

agonist. This was exhibited by CD8 T cell activation seen by an increase in CD69 expression on the surface of CD8 T cells as well a dose dependent induction of IFN-γ in the culture supernatant. Furthermore, activation of the monocyte lineage was indicated by an increase in the level of CD86 on the surface of these cells in an ADC dose dependent manner. These phenotypic changes were also seen in the co-culture with the lower expressing PDL1 cell line EBC-1 but generally to a lesser extent.

EXAMPLE 51

PDL1-Targeted TLR7/8 ADC Tumor Assays

[0735] In this example, dissociated human tumors from 10 different non-small cell lung cancer (NSCLC) subjects were treated and assessed to determine whether immune cell activation could be seen in a primary human tumor. **FIGURE 43** summarizes the frequencies of CD45+ PDL1+ immune cells and CD45- PDL1+ tumor cells from tumors from each subject. Cytokine induction from the tumors was measured following treatment with 50 ug/ml non-targeting non targeted-compound 14 adduct, PDL1-targeted (SEQ ID NO: 3 and 5) compound 14, and naked PDL1 antibody (SEQ ID NO: 3 and 5).

[0736] As shown in **FIGURES 44A-B**, in almost all subjects, marked cytokine induction was seen in response to the PDL1 targeted TLR7/8 agonist. PDL1-targeted compound 14 induced higher IL-6 (**FIGURE 44A**) and TNFα (**FIGURE 44B**) responses than for either the mAb alone or for the non-targeting control. A lower ADC concentration was also tested, and a dose dependent relationship was seen (data not shown). Clear correlations between PDL1 expression at baseline and immune activation were difficult to discern. These data may suggest that PDL1 TLR7/8 ADC activity may require a PDL1 expression threshold, and can therefore demonstrate activity across a wide range of patients and tumors.

EXAMPLE 52

Tumor Volume Reduction by PDL1-Targeted ADCs Bearing TLR7/8 Payloads

[0737] This example covers activity of PDL1-targeted TLR7/8 agonist payload ADCs in a mouse *in vivo* tumor model. The ADCs were evaluated in a mouse syngeneic system in order to assess the effects of a fully competent immune system. Genetically engineered mice containing human PD1 and PDL1 in place of the mice orthologs were used in conjunction with a mouse colon carcinoma line, MC38, that had been engineered to express human PDL1. When tumors reached ~ 100 mm^3 in size, the animals were treated with biweekly doses of ADC or naked antibody, and tumor growth was followed over time.

[0738] **FIGURE 45** summarizes changes in tumor volume over 4 weeks of treatment with untargeted and two PDL1-targeted (SEQ ID NO: 3 and 5; Atezolizumab) compound 14 payload ADCs, as well as naked PDL1 antibody (SEQ ID NO: 3 and 5). Untreated mice were tracked as a further control. Treatment with the naked PDL1 blocking antibody in this model only resulted in mild tumor growth delay. However, use of a PDL1 targeted TLR7/8 agonist was able to drive substantial anti-tumor activity resulting in curative responses in 100% of the animals. Moderate curative activity was also seen with a non-targeted TLR7/8 ADC, though a marked reduction in curative rate (75%) was observed.

[0739] **FIGURES 46A-C** provide tumor volume time courses for 2 mg/kg (**FIGURE 46A**), 1 mg/kg (**FIGURE 46B**), and 0.5 mg/kg (**FIGURE 46C**) doses of the PDL1-targeted (SEQ ID NO: 3 and 5) compound 14 payload ADC. As can be seen in **FIGURE 46C**, strong anti-tumor activity was also retained at lower doses of PDL1 targeted TLR7/8 agonist ADC. Even at relatively low doses of 0.5 mg/kg, 75% of animals were able to reach full complete response and rejection of their tumors, demonstrating the potent anti-tumor capacity of PDL1-targeted TLR7/8 agonist payload ADCs.

EXAMPLE 53

ADC-Mediated Tumor Growth Inhibition

[0740] This example covers tumor growth inhibition by PDL1-targeted ADCs with TLR7/8 agonist payloads in a mouse *in vivo* tumor model. Syngeneic mice were used in conjunction with human PDL1 expressing renal carcinoma Renca cells. Once tumors reached ~ 100 mm^3 in size, tumor growth was followed during 4 week ADC and naked antibody treatments as outlined in **EXAMPLE 51**.

[0741] **FIGURES 47A-D** provide tumor growth responses of the Renca tumors expressing human PDL1 for untreated mice (**FIGURE 47A**), naked PDL1 antibody-treated mice (**FIGURE 47B**), mice treated with non-targeted compound 14 payload bearing ADCs (**FIGURE 47C**), and mice treated with PDL1-targeted (SEQ ID NO: 3 and 5) compound 14 payload-bearing ADCs (**FIGURE 47D**). In this tumor model the naked PDL1 antibody demonstrated no response relative to the untreated mice. However use of the PDL1 targeted TLR7/8 agonist ADC resulted in tumor growth delay and inhibition of over 50% (**FIGURE 48**).

EXAMPLE 54

Immune Repertoires from Various Tumors

[0742] This example assesses whether differences in baseline tumor microenvironment can contribute to responsiveness to a PDL1 TLR IDC. The immune repertoire of various tumors were assessed using immunohistochemistry. The tumors were harvested at the time of dosing and stained for markers of CD8 T cells, CD4 T cells, T regulatory cells and macrophages (F4/80). As shown in **FIGURES 49A-D** (comparing MC38 (left) and Renca tumors (right)), only minimal differences in CD4 T cell levels between the two models were seen (**FIGURE 49A**). However, while there were not statistically significant differences, there were trends for higher levels of Tregs (FIGURE 49B, p value 0.08) and CD8 T cells (**FIGURE 49C**, p value 0.18) seen at baseline in the most responsive MC38 model. Furthermore, for the F4/80 stain there was a statistically significant (**FIGURE 49D**, p value 0.02) increase in the level of macrophages seen at the time of treatment in the MC38 model compared to the Renca model.

[0743] **FIGURES 50A-B** provide tumor growth responses of MC38 (**FIGURE 50A**) and Renca tumors (**FIGURE 50B**) implanted in mouse models treated with 2 mg/kg PDL1-targeted ADCs with Compound 14 payloads. The MC38 tumors, which contained higher levels of macrophages than the Renca tumors, also displayed greater responsiveness to the PDL1-targeted treatments. These data suggest that macrophages may be important for driving immune activation in response to a TLR7/8 IDC.

EXAMPLE 55

Immune Repertoires from Various Tumors

[0744] In this example, two different CT26 colon carcinoma tumor models were used to determine how tumor and immune cell expression impacts anti-tumor activity of PDL1-targeted and non-targeted TLR7/8 agonist. Both tumor models included immune and tumor cells. In the first tumor model, PDL1 was only expressed by the immune cells. In the second tumor model, PDL1 was expressed by the immune and tumor cells.

[0745] Tumor growth over time in each of these models was monitored post-treatment with an isotype (non-targeted) antibody conjugated to compound 14 or a PDL1 antibody conjugated to compound 14. Tumor growth and associated AUC data are summarized in **FIGURE 51** for a tumor model with tumor and immune cell PDL1 expression (left column) and for the tumor model in which PDL1 was only expressed by immune cells (right column). In the model that expressed high levels of PDL1 on the tumor and the immune cells, tumor growth delay was observed in response to both targeted (PDL1 antibody) and non-targeted (isotype) treatments. In this model,

an increase in anti-tumor activity (delineated by an increase in area under the tumor growth curve (AUC.3)) was observed following treatment with PDL1-targeted compound 14 over the isotype (non-targeted) conjugated compound 14. Substantially increased levels of anti-tumor activity were observed in the model in which only immune cells expressed PDL1 relative to the model in which the tumor and immune cells expressed PDL1. In the immune PDL1 model, curative activity was seen in 50% of animals in response to a TLR7/8 conjugated IDC. No statistically significant differences were observed between isotype conjugated and PDL1-targeted compound 14.

[0746] Next, cytokine induction 6 h post-dose was measured in the two tumor models to determine how treatments with PDL1-targeted and isotype-conjugated compound 14 affect systemic cytokine responses. The results of these analyses are summarized in **FIGURE 52**. In this figure, the plots provide IFNg, IL-6, IL-10, IL-12p70, IP10, and MCP1, MIP1a, MIP1b, and TNFa systemic levels. In each plot, the data (from left to right) correspond to untreated CT26 tumors with immune and tumor cell PDL1 expression, CT26 tumors with immune and tumor cell PDL1 expression treated with PDL1-targeted compound 14, CT26 tumors with immune and tumor cell PDL1 expression treated with isotype conjugated compound 14, untreated CT26 tumors with immune cell PDL1 expression, CT26 tumors with immune cell PDL1 expression treated with PDL1-targeted compound 14, CT26 tumors with immune cell PDL1 expression treated with isotype conjugated compound 14.

[0747] For the majority of the nine cytokines measured, isotype conjugated compound 14 induced higher levels of systemic cytokine induction 6 h pose dose than PDL1-targeted compound 14, possibly correlating with non-specific uptake and activity. PDL1-targeted compound 14 generated similar or higher levels of IFNg and IL-6 than isotype conjugated compound 14, demonstrating on target activity of the PDL1-targeted complex. Overall, the trends for systemic cytokine induction were similar for the two tumor models, suggesting that systemic cytokine induction is not affected by levels of PDL1 in the tumor, but are instead likely driven through immune expression and delivery.

[0748] IHC was performed on each of the tumor models to determine why the models responded differently to isotype conjugated and PDL1-targeted compound 14. The results of these analyses are summarized in **FIGURE 53**, which includes multiple plots that show total PDL1 expression in tumor cells from the two models, CD8 expression in tumor cells from the two models, total CD8 expression in stromal cells from the two models, CD4 expression levels in the two tumor models, tumor CD4 levels in the two models, stromal CD4 levels in the two models, F4/80 expression in tumor cells from the two models, and F4/80 expression in stromal cells from the two models. In each plot in **FIGURE 53**, the left column corresponds to the tumor model in

which only immune cells expressed PDL1, while the right column corresponds to the tumor model in which immune and tumor cells expressed PDL1.

[0749] PDL1 expression was only observed in tumor cells from the first model (upper left). There was a significant difference in CD4 expression between the model with immune only PDL1 expression and the tumor model with tumor and immune cell PDL1 expression in whole tissue analysis. However, no statistically significant difference in CD4 levels was observed in tumor or stromal cell-specific measurements. The lower levels of CD4 in the model lacking tumor cell PDL1 expression could suggest a that this tumor model has a less immunosuppressive environment that is more receptive to immunostimulation.

Exemplary Embodiments

[0750] The present disclosure is further described by the following embodiments. The features of each of the embodiments are combinable with any of the other embodiments where appropriate and practical.

[0751] Embodiment 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;

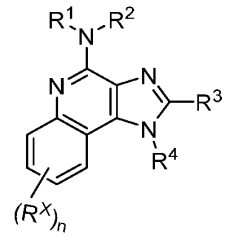
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide;

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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is optionally the point of covalent attachment to L;

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 selected from the group consisting of: the point of covalent attachment to L; hydrogen; -OR^C; -$S(=O)_2R^C$; -C(=O)NR^DR^E; -C(=O)OR^C; -C(=O)SR^C; -C(=S)R^C; -PO_3R^C; and -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 the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, -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, -NR^DR^E, -$C(=O)NR^DR^E$ or -CO_2H; (xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the (-5-10 membered heteroaryl)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_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L;

each R^X is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) 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 instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, (b) the group consisting of hydrogen and C_1-C_6 alkyl; and (c) 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 at most one instance of R^A and R^B is the point of covalent attachment to L;

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

each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) 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)-; and (c) 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;

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

wherein at most one of R^I, R^J, and R^K is the point of covalent attachment to L;

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

wherein Ab comprises a heavy chain variable region having at least 80% sequence identity to a first sequence and a light chain variable region having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20; the first sequence is SEQ ID NO: 44 and the second sequence is SEQ ID NO: 45; the first sequence is SEQ ID NO: 55 and the second sequence is SEQ ID NO: 56; the first sequence is SEQ ID NO: 69 and the second sequence is SEQ ID NO: 70; the first sequence is SEQ ID NO: 83 and the second sequence is SEQ ID NO: 84; the first sequence is SEQ ID NO: 97 and the second sequence is SEQ ID NO: 98; the first sequence is SEQ ID NO: 105 and the second sequence is SEQ ID NO: 106; the first sequence is SEQ ID NO:113 and the second sequence is SEQ ID NO: 114; the first sequence is SEQ ID NO: 121 and the second sequence is SEQ ID NO: 122; the first sequence is SEQ ID NO: 129 and the second sequence is SEQ ID NO: 130; the first sequence is SEQ ID NO: 137 and the second sequence is SEQ ID NO: 138; the first sequence is SEQ ID NO: 153 and the second sequence is SEQ ID NO: 154; the first sequence is SEQ ID NO: 161 and the second sequence is SEQ ID NO: 162; the first sequence is SEQ ID NO: 169 and the second sequence is SEQ ID NO: 170; the first sequence is SEQ ID NO: 177 and the second sequence is SEQ ID NO: 178; the first sequence is SEQ ID NO: 185 and the second sequence is SEQ ID NO: 186; the first sequence is SEQ ID NO: 193 and the second sequence is SEQ ID NO: 194; the first sequence is SEQ ID NO: 201 and the second sequence is SEQ ID NO: 202; the first sequence is SEQ ID NO: 209 and the second sequence is SEQ ID NO: 210; the first sequence is SEQ ID NO: 217 and the second sequence is SEQ ID NO: 218; the first sequence is SEQ ID NO: 225 and the second sequence is SEQ ID NO: 226; the first sequence is SEQ ID NO: 233 and the second sequence is SEQ ID NO: 234; the first sequence is SEQ ID NO: 241 and the second sequence is SEQ ID NO: 242; the first sequence is SEQ ID NO: 249 and the second sequence is SEQ ID NO: 250; the first sequence is SEQ ID NO: 297 and the second sequence is SEQ ID NO: 298; the first sequence is SEQ ID NO: 307 and the second sequence is SEQ ID NO: 308; the first

sequence is SEQ ID NO: 315 and the second sequence is SEQ ID NO: 316; the first sequence is SEQ ID NO: 323 and the second sequence is SEQ ID NO: 324; the first sequence is SEQ ID NO: 331 and the second sequence is SEQ ID NO: 332; the first sequence is SEQ ID NO: 339 and the second sequence is SEQ ID NO: 340; the first sequence is SEQ ID NO: 347 and the second sequence is SEQ ID NO: 348; the first sequence is SEQ ID NO: 355 and the second sequence is SEQ ID NO: 356; the first sequence is SEQ ID NO: 363 and the second sequence is SEQ ID NO: 364; the first sequence is SEQ ID NO: 371 and the second sequence is SEQ ID NO: 372; the first sequence is SEQ ID NO: 379 and the second sequence is SEQ ID NO: 380; the first sequence is SEQ ID NO: 387 and the second sequence is SEQ ID NO: 388; the first sequence is SEQ ID NO: 395 and the second sequence is SEQ ID NO: 396; the first sequence is SEQ ID NO: 403 and the second sequence is SEQ ID NO: 404; the first sequence is SEQ ID NO: 411 and the second sequence is SEQ ID NO: 412; the first sequence is SEQ ID NO: 419 and the second sequence is SEQ ID NO: 420; the first sequence is SEQ ID NO: 427 and the second sequence is SEQ ID NO: 428; the first sequence is SEQ ID NO: 435 and the second sequence is SEQ ID NO: 436; the first sequence is SEQ ID NO: 443 and the second sequence is SEQ ID NO: 444; the first sequence is SEQ ID NO: 451 and the second sequence is SEQ ID NO: 452; the first sequence is SEQ ID NO: 459 and the second sequence is SEQ ID NO: 460; the first sequence is SEQ ID NO: 467 and the second sequence is SEQ ID NO: 468; the first sequence is SEQ ID NO: 475 and the second sequence is SEQ ID NO: 476; the first sequence is SEQ ID NO: 483 and the second sequence is SEQ ID NO: 484; the first sequence is SEQ ID NO: 491 and the second sequence is SEQ ID NO: 492; the first sequence is SEQ ID NO: 501 and the second sequence is SEQ ID NO: 502; the first sequence is SEQ ID NO: 509 and the second sequence is SEQ ID NO: 510; the first sequence is SEQ ID NO: 517 and the second sequence is SEQ ID NO: 518; the first sequence is SEQ ID NO: 525 and the second sequence is SEQ ID NO: 526; the first sequence is SEQ ID NO: 533 and the second sequence is SEQ ID NO: 534; the first sequence is SEQ ID NO: 541 and the second sequence is SEQ ID NO: 542; the first sequence is SEQ ID NO: 549 and the second sequence is SEQ ID NO: 550; the first sequence is SEQ ID NO: 557 and the second sequence is SEQ ID NO: 558; the first sequence is SEQ ID NO: 565 and the second sequence is SEQ ID NO: 566; the first sequence is SEQ ID NO: 574 and the second sequence is SEQ ID NO: 574; the first sequence is SEQ ID NO: 581 and the second sequence is SEQ ID NO: 582; the first sequence is SEQ ID NO: 589 and the second sequence is SEQ ID NO: 590; the first sequence is SEQ ID NO: 597 and the second sequence is SEQ ID NO: 598; the first sequence is SEQ ID NO: 605 and the second sequence is SEQ ID NO: 606; the first sequence is SEQ ID NO: 613 and the second sequence is SEQ ID NO: 614; the first sequence is SEQ ID NO: 621 and the second sequence is SEQ ID NO:

622; the first sequence is SEQ ID NO: 629 and the second sequence is SEQ ID NO: 630; the first sequence is SEQ ID NO: 637 and the second sequence is SEQ ID NO: 638; the first sequence is SEQ ID NO: 645 and the second sequence is SEQ ID NO: 646; the first sequence is SEQ ID NO: 653 and the second sequence is SEQ ID NO: 654; the first sequence is SEQ ID NO: 661 and the second sequence is SEQ ID NO: 662; the first sequence is SEQ ID NO: 669 and the second sequence is SEQ ID NO: 670; the first sequence is SEQ ID NO: 677 and the second sequence is SEQ ID NO: 678; the first sequence is SEQ ID NO: 685 and the second sequence is SEQ ID NO: 686; the first sequence is SEQ ID NO: 693 and the second sequence is SEQ ID NO: 694; the first sequence is SEQ ID NO: 701 and the second sequence is SEQ ID NO: 702; the first sequence is SEQ ID NO: 703 and the second sequence is SEQ ID NO: 704; the first sequence is SEQ ID NO: 711 and the second sequence is SEQ ID NO: 712; the first sequence is SEQ ID NO: 713 and the second sequence is SEQ ID NO: 714; the first sequence is SEQ ID NO: 715 and the second sequence is SEQ ID NO: 716; the first sequence is SEQ ID NO: 731 and the second sequence is SEQ ID NO: 732; the first sequence is SEQ ID NO: 739 and the second sequence is SEQ ID NO: 740; the first sequence is SEQ ID NO: 747 and the second sequence is SEQ ID NO: 748; the first sequence is SEQ ID NO: 755 and the second sequence is SEQ ID NO: 756; the first sequence is SEQ ID NO: 765 and the second sequence is SEQ ID NO: 766; the first sequence is SEQ ID NO: 773 and the second sequence is SEQ ID NO: 774; the first sequence is SEQ ID NO: 781 and the second sequence is SEQ ID NO: 782; the first sequence is SEQ ID NO: 789 and the second sequence is SEQ ID NO: 790; the first sequence is SEQ ID NO: 797 and the second sequence is SEQ ID NO: 798; the first sequence is SEQ ID NO: 805 and the second sequence is SEQ ID NO: 806; the first sequence is SEQ ID NO: 813 and the second sequence is SEQ ID NO: 814; the first sequence is SEQ ID NO: 821 and the second sequence is SEQ ID NO: 822; the first sequence is SEQ ID NO: 829 and the second sequence is SEQ ID NO: 830; the first sequence is SEQ ID NO: 837 and the second sequence is SEQ ID NO: 838; the first sequence is SEQ ID NO: 845 and the second sequence is SEQ ID NO: 846; the first sequence is SEQ ID NO: 853 and the second sequence is SEQ ID NO: 854; the first sequence is SEQ ID NO: 861 and the second sequence is SEQ ID NO: 862; the first sequence is SEQ ID NO: 869 and the second sequence is SEQ ID NO: 870; the first sequence is SEQ ID NO: 877 and the second sequence is SEQ ID NO: 878; the first sequence is SEQ ID NO: 885 and the second sequence is SEQ ID NO: 886; the first sequence is SEQ ID NO: 893 and the second sequence is SEQ ID NO: 894; the first sequence is SEQ ID NO: 900 and the second sequence is SEQ ID NO: 901; the first sequence is SEQ ID NO: 909 and the second sequence is SEQ ID NO: 910; the first sequence is SEQ ID NO: 917 and the second sequence is SEQ ID NO: 918; the first sequence is SEQ ID NO: 925 and the second sequence is

SEQ ID NO: 926; the first sequence is SEQ ID NO: 933 and the second sequence is SEQ ID NO: 934; the first sequence is SEQ ID NO: 941 and the second sequence is SEQ ID NO: 942; the first sequence is SEQ ID NO: 943 and the second sequence is SEQ ID NO: 944; the first sequence is SEQ ID NO: 951 and the second sequence is SEQ ID NO: 952; the first sequence is SEQ ID NO: 959 and the second sequence is SEQ ID NO: 960; the first sequence is SEQ ID NO: 967 and the second sequence is SEQ ID NO: 968; the first sequence is SEQ ID NO: 975 and the second sequence is SEQ ID NO: 976; the first sequence is SEQ ID NO: 983 and the second sequence is SEQ ID NO: 984; the first sequence is SEQ ID NO: 991 and the second sequence is SEQ ID NO: 992; the first sequence is SEQ ID NO: 993 and the second sequence is SEQ ID NO: 994; the first sequence is SEQ ID NO: 995 and the second sequence is SEQ ID NO: 996; the first sequence is SEQ ID NO: 1003 and the second sequence is SEQ ID NO: 1004; the first sequence is SEQ ID NO: 1011 and the second sequence is SEQ ID NO: 1012; the first sequence is SEQ ID NO: 1019 and the second sequence is SEQ ID NO: 1020; the first sequence is SEQ ID NO: 1027 and the second sequence is SEQ ID NO: 1028; the first sequence is SEQ ID NO: 1035 and 1036; or the first sequence is SEQ ID NO: 1043 and the second sequence is SEQ ID NO: 1044.

[0752] Embodiment 2. The ADC of embodiment 1, wherein: the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20; the first sequence is SEQ ID NO: 83 and the second sequence is SEQ ID NO: 84; the first sequence is SEQ ID NO: 97 and the second sequence is SEQ ID NO: 98; the first sequence is SEQ ID NO: 105 and the second sequence is SEQ ID NO: 106; the first sequence is SEQ ID NO:113 and the second sequence is SEQ ID NO: 114; the first sequence is SEQ ID NO: 121 and the second sequence is SEQ ID NO: 122; the first sequence is SEQ ID NO: 129 and the second sequence is SEQ ID NO: 130; the first sequence is SEQ ID NO: 137 and the second sequence is SEQ ID NO: 138; the first sequence is SEQ ID NO: 153 and the second sequence is SEQ ID NO: 154; the first sequence is SEQ ID NO: 161 and the second sequence is SEQ ID NO: 162; the first sequence is SEQ ID NO: 169 and the second sequence is SEQ ID NO: 170; the first sequence is SEQ ID NO: 177 and the second sequence is SEQ ID NO: 178; the first sequence is SEQ ID NO: 185 and the second sequence is SEQ ID NO: 186; the first sequence is SEQ ID NO: 193 and the second sequence is SEQ ID NO: 194; the first sequence is SEQ ID NO: 201 and the second sequence is SEQ ID NO: 202; the first sequence is SEQ ID NO: 209 and the second sequence is SEQ ID NO: 210; the first sequence is SEQ ID NO: 217 and the second sequence is SEQ ID NO: 218; the first sequence is SEQ ID NO: 225 and the second sequence is SEQ ID NO: 226; the first sequence is SEQ ID NO: 233 and the second sequence is SEQ ID NO: 234; the first sequence is SEQ ID NO: 241 and the second sequence is SEQ ID NO: 242; the first sequence is SEQ ID NO: 249 and the second sequence is SEQ ID NO: 250; the first

sequence is SEQ ID NO: 629 and the second sequence is SEQ ID NO: 630; the first sequence is SEQ ID NO: 637 and the second sequence is SEQ ID NO: 638; the first sequence is SEQ ID NO: 645 and the second sequence is SEQ ID NO: 646; the first sequence is SEQ ID NO: 653 and the second sequence is SEQ ID NO: 654; the first sequence is SEQ ID NO: 661 and the second sequence is SEQ ID NO: 662; the first sequence is SEQ ID NO: 669 and the second sequence is SEQ ID NO: 670; the first sequence is SEQ ID NO: 677 and the second sequence is SEQ ID NO: 678; the first sequence is SEQ ID NO: 685 and the second sequence is SEQ ID NO: 686; the first sequence is SEQ ID NO: 693 and the second sequence is SEQ ID NO: 694; the first sequence is SEQ ID NO: 701 and the second sequence is SEQ ID NO: 702; the first sequence is SEQ ID NO: 703 and the second sequence is SEQ ID NO: 704; the first sequence is SEQ ID NO: 711 and the second sequence is SEQ ID NO: 712; the first sequence is SEQ ID NO: 713 and the second sequence is SEQ ID NO: 714; the first sequence is SEQ ID NO: 715 and the second sequence is SEQ ID NO: 716; or the first sequence is SEQ ID NO: 1027 and the second sequence is SEQ ID NO: 1028.

[0753] Embodiment 3. The ADC of embodiment 1 or 2, wherein the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20.

[0754] Embodiment 4. The ADC of any one of embodiments 1-3 wherein the heavy chain variable region has at least 90% sequence identity to the first sequence and the light chain variable region has at least 90% sequence identity to the second sequence.

[0755] Embodiment 5. The ADC of any one of embodiments 1-4, wherein the heavy chain variable region has at least 98% sequence identity to the first sequence and the light chain variable region has at least 98% sequence identity to the second sequence.

[0756] Embodiment 6. 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;

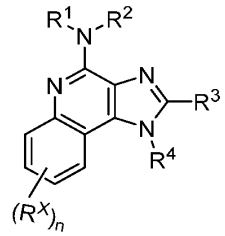
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide;

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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is optionally the point of covalent attachment to L;

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 selected from the group consisting of: the point of covalent attachment to L; hydrogen; $-OR^C$; $-S(=O)_2R^C$; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; $-C(=S)R^C$; $-PO_3R^C$; and -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 the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, $-NR^DR^E$, $-[N(C_1\text{-}C_6\text{ alkyl})R^DR^E]^+$, or 1-3 independently selected halogen; (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-NR^DR^E$, $-C(=O)NR^DR^E$ or $-CO_2H$; (xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the (-5-10 membered heteroaryl)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 C_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L;

each R^X is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) 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 instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, (b) the group consisting of hydrogen and C_1-C_6 alkyl; and (c) 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 at most one instance of R^A and R^B is the point of covalent attachment to L;

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

each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) 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)-; and (c) 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;

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

wherein at most one of R^I, R^J, and R^K is the point of covalent attachment to L;

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

wherein Ab comprises a heavy chain having at least 80% sequence identity to a first sequence and a light chain having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 1 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 2 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 4 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 6 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 7 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 8 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 9 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 46 and the second sequence is SEQ ID NO: 48; the first sequence is SEQ ID NO: 47 and the second sequence is SEQ ID NO: 48; the first sequence is SEQ ID NO: 57 and the second sequence is SEQ ID NO: 59; the first sequence is SEQ ID NO: 58 and the second sequence is SEQ ID NO: 59; the first sequence is SEQ ID NO: 60 and the second sequence is SEQ ID NO: 62; the first sequence is SEQ ID NO: 61 and the second sequence is SEQ ID NO: 62; the first sequence is SEQ ID NO: 71 and the second sequence is SEQ ID NO: 73; the first sequence is SEQ ID NO: 72 and the second sequence is SEQ ID NO: 73; the first sequence is SEQ ID NO: 74 and the second sequence

is SEQ ID NO: 76; the first sequence is SEQ ID NO: 75 and the second sequence is SEQ ID NO: 76; the first sequence is SEQ ID NO: 85 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 86 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 88 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 89 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 251 and the second sequence is SEQ ID NO: 252; the first sequence is SEQ ID NO: 253 and the second sequence is SEQ ID NO: 254; the first sequence is SEQ ID NO: 255 and the second sequence is SEQ ID NO: 256; the first sequence is SEQ ID NO: 257 and the second sequence is SEQ ID NO: 258; the first sequence is SEQ ID NO: 259 and the second sequence is SEQ ID NO: 260; the first sequence is SEQ ID NO: 261 and the second sequence is SEQ ID NO: 262; the first sequence is SEQ ID NO: 263 and the second sequence is SEQ ID NO: 264; the first sequence is SEQ ID NO: 265 and the second sequence is SEQ ID NO: 266; the first sequence is SEQ ID NO: 267 and the second sequence is SEQ ID NO: 268; the first sequence is SEQ ID NO: 269 and the second sequence is SEQ ID NO: 270; the first sequence is SEQ ID NO: 271 and the second sequence is SEQ ID NO: 272; the first sequence is SEQ ID NO: 273 and the second sequence is SEQ ID NO: 274; the first sequence is SEQ ID NO: 275 and the second sequence is SEQ ID NO: 276; the first sequence is SEQ ID NO: 277 and the second sequence is SEQ ID NO: 278; the first sequence is SEQ ID NO: 279 and the second sequence is SEQ ID NO: 280; the first sequence is SEQ ID NO: 281 and the second sequence is SEQ ID NO: 282; the first sequence is SEQ ID NO: 283 and the second sequence is SEQ ID NO: 284; the first sequence is SEQ ID NO: 285 and the second sequence is SEQ ID NO: 286; the first sequence is SEQ ID NO: 287 and the second sequence is SEQ ID NO: 288; the first sequence is SEQ ID NO: 289 and the second sequence is SEQ ID NO: 290; the first sequence is SEQ ID NO: 299 and the second sequence is SEQ ID NO: 300; the first sequence is SEQ ID NO: 493 and the second sequence is SEQ ID NO: 494; the first sequence is SEQ ID NO: 717 and the second sequence is SEQ ID NO: 718; the first sequence is SEQ ID NO: 719 and the second sequence is SEQ ID NO: 720; the first sequence is SEQ ID NO: 721 and the second sequence is SEQ ID NO: 722; the first sequence is SEQ ID NO: 723 and the second sequence is SEQ ID NO: 724; or the first sequence is SEQ ID NO: 757 and the second sequence is SEQ ID NO: 758.

[0757] Embodiment 7. The ADC of embodiment 6, wherein: the first sequence is SEQ ID NO: 1 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 2 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 4 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 6 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ

ID NO: 7 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 8 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 9 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 85 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 86 and the second sequence is SEQ ID NO: 87; the first sequence is SEQ ID NO: 88 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 89 and the second sequence is SEQ ID NO: 90; the first sequence is SEQ ID NO: 251 and the second sequence is SEQ ID NO: 252; the first sequence is SEQ ID NO: 253 and the second sequence is SEQ ID NO: 254; the first sequence is SEQ ID NO: 255 and the second sequence is SEQ ID NO: 256; the first sequence is SEQ ID NO: 257 and the second sequence is SEQ ID NO: 258; the first sequence is SEQ ID NO: 259 and the second sequence is SEQ ID NO: 260; the first sequence is SEQ ID NO: 261 and the second sequence is SEQ ID NO: 262; the first sequence is SEQ ID NO: 263 and the second sequence is SEQ ID NO: 264; the first sequence is SEQ ID NO: 265 and the second sequence is SEQ ID NO: 266; the first sequence is SEQ ID NO: 267 and the second sequence is SEQ ID NO: 268; the first sequence is SEQ ID NO: 269 and the second sequence is SEQ ID NO: 270; the first sequence is SEQ ID NO: 271 and the second sequence is SEQ ID NO: 272; the first sequence is SEQ ID NO: 273 and the second sequence is SEQ ID NO: 274; the first sequence is SEQ ID NO: 275 and the second sequence is SEQ ID NO: 276; the first sequence is SEQ ID NO: 277 and the second sequence is SEQ ID NO: 278; the first sequence is SEQ ID NO: 279 and the second sequence is SEQ ID NO: 280; the first sequence is SEQ ID NO: 281 and the second sequence is SEQ ID NO: 282; the first sequence is SEQ ID NO: 283 and the second sequence is SEQ ID NO: 284; the first sequence is SEQ ID NO: 285 and the second sequence is SEQ ID NO: 286; the first sequence is SEQ ID NO: 287 and the second sequence is SEQ ID NO: 288; the first sequence is SEQ ID NO: 289 and the second sequence is SEQ ID NO: 290; the first sequence is SEQ ID NO: 717 and the second sequence is SEQ ID NO: 718; the first sequence is SEQ ID NO: 719 and the second sequence is SEQ ID NO: 720; the first sequence is SEQ ID NO: 721 and the second sequence is SEQ ID NO: 722; or the first sequence is SEQ ID NO: 723 and the second sequence is SEQ ID NO: 724.

[0758] Embodiment 8. The ADC of embodiment 6 or 7, wherein: the first sequence is SEQ ID NO: 1 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 2 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 4 and the second sequence is SEQ ID NO: 5; the first sequence is SEQ ID NO: 6 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO: 7 and the second sequence is SEQ ID NO: 10; the first sequence is SEQ ID NO:

8 and the second sequence is SEQ ID NO: 10; or the first sequence is SEQ ID NO: 9 and the second sequence is SEQ ID NO: 10.

[0759] Embodiment 9. The ADC of any one of embodiments 6-8, wherein the heavy chain has at least 90% sequence identity to the first sequence and the light chain has at least 90% sequence identity to the second sequence.

[0760] Embodiment 10. The ADC of any one of embodiments 6-9, wherein the heavy chain has at least 98% sequence identity to the first sequence and the light chain has at least 98% sequence identity to the second sequence.

[0761] Embodiment 11. 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;

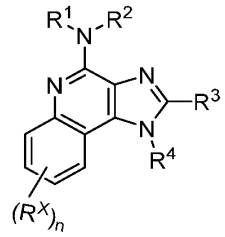
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide;

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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is optionally the point of covalent attachment to L;

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 selected from the group consisting of: the point of covalent attachment to L; hydrogen; -OR^C; -$S(=O)_2R^C$; -C(=O)NR^DR^E; -C(=O)OR^C; -C(=O)SR^C; -C(=S)R^C; -PO_3R^C; and -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 the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, -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, -NR^DR^E, -C(=O)NR^DR^E or -CO_2H; (xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the (-5-10 membered heteroaryl)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_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L;

each R^X is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) 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 instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, (b) the group consisting of hydrogen and C_1-C_6 alkyl; and (c) 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 at most one instance of R^A and R^B is the point of covalent attachment to L;

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

each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) 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)-; and (c) 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;

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

wherein at most one of R^I, R^J, and R^K is the point of covalent attachment to L;

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

wherein Ab comprises a CDR-H1 comprising at least 80% sequence identity to a first sequence, a CDR-H2 comprising at least 80% sequence identity to a second sequence, a CDR-H3 comprising at least 80% sequence identity to a third sequence, a CDR-L1 comprising at least 80% sequence identity to a fourth sequence, a CDR-L2 comprising at least 80% sequence identity to a fifth sequence, and a CDR-L3 comprising at least 80% sequence identity to a sixth sequence, wherein the first, second, third, fourth, fifth, and sixth sequences are: SEQ ID NO: 13, 14, 15, 16, 17, and 18, respectively; SEQ ID NO: 21, 22, 23, 24, 25, and 26, respectively; SEQ ID NO: 38, 39, 40, 41, 42, and 43, respectively; SEQ ID NO: 49, 50, 51, 52, 53, and 54, respectively; SEQ ID NO: 63, 64, 65, 66, 67, and 68, respectively; SEQ ID NO: 77, 78, 79, 80, 81, and 82, respectively; SEQ ID NO: 91, 92, 93, 94, 95, and 96, respectively; SEQ ID NO: 99, 100, 101, 102, 103, and 104, respectively; SEQ ID NO: 107, 108, 109, 110, 111, and 112, respectively; SEQ ID NO: 115, 116, 117, 118, 119, and 120, respectively; SEQ ID NO: 123, 124, 125, 126, 127, and 128, respectively; SEQ ID NO: 131, 132, 133, 134, 135, and 136, respectively; SEQ ID NO: 139, 140, 141, 142, 143, and 144, respectively; SEQ ID NO: 147, 148, 149, 150, 151, and 152, respectively; SEQ ID NO: 155, 156, 157, 158, 159, and 160, respectively; SEQ ID NO: 163, 164, 165, 166, 167, and 168, respectively; SEQ ID NO: 171, 172, 173, 174, 175, and 176, respectively; SEQ ID NO: 179, 180, 181, 182, 183, and 184, respectively; SEQ ID NO: 187, 188, 189, 190, 191, and 192, respectively; SEQ ID NO: 195, 196, 197, 198, 199, and 200, respectively; SEQ ID NO: 203, 204, 205, 206, 207 and 208, respectively; SEQ ID NO: 211, 212, 213, 214, 215, and 216, respectively; SEQ ID NO: 219, 220, 221, 222, 223, and 224, respectively; SEQ ID NO: 227, 228, 229, 230, 231, and 232, respectively; SEQ ID NO: 235, 236, 237, 238, 239, and 240, respectively; SEQ ID NO: 243, 244, 245, 246, 247, and 248, respectively; SEQ ID NO: 291, 292, 293, 294, 295, and 296, respectively; SEQ ID NO: 301, 302, 303, 304, 305, and 306, respectively; SEQ ID NO: 309, 310, 311, 312, 313, and 314, respectively; SEQ ID NO: 317, 318, 319, 320, 321, and 322, respectively; SEQ ID NO: 325, 326, 327, 328, 329, and 330, respectively; SEQ ID NO: 333, 334, 335, 336, 337, and 338, respectively; SEQ ID NO: 341, 342, 343, 344, 345, and 346, respectively; SEQ ID NO: 349, 350, 351, 352, 353, and 354, respectively; SEQ ID NO: 357, 358, 359, 360, 361, and 362, respectively; SEQ ID NO: 365, 366, 367, 368, 369, and 370, respectively; SEQ ID NO: 373, 374, 375, 376, 377, and 378, respectively; SEQ ID NO: 381, 382, 383, 384, 385, and 386, respectively; SEQ ID NO: 389, 390, 391, 392, 393, and 394, respectively; SEQ ID NO: 397, 398, 399, 400, 401, and 402, respectively; SEQ ID NO: 405, 406, 407, 408, 409, and 410, respectively; SEQ ID NO: 413, 414, 415, 416, 417, and 418, respectively; SEQ ID NO: 421, 422, 423, 424, 425, and 426, respectively; SEQ ID NO: 429, 430, 431, 432, 433, and 434,

respectively; SEQ ID NO: 437, 438, 439, 440, 441, and 442, respectively; SEQ ID NO: 445, 446, 447, 448, 449, and 450, respectively; SEQ ID NO: 453, 454, 455, 456, 457, and 458, respectively; SEQ ID NO: 461, 462, 463, 464, 465, and 466, respectively; SEQ ID NO: 469, 470, 471, 472, 473, and 474, respectively; SEQ ID NO: 477, 478, 479, 480, 481, and 482, respectively; SEQ ID NO: 485, 486, 487, 488, 489, and 490, respectively; SEQ ID NO: 495, 496, 497, 498, 499, and 500, respectively; SEQ ID NO: 503, 504, 505, 506, 507, and 508, respectively; SEQ ID NO: 511, 512, 513, 514, 515, and 516, respectively; SEQ ID NO: 519, 520, 521, 522, 523, and 524, respectively; SEQ ID NO: 527, 528, 529, 530, 531, and 532, respectively; SEQ ID NO: 535, 536, 537, 538, 539, and 540, respectively; SEQ ID NO: 543, 544, 545, 546, 547, and 548, respectively; SEQ ID NO: 551, 552, 553, 554, 555, and 556, respectively; SEQ ID NO: 559, 560, 561, 562, 563, and 564, respectively; SEQ ID NO: 567, 568, 569, 570, 571, and 572, respectively; SEQ ID NO: 575, 576, 577, 578, 579, and 580, respectively; SEQ ID NO: 583, 584, 585, 586, 587, and 588, respectively; SEQ ID NO: 591, 592, 593, 594, 595, and 596, respectively; SEQ ID NO: 599, 600, 601, 602, 603, and 604, respectively; SEQ ID NO: 607, 608, 609, 610, 611, and 612, respectively; SEQ ID NO: 615, 616, 617, 618, 619, and 620, respectively; SEQ ID NO: 623, 624, 625, 626, 627, and 628, respectively; SEQ ID NO: 631, 632, 633, 634, 635, and 636, respectively; SEQ ID NO: 639, 640, 641, 642, 643, and 644, respectively; SEQ ID NO: 647, 648, 649, 650, 651, and 652, respectively; SEQ ID NO: 655, 656, 657, 658, 659, and 660, respectively; SEQ ID NO: 663, 664, 665, 666, 667, and 668, respectively; SEQ ID NO: 671, 672, 673, 674, 675, and 676, respectively; SEQ ID NO: 679, 680, 681, 682, 683, and 684, respectively; SEQ ID NO: 687, 688, 689, 690, 691, and 692, respectively; SEQ ID NO: 695, 696, 697, 698, 699, and 700, respectively; SEQ ID NO: 705, 706, 707, 708, 709, and 710, respectively; SEQ ID NO: 725, 726, 727, 728, 729, and 730, respectively; SEQ ID NO: 733, 734, 735, 736, 737, and 738, respectively; SEQ ID NO: 741, 742, 743, 744, 745, and 746, respectively; SEQ ID NO: 749, 750, 751, 752, 753, and 754, respectively; SEQ ID NO: 759, 760, 761, 762, 763, and 764, respectively; SEQ ID NO: 767, 768, 769, 770, 771, and 772, respectively; SEQ ID NO: 775, 776, 777, 778, 779, and 780, respectively; SEQ ID NO: 783, 784, 785, 786, 787, and 788, respectively; SEQ ID NO: 791, 792, 793, 794, 795, and 796, respectively; SEQ ID NO: 799, 800, 801, 802, 803, and 804, respectively; SEQ ID NO: 807, 808, 809, 810, 811, and 812, respectively; SEQ ID NO: 815, 816, 817, 818, 819, and 820, respectively; SEQ ID NO: 823, 824, 825, 826, 827, and 828, respectively; SEQ ID NO: 831, 832, 833, 834, 835, and 836, respectively; SEQ ID NO: 839, 840, 841, 842, 843, and 844, respectively; SEQ ID NO: 847, 848, 849, 850, 851, and 852, respectively; SEQ ID NO: 855, 856, 857, 858, 859, and 860, respectively; SEQ ID NO: 863, 864, 865, 866, 867, and 868, respectively; SEQ ID NO: 871, 872, 873, 874, 875, and 876, respectively; SEQ ID NO: 879,

880, 881, 882, 883, and 884, respectively; SEQ ID NO: 887, 888, 889, 890, 891, and 892, respectively; SEQ ID NO: 895, 896, 897, 898, 899, and 900, respectively; SEQ ID NO: 903, 904, 905, 906, 907, and 908, respectively; SEQ ID NO: 911, 912, 913, 914, 915, and 916, respectively; SEQ ID NO: 919, 920, 921, 922, 923, and 924, respectively; SEQ ID NO: 927, 928, 929, 930, 931, and 932, respectively; SEQ ID NO: 935, 936, 937, 938, 939, and 940, respectively; SEQ ID NO: 945, 946, 947, 948, 949, and 950, respectively; SEQ ID NO: 953, 954, 955, 956, 957, and 958, respectively; SEQ ID NO: 961, 962, 963, 964, 965, and 966, respectively; SEQ ID NO: 969, 970, 971, 972, 973, and 974, respectively; SEQ ID NO: 977, 978, 979, 980, 981, and 982, respectively; SEQ ID NO: 985, 986, 987, 988, 989, and 990, respectively; SEQ ID NO: 997, 998, 999, 1000, 1001, and 1002, respectively; SEQ ID NO: 1005, 1006, 1007, 1008, 1009, and 1010, respectively; SEQ ID NO: 1013, 1014, 1015, 1016, 1017, and 1018, respectively; SEQ ID NO: 1021, 1022, 1023, 1024, 1025, and 1026, respectively; SEQ ID NO: 1029, 1030, 1031, 1032, 1033, and 1034, respectively; or SEQ ID NO: 1037, 1038, 1039, 1040, 1041, and 1042, respectively.

[0762] Embodiment 12. The ADC of embodiment 11, wherein the first, second, third, fourth, fifth, and sixth sequences are: SEQ ID NO: 13, 14, 15, 16, 17, and 18, respectively; SEQ ID NO: 77, 78, 79, 80, 81, and 82, respectively; SEQ ID NO: 91, 92, 93, 94, 95, and 96, respectively; SEQ ID NO: 99, 100, 101, 102, 103, and 104, respectively; SEQ ID NO: 107, 108, 109, 110, 111, and 112, respectively; SEQ ID NO: 115, 116, 117, 118, 119, and 120, respectively; SEQ ID NO: 123, 124, 125, 126, 127, and 128, respectively; SEQ ID NO: 131, 132, 133, 134, 135, and 136, respectively; SEQ ID NO: 139, 140, 141, 142, 143, and 144, respectively; SEQ ID NO: 147, 148, 149, 150, 151, and 152, respectively; SEQ ID NO: 155, 156, 157, 158, 159, and 160, respectively; SEQ ID NO: 163, 164, 165, 166, 167, and 168, respectively; SEQ ID NO: 171, 172, 173, 174, 175, and 176, respectively; SEQ ID NO: 179, 180, 181, 182, 183, and 184, respectively; SEQ ID NO: 187, 188, 189, 190, 191, and 192, respectively; SEQ ID NO: 195, 196, 197, 198, 199, and 200, respectively; SEQ ID NO: 203, 204, 205, 206, 207 and 208, respectively; SEQ ID NO: 211, 212, 213, 214, 215, and 216, respectively; SEQ ID NO: 219, 220, 221, 222, 223, and 224, respectively; SEQ ID NO: 227, 228, 229, 230, 231, and 232, respectively; SEQ ID NO: 235, 236, 237, 238, 239, and 240, respectively; SEQ ID NO: 243, 244, 245, 246, 247, and 248, respectively; SEQ ID NO: 623, 624, 625, 626, 627, and 628, respectively; SEQ ID NO: 631, 632, 633, 634, 635, and 636, respectively; SEQ ID NO: 639, 640, 641, 642, 643, and 644, respectively; SEQ ID NO: 647, 648, 649, 650, 651, and 652, respectively; SEQ ID NO: 655, 656, 657, 658, 659, and 660, respectively; SEQ ID NO: 663, 664, 665, 666, 667, and 668, respectively; SEQ ID NO: 671, 672, 673, 674, 675, and 676, respectively; SEQ ID NO: 679, 680, 681, 682, 683, and 684,

respectively; SEQ ID NO: 687, 688, 689, 690, 691, and 692, respectively; SEQ ID NO: 695, 696, 697, 698, 699, and 700, respectively; SEQ ID NO: 705, 706, 707, 708, 709, and 710, respectively; or SEQ ID NO: 1021, 1022, 1023, 1024, 1025, and 1026, respectively.

[0763] Embodiment 13. The ADC of embodiment 11 or 12, wherein the CDR-H1 comprises at most one mutation relative to the first sequence, the CDR-H2 comprises at most one mutation relative to the second sequence, the CDR-H3 comprises at most one mutation relative to the third sequence, the CDR-L1 comprises at most one mutation relative to the fourth sequence, the CDR-L2 comprises at most one mutation relative to the fifth sequence, and the CDR-L3 comprises at most one mutation relative to the sixth sequence.

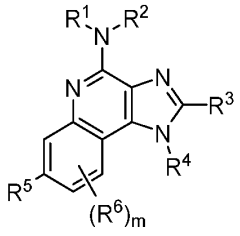
[0764] Embodiment 14. The ADC of any one of embodiments 11-13, wherein the first, second, third, fourth, fifth, and sixth sequences are: SEQ ID NO: 13, 14, 15, 16, 17, and 18, respectively.

[0765] Embodiment 15. The ADC of any one of embodiments 1-14, wherein Ab comprises an effector function-diminishing mutation.

[0766] Embodiment 16. The ADC of embodiment 15, wherein the effector function diminishing mutation is selected from the group consisting of L234A/L235A, D265A/N297A, D270A, K322A, P329A, P329G, and combinations thereof.

[0767] Embodiment 17. The ADC of embodiment 15 or 16, wherein the effector function diminishing mutation is L234A/L235A.

[0768] Embodiment 18. The ADC of any one of embodiments 1-17, wherein each D has the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

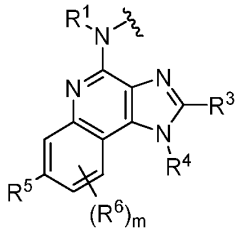
R^5 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of -C(=O)OR^F, -NO_2, -CN, -CF_3 -C(=O)NR^GR^H, -S(O_2)NR^GR^H, -N(R^I)-C(=O)R^J, -N(R^I)-S(O_2)R^K, and SO_3R^K;

each R^6 is independently selected from the group consisting of (a) the point of covalent attachment to L; or (b) 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 $-NR^AR^B$; and

m is 0, 1, 2, or 3

[0769] Embodiment 19. The ADC of any one of embodiments 1-18, wherein each D has the structure of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein

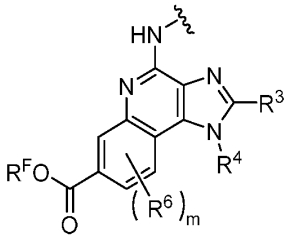
〰 is the point of covalent attachment to L;

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

each R^6 is independently selected from the group consisting of (a) the point of covalent attachment to L; or (b) 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 $-NR^AR^B$; and

m is 0, 1, 2, or 3.

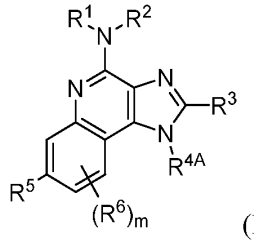
[0770] Embodiment 20. The ADC of embodiment 19, wherein each D has the structure of Formula (IIa):



(IIa)

or a pharmaceutically acceptable salt thereof, wherein each R^6 is independently selected from the group consisting of (a) the point of covalent attachment to L; or (b) 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 $-NR^AR^B$; and m is 0, 1, 2, or 3.

[0771] Embodiment 21. The ADC of any one of embodiments 1-18, wherein each D has the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

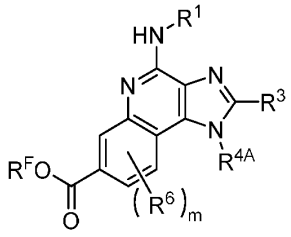
R^{4A} is (a) the point of covalent attachment to L or (b) C_1-C_6 alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) $-OR^C$; (iii) $-SR^C$; (iv) $-NH-S(O_2)R^C$; (v) $-OC(=O)R^C$; (vi) $-CO_2H$; (vii) -C_1-C_6 alkoxycarbonyl; (viii) $-C(=O)NR^DR^E$; (ix) $-NR^DR^E$; (ix) -$[N(C_1$-C_6 alkyl$)R^DR^E]^+$; (x) -(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; (xi) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-C(=O)NR^DR^E$ or $-CO_2H$; (xii) -(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 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, the C_1-C_6 alkyl or a substituent thereof is 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 $-C(=O)OR^F$, $-NO_2$, -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 (a) the point of covalent attachment to L; or (b) 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 $–NR^AR^B$; and

m is 0, 1, 2, or 3.

[0772] Embodiment 22. The ADC of embodiment 21, wherein each D has the structure of Formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt thereof.

[0773] Embodiment 23. The ADC of any one of embodiments 1-18, wherein R^1 or R^4 is the point of covalent attachment to L.

[0774] Embodiment 24. The ADC of any one of embodiments 1-23, wherein R^1 selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, phenyl, and 5-10 membered heteroaryl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, phenyl, or 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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide.

[0775] Embodiment 25. The ADC of any one of embodiments 1-24, wherein R^1 selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, or phenyl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, C_1-C_6 alkoxy, –NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, and acylated C_5-C_9 monosaccharide.

[0776] Embodiment 26. The ADC of any one of embodiments 1-26, wherein R^1 is hydrogen or C_1-C_3 alkyl optionally substituted with a substituent selected from the group consisting of hydroxyl, halogen, and –NH_2.

[0777] Embodiment 27. The ADC of any one of embodiments 1-27, wherein R^1 is hydrogen or C_1-C_3 alkyl.

[0778] Embodiment 28. The ADC of any one of embodiments 1-28, wherein R^1 is hydrogen.

[0779] Embodiment 29. The ADC of any one of embodiments 1-18 or 21-28, wherein R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, or

phenyl 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 $-NR^AR^B$.

[0780] Embodiment 30. The ADC of any one of embodiments 1-18 or 21-29, wherein R^2 is selected from the group consisting of hydrogen and C_1-C_3 alkyl, wherein the of C_1-C_3 alkyl 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 $-NR^AR^B$.

[0781] Embodiment 31. The ADC of any one of embodiments 1-18 or 21-30, wherein R^2 is hydrogen or C_1-C_3 alkyl.

[0782] Embodiment 32. The ADC of any one of embodiments 1-18 or 21-31, wherein R^2 is hydrogen.

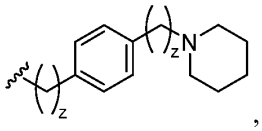
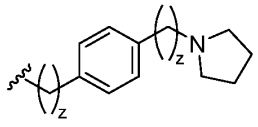
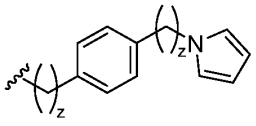
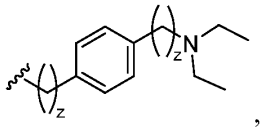
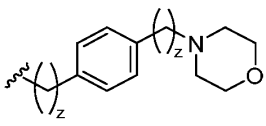
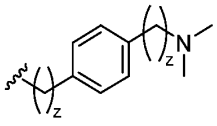
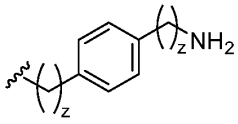
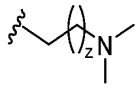
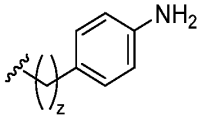
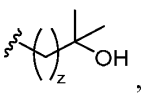
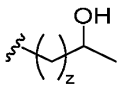
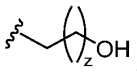
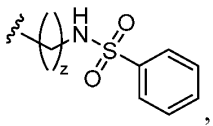
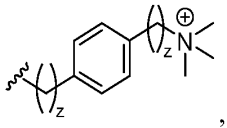
[0783] Embodiment 33. The ADC of any one of embodiments 1-32, wherein R^3 is selected from the group consisting of $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl, and 5-10 membered heteroaryl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl, or 5-10 membered heteroaryl 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 $-NR^AR^B$.

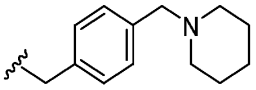
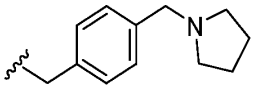
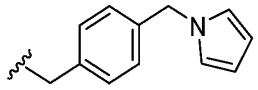
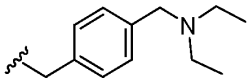
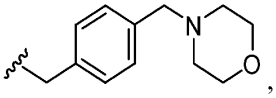
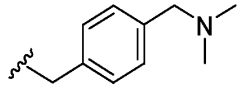
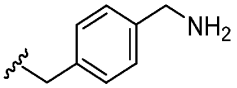
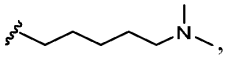
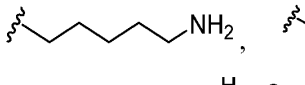
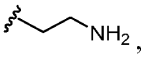
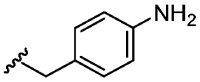
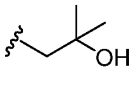
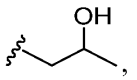
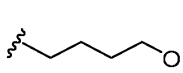
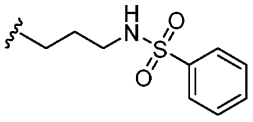
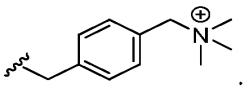
[0784] Embodiment 34. The ADC of any one of embodiments 1-33, wherein R^3 is C_1-C_5 alkyl optionally substituted with 1 substituent selected from the group consisting of hydroxyl, halogen, cyano, oxo, C_1-C_3 alkoxy, C_1-C_3 alkylthio, and $-NR^AR^B$.

[0785] Embodiment 35. The ADC of any one of embodiments 1-34, wherein R^3 is selected from the group consisting of butyl, $-CH_2-O-CH_2CH_3$, $-CH_2-CH_2-O-CH_3$, and $-CH_2-NH-CH_2CH_3$.

[0786] Embodiment 36. The ADC of any one of embodiments 1-20 or 23-35, wherein R^4 is hydrogen; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; $-C(=S)R^C$; or C_1-C_6 alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) $-O(C_1$-C_6 alkyl); (iii) $-S(C_1$-C_6 alkyl); (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) $-NR^DR^E$, wherein the R^D of $-NR^DR^E$ is C_1-C_6 alkyl; (x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$; (xi) -(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, 5-10 membered heterocycle, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-NR^DR^E$, $-C(=O)NR^DR^E$ or $-CO_2H$.

[0787] Embodiment 37. The ADC of any one of embodiments 1-20 or 23-36, wherein R^4 is hydrogen or C_1-C_6 alkyl substituted with: (ix) $-NR^DR^E$, wherein the R^D of $-NR^DR^E$ is C_1-C_6 alkyl; or (xi) -(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, 5-10 membered heterocycle, $-[N(C_1\text{-}C_6 \text{ alkyl})R^DR^E]^+$.

[0788] Embodiment 38. The ADC of any one of embodiments 1-20 or 23-37, wherein R^4 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  , and  , wherein each instance of subscript z is independently 1, 2, or 3.

[0789] Embodiment 39. The ADC of embodiment 1-20 or 23-38, wherein R^4 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

[0790] Embodiment 40. The ADC of any one of embodiments 1-19, 21, or 23-39, wherein R^5 is selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-S(O_2)NR^GR^H$, $-N(R^I)$-$C(=O)R^J$, $-N(R^I)$-$S(O_2)R^K$, and SO_3R^K; and each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and $-NR^AR^B$.

[0791] Embodiment 41. The ADC of any one of embodiments 1-19, 21, or 23-40, wherein R^5 is -C(=O)OH or -C(=O)O(C_1-C_3 alkyl); and each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and $-NR^AR^B$.

[0792] Embodiment 42. The ADC of any one of embodiments 1-19, 21, or 23-41, wherein R^5 is -C(=O)OH or -C(=O)O(C_1-C_3 alkyl); and subscript m is zero.

[0793] Embodiment 43. The ADC of any one of embodiments 1-19, 21, or 23-42, 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).

[0794] Embodiment 44. The ADC of any one of embodiments 1-17 or 23-39, wherein each R^X is 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, -S(O_3)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 $-NR^AR^B$.

[0795] Embodiment 45. The ADC of any one of embodiments 1-17, 23-39 or 44, wherein subscript n is 1.

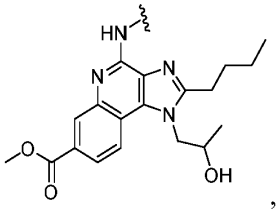
[0796] Embodiment 46. The ADC of any one of embodiments 1-45, wherein each instance of R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_3 alkyl.

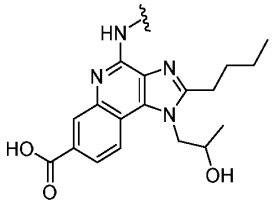
[0797] Embodiment 47. The ADC of any one of embodiments 1-46, wherein each instance of R^C is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl.

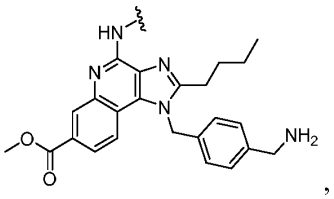
[0798] Embodiment 48. The ADC of any one of embodiments 1-47, wherein each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, C_4-C_6 cycloalkyl(C_1-C_3 alkyl)-, aryl, and aryl(C_1-C_3 alkyl).

[0799] Embodiment 49. The ADC of any one of embodiments 1-48, wherein each instance of R^F is independently selected from the group consisting of hydrogen, trifluoromethyl, and C_1-C_6 alkyl.

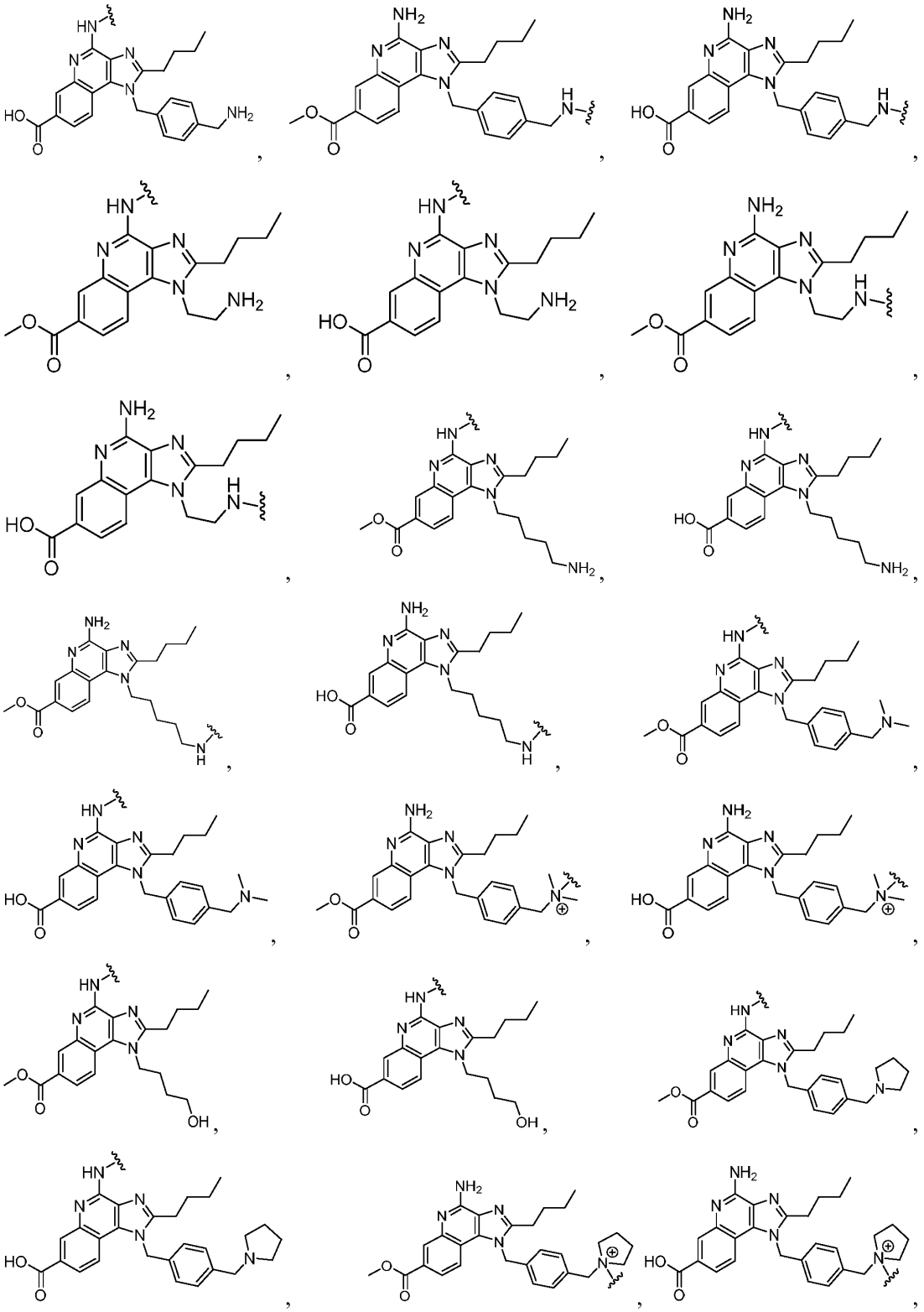
[0800] Embodiment 50. The ADC of any one of embodiments 1-49, wherein each D is

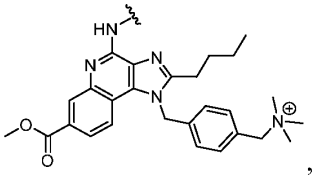
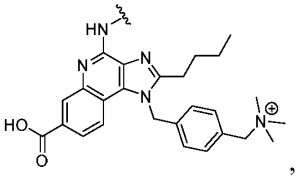
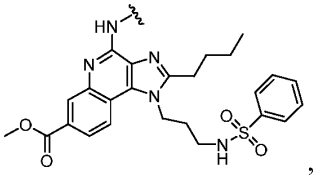
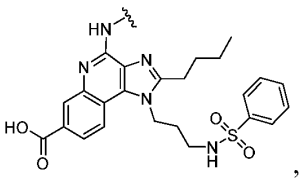
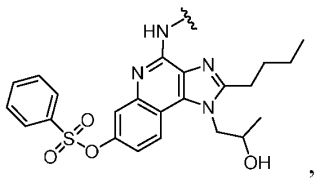
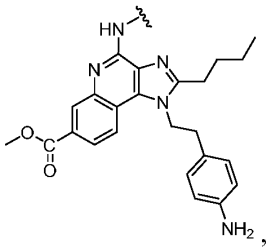
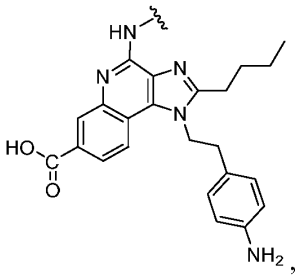
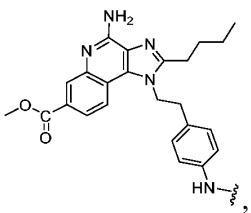
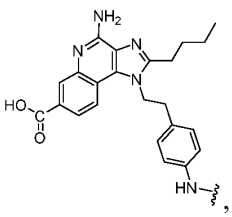
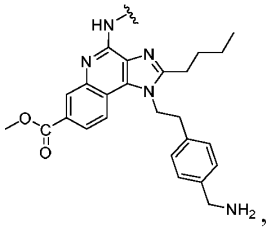
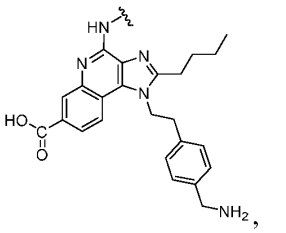
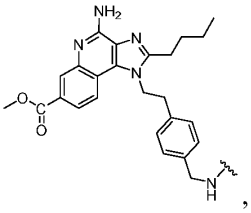
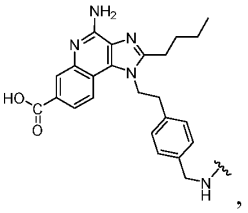
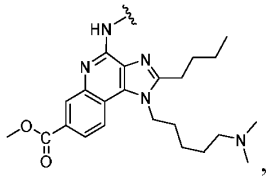
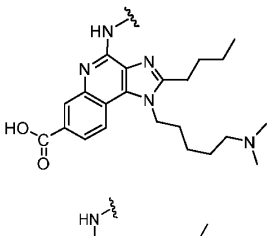
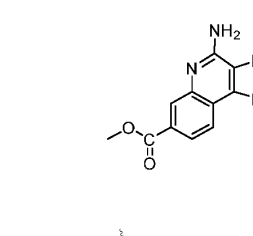
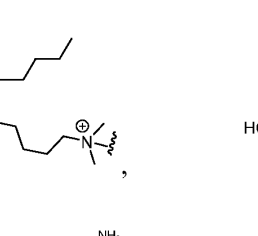


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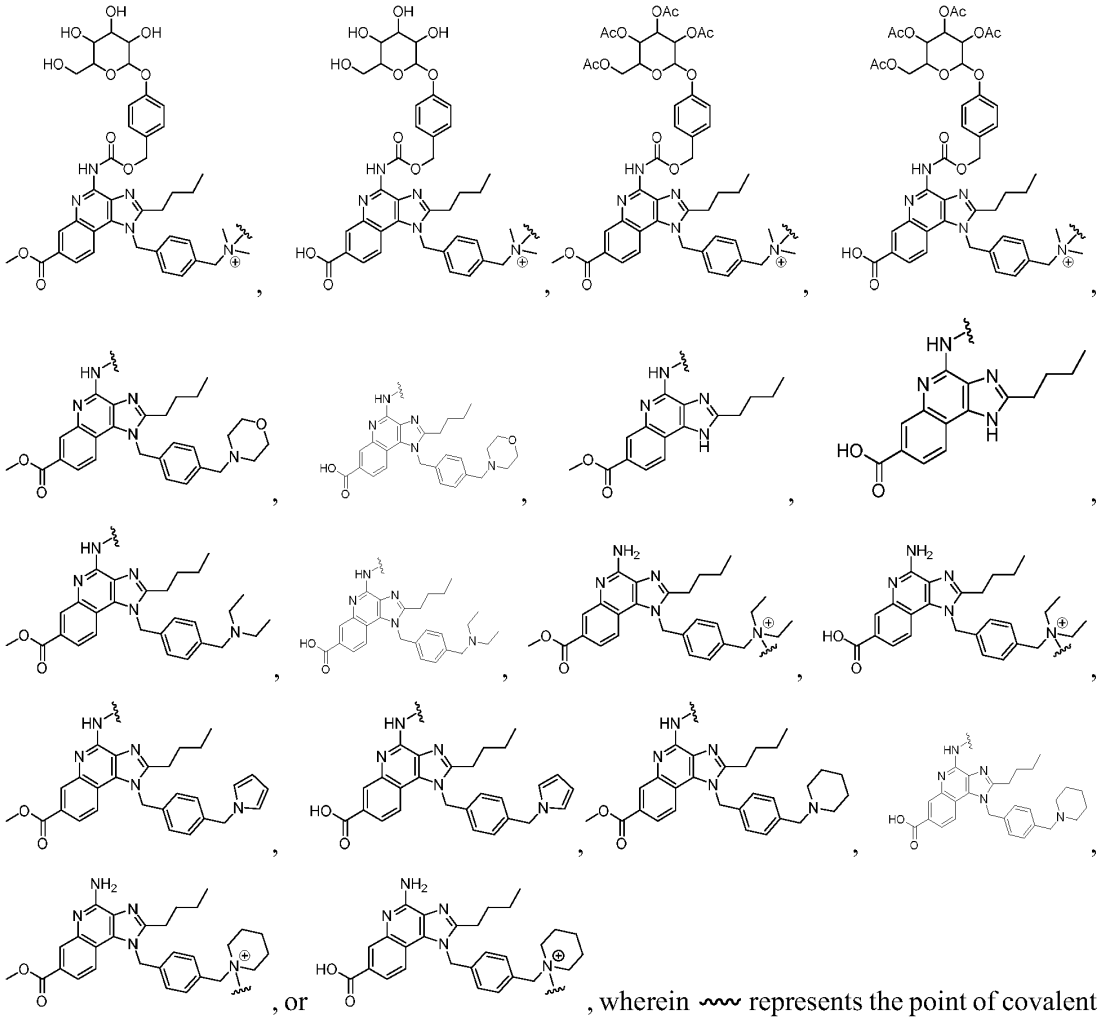
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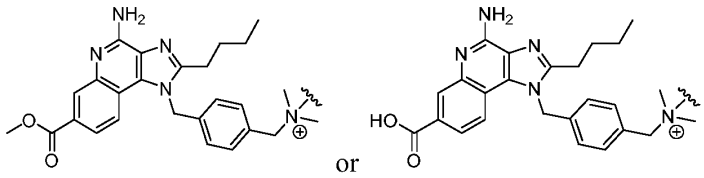
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, wherein ~~~ represents the point of covalent attachment to L.

[0801] Embodiment 51. The ADC of any one of embodiments 1-50, wherein each D is



, wherein ~~~ represents the point of covalent attachment to L.

[0802] Embodiment 52. The ADC of embodiment 50 or 51, wherein Ab comprises a heavy chain with at least 80% sequence identity to SEQ ID NO: 3 and a light chain with at least 80% sequence identity to SEQ ID NO: 5.

[0803] Embodiment 53. The ADC of any one of embodiments 1-52, wherein the linker comprises a length of between 10 and 40 atoms as defined by the pathway between D and Ab through the fewest number of bonds.

[0804] Embodiment 54. The ADC of any one of embodiments 1-53, wherein the linker comprises a length of between 15 and 30 atoms as defined by the pathway between D and Ab through the fewest number of bonds.

[0805] Embodiment 55. The ADC of any one of embodiments 1-54, wherein the linker comprises a PEG Unit from PEG1 to PEG72, a monosaccharide, a disaccharide, a trisaccharide, an oligopeptide, or a combination thereof.

[0806] Embodiment 56. The ADC of any one of embodiments 1-55, wherein 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, a disulfide, a dihydropyridazine, or a triazole;

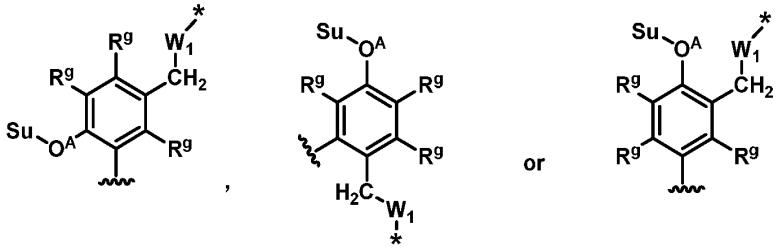
A is a C_{2-20} alkylene optionally substituted with 1-4 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1};

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.

[0807] Embodiment 57. The ADC of embodiment 56, wherein subscript x is 1.

[0808] Embodiment 58. The ADC of embodiment 56 or 57 wherein X is a C_1-C_6 alkylene.

[0809] Embodiment 59. The ADC of embodiment 56-58, wherein X is a C_1-C_3 alkylene.

[0810] Embodiment 60. The ADC of embodiment 56 or 57, wherein X is a 3-6 membered heteroalkylene.

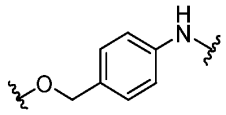
[0811] Embodiment 61. The ADC of any one of embodiments 56, 57, or 60, wherein X is a 3-4 membered heteroalkylene.

[0812] Embodiment 62. The ADC of embodiment 56, wherein subscript x is 0.

[0813] Embodiment 63. The ADC of any one of embodiments 56-62, wherein subscript y is 1.

[0814] Embodiment 64. The ADC of any one of embodiments 56-63, wherein Y is a self-immolative moiety.

[0815] Embodiment 65. The ADC of any one of embodiments 56-64, wherein Y is



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[0816] Embodiment 66. The ADC of any one of embodiments 56-62, wherein Y is a non-cleavable moiety.

[0817] Embodiment 67. The ADC of any one of embodiments 56-62 or 66, wherein Y is a cyclohexanecarboxyl, undecanoyl, caproyl, hexanoyl, butanoyl or propionyl group.

[0818] Embodiment 68. The ADC of any one of embodiments 56-62, wherein Y is PEG4 to PEG12.

[0819] Embodiment 69. The ADC of any one of embodiments 56-62, wherein subscript y is 0.

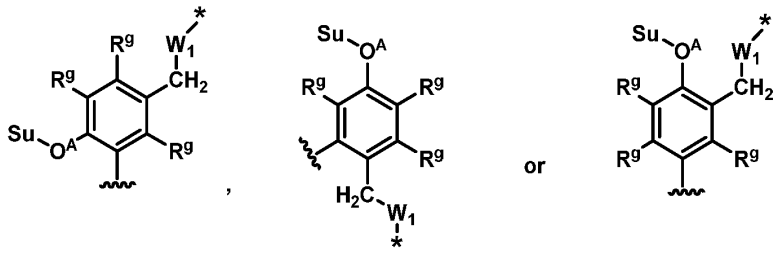
[0820] Embodiment 70. The ADC of any one of embodiments 56-69, wherein subscript w is 1.

[0821] Embodiment 71. The ADC of any one of embodiments 56-70, wherein W is from 6-12 amino acids.

[0822] Embodiment 72. The ADC of any one of embodiments 56-71, wherein W is from 6-9 amino acids.

[0823] Embodiment 73. The ADC of any one of embodiments 56-72, 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.

[0824] Embodiment 74. The ADC of any one of embodiments 56-70, wherein W has the structure:



wherein Su is a Sugar moiety;

-OA- 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.

[0825] Embodiment 75. The ADC of embodiment 74, wherein W^1 is absent.

[0826] Embodiment 76. The ADC of embodiment 74, wherein W^1 is *-C(=O)-O-.

[0827] Embodiment 77. The ADC of embodiment 74, wherein W^1 is *-O-C(=O)-.

[0828] Embodiment 78. The ADC of any one of embodiments 74-77, 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.

[0829] Embodiment 79. The ADC of any one of embodiments 74-78, wherein each R^g is hydrogen.

[0830] Embodiment 80. The ADC of any one of embodiments 56-69, wherein subscript w is 0.

[0831] Embodiment 81. The ADC of any one of embodiments 56-80, wherein subscript a is 1.

[0832] Embodiment 82. The ADC of any one of embodiments 56-81, wherein A is C_{2-20} alkylene optionally substituted with 1-4 R^{a1}.

[0833] Embodiment 83. The ADC of any one of embodiments 56-82, wherein A is C_{4-10} alkylene optionally substituted with 1-4 R^{a1}.

[0834] Embodiment 84. The ADC of any one of embodiments 56-82, wherein A is C_{2-20} alkylene substituted with one R^{a1}.

[0835] Embodiment 85. The ADC of any one of embodiments 56-84, wherein A is C_{4-10} alkylene substituted with one R^{a1}.

[0836] Embodiment 86. The ADC of any one of embodiments 56-81, wherein A is C_{2-20} alkylene.

[0837] Embodiment 87. The ADC of any one of embodiments 56-81 or 86, wherein A is C_{4-10} alkylene.

[0838] Embodiment 88. The ADC of any one of embodiments 56-81, wherein A is a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1}.

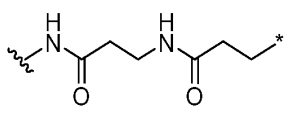
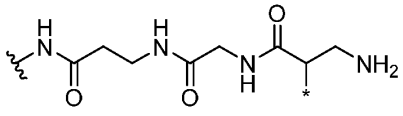
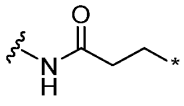
[0839] Embodiment 89. The ADC of any one of embodiments 56-81 or 88, wherein A is a 4 to 12 membered heteroalkylene optionally substituted with 1-4 R^{b1}.

[0840] Embodiment 90. The ADC of any one of embodiments 56-81 or 88, wherein A is a 2 to 40 membered heteroalkylene optionally substituted with one R^{b1}.

[0841] Embodiment 91. The ADC of any one of embodiments 56-81 or 88-90, wherein A is a 4 to 12 membered heteroalkylene optionally substituted with one R^{b1}.

[0842] Embodiment 92. The ADC of any one of embodiments 56-81, wherein A is a 2 to 40 membered heteroalkylene.

[0843] Embodiment 93. The ADC of any one of embodiments 56-81 or 92, wherein A is a 4 to 12 membered heteroalkylene.

[0844] Embodiment 94. The ADC of any one of embodiments 56-81, wherein A is  ,  , or  , wherein ~~~ represents covalent attachment to W, and * represents covalent linkage to M.

[0845] Embodiment 95. The ADC of any one of embodiments 56-80, wherein subscript a is 0.

[0846] Embodiment 96. The ADC of any one of embodiments 56-95, wherein L is substituted with a PEG Unit from PEG1 to PEG72.

[0847] Embodiment 97. The ADC of any one of embodiments 56-94, wherein A is substituted with a PEG Unit from PEG1 to PEG72.

[0848] Embodiment 98. The ADC of any one of 56-97, wherein M is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, a disulfide, a dihydropyridazine, or a triazole.

[0849] Embodiment 99. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the ADC of any one of embodiments 1-98, or a pharmaceutically acceptable salt thereof.

[0850] Embodiment 100. The method of embodiment 99, wherein the ADC is configured to internalize within a cell.

[0851] Embodiment 101. The method of embodiment 99 or 100, wherein the ADC targets a cancer-associated antigen.

[0852] Embodiment 102. The method of any one of embodiments 99-101, wherein the cell expresses the cancer-associated antigen.

[0853] Embodiment 103. The method of any one of embodiments 99-102, wherein the cell does not express the cancer-associated antigen.

[0854] Embodiment 104. The method of any one of embodiments 99-103, wherein the cell is an immune cell.

[0855] Embodiment 105. The method of embodiment 104, wherein the immune cell is a $CD8^+$ T-cell, a $CD4^+$ T-Cell, a T-regulatory cell, a macrophage, or a natural killer cell.

[0856] Embodiment 106. The method of embodiment 104 or 105, wherein the immune cell is a macrophage.

[0857] Embodiment 107. The method of any one of embodiments 104-106, wherein the immune cell expresses TLR7, TLR8, or TLR7 and TLR8.

[0858] Embodiment 108. The method of embodiment 104-107, wherein the cancer does not express TLR7 or TLR8.

[0859] Embodiment 109. The method of any one of embodiments 104-108, wherein the immune cell expresses a surface protein which binds to the cancer-associated antigen.

[0860] Embodiment 110. The method of any one of embodiments 100-109, wherein the internalizing comprises endocytosis or micropinocytosis.

[0861] Embodiment 111. The method of embodiment 99-110, 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.

[0862] Embodiment 112. The method of any one of embodiments 99-111, wherein the linker (L) of the ADC is configured to undergo cleavage subsequent to internalizing within the immune cell.

[0863] Embodiment 113. The method of any one of embodiments 99-112, wherein the cancer does not express CD4, CD8, an immune checkpoint, or a combination thereof.

[0864] Embodiment 114. The method of embodiment 113, wherein less than about 10%, less than about 7.5%, less than about 5%, less than about 4.5%, less than about 4%, less than about 3.5%, less than about 3%, less than about 2.5%, less than about 2%, less than about 1.5%, less than about 1%, or less than about 0.5% of cancer cells of the cancer express the CD4, the CD8, the immune checkpoint, or the combination thereof.

[0865] Embodiment 115. The method of embodiment 114, wherein the CD4 expression, the CD8 expression, the immune checkpoint expression, or the combination thereof is membrane expression.

[0866] Embodiment 116. The method of any one of embodiments 113-115, wherein the immune checkpoint is PDL1, PD1, CTLA-4, B7H4, B7H3, TIGIT, TIM-3, VISTA, GITR/GITRL, CD80/CD86, CD155, PDL1, PDL2, galectin 9, CD40, OX40L, 4-1BB/4-1BBL, ICOS/ICOSL, CD70, or a combination thereof.

[0867] Embodiment 117. The method of any one of embodiments 113-116, wherein the immune checkpoint is PDL1.

[0868] Embodiment 118. The method of any one of embodiments 113-117, wherein the expression is in cancer cells derived from a tumor.

[0869] Embodiment 119. The method of embodiment 118, wherein the cancer cells derived from the tumor do not comprise tumor-associated immune cells.

[0870] Embodiment 120. The method of embodiment 118 or embodiment 119, wherein the cancer cells derived from the tumor comprise stromal cells from the tumor.

[0871] Embodiment 121. The method of any one of embodiments 113-120, wherein the determining comprises flow cytometry, immunohistochemistry, immunocytochemistry, immunofluorescence, immunoprecipitation, western blotting, ELISA, or mRNA analysis.

[0872] Embodiment 122. The method of embodiment 121, wherein the mRNA analysis comprises quantitative polymerase chain reaction (qPCR), reverse transcription qPCR (RT-qPCR), RNA sequencing, microarray analysis, in situ hybridization, or sequential gene expression analysis.

CLAIMS

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;

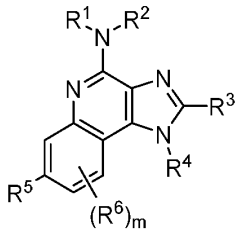
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide;

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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is optionally the point of covalent attachment to L;

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 selected from the group consisting of: the point of covalent attachment to L; hydrogen; $-OR^C$; $-S(=O)_2R^C$; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; $-C(=S)R^C$; $-PO_3R^C$; and -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 the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, -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, -NR^DR^E, -C(=O)NR^DR^E or -CO_2H;

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the (-5-10 membered heteroaryl)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_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof is optionally 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 (a) the point of covalent attachment to L; or (b) 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; and

m is 0, 1, 2, or 3;

each instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, (b) the group consisting of hydrogen and C_1-C_6 alkyl; and (c) 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 at most one instance of R^A and R^B is the point of covalent attachment to L;

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

each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) 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)-; and (c) 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;

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

wherein at most one of R^I, R^J, and R^K is the point of covalent attachment to L;

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

wherein Ab comprises a heavy chain variable region having at least 80% sequence identity to a first sequence and a light chain variable region having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20.

2. The ADC of claim 1 wherein the heavy chain variable region has at least 90% sequence identity to the first sequence and the light chain variable region has at least 90% sequence identity to the second sequence.

3. The ADC of claim 1 or claim 2, wherein the heavy chain variable region has at least 98% sequence identity to the first sequence and the light chain variable region has at least 98% sequence identity to the second sequence.

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;

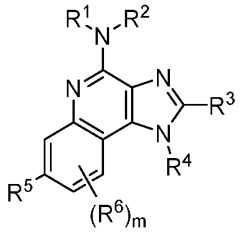
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide;

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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is optionally the point of covalent attachment to L;

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 selected from the group consisting of: the point of covalent attachment to L; hydrogen; $-OR^C$; $-S(=O)_2R^C$; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; $-C(=S)R^C$; $-PO_3R^C$; and -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 the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, $-NR^DR^E$, $-[N(C_1\text{-}C_6$ alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;

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

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the (-5-10 membered heteroaryl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, $-NR^DR^E$, $-[N(C_1\text{-}C_6$ 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_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof is optionally 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 (a) the point of covalent attachment to L; or (b) 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 $-NR^AR^B$; and

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

each instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, (b) the group consisting of hydrogen and C_1-C_6 alkyl; and (c) 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 at most one instance of R^A and R^B is the point of covalent attachment to L;

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

each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) 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)-; and (c) 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;

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

wherein at most one of R^I, R^J, and R^K is the point of covalent attachment to L;

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

wherein Ab comprises a heavy chain having at least 80% sequence identity to a first sequence and a light chain having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5.

5. The ADC of claim 4, wherein the heavy chain has at least 90% sequence identity to the first sequence and the light chain has at least 90% sequence identity to the second sequence.

6. The ADC of claim 4 or claim 5, wherein the heavy chain has at least 98% sequence identity to the first sequence and the light chain has at least 98% sequence identity to the second sequence.

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

Ab-(L-D)$_p$

or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

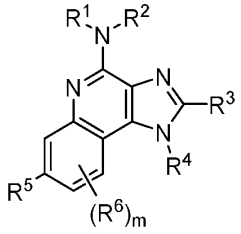
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide;

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, wherein the heterocyclyl or one of the 1-3 independently selected C_1-C_6 alkyl is optionally the point of covalent attachment to L;

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 selected from the group consisting of: the point of covalent attachment to L; hydrogen; $-OR^C$; $-S(=O)_2R^C$; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; $-C(=S)R^C$; $-PO_3R^C$; and -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 the C_1-C_6 alkyl of the -(phenyl)C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, $-NR^DR^E$, $-[N(C_1\text{-}C_6$ alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen;

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

(xiii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein the C_1-C_6 alkyl of the (-5-10 membered heteroaryl)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_1-C_6 alkyl, the C_1-C_6 alkyl or a substituent thereof is optionally 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 (a) the point of covalent attachment to L; or (b) 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; and

m is 0, 1, 2, or 3;

each instance of R^A and R^B is independently selected from the group consisting of: (a) the point of covalent attachment to L, (b) the group consisting of hydrogen and C_1-C_6 alkyl; and (c) 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 at most one instance of R^A and R^B is the point of covalent attachment to L;

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

each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) 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)-; and (c) 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;

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

wherein at most one of R^I, R^J, and R^K is the point of covalent attachment to L;

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

wherein Ab comprises a CDR-H1 comprising at least 80% sequence identity to a first sequence, a CDR-H2 comprising at least 80% sequence identity to a second sequence, a CDR-H3 comprising at least 80% sequence identity to a third sequence, a CDR-L1 comprising at least 80% sequence identity to a fourth sequence, a CDR-L2 comprising at least 80% sequence identity to a fifth sequence, and a CDR-L3 comprising at least 80% sequence identity to a sixth sequence, wherein the first, second, third, fourth, fifth, and sixth sequences are: SEQ ID NO: 13, 14, 15, 16, 17, and 18, respectively.

8. The ADC of claim 7, wherein the CDR-H1 comprises at most one mutation relative to the first sequence, the CDR-H2 comprises at most one mutation relative to the second sequence, the CDR-H3 comprises at most one mutation relative to the third sequence, the CDR-L1 comprises at most one mutation relative to the fourth sequence, the CDR-L2 comprises at most one mutation relative to the fifth sequence, and the CDR-L3 comprises at most one mutation relative to the sixth sequence.

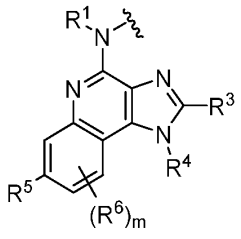
9. The ADC of claim 7 or claim 8, wherein the first, second, third, fourth, fifth, and sixth sequences are: SEQ ID NO: 13, 14, 15, 16, 17, and 18, respectively.

10. The ADC of any one of claims 1-9, wherein Ab comprises an effector function-diminishing mutation.

11. The ADC of claim 10, wherein the effector function diminishing mutation is selected from the group consisting of L234A/L235A, D265A/N297A, D270A, K322A, P329A, P329G, and combinations thereof.

12. The ADC of claim 10 or 11, wherein the effector function diminishing mutation is L234A/L235A.

13. The ADC of any one of claims 1-12, wherein each D has the structure of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein

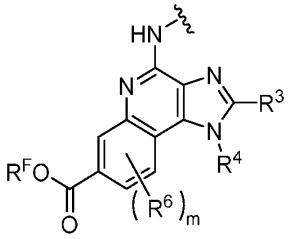
〰 is the point of covalent attachment to L;

R^5 is (a) the point of covalent attachment to L; or (b) selected from the group consisting of -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; and

m is 0, 1, 2, or 3.

14. The ADC of claim 13, wherein each D has the structure of Formula (IIa):

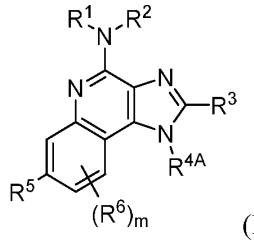


(IIa)

or a pharmaceutically acceptable salt thereof, 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; and

m is 0, 1, 2, or 3.

15. The ADC of any one of claims 1-12, wherein each D has the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

R^{4A} is (a) the point of covalent attachment to L 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; (ix) -[N(C_1-C_6 alkyl)R^DR^E]$^+$; (x) -(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;

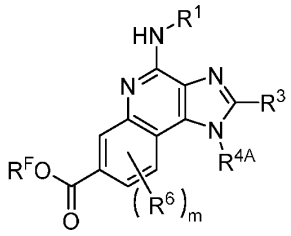
(xi) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, -C(=O)NR^DR^E or -CO_2H; (xii) -(5-10 membered heteroaryl)C_1-C_6 alkyl, wherein its C_1-C_6 alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -[N(C_1-C_6 alkyl)R^DR^E]$^+$, or 1-3 independently selected halogen; or 5-10 membered 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, 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; and

m is 0, 1, 2, or 3.

16. The ADC of claim 15, wherein each D has the structure of Formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt thereof.

17. The ADC of any one of claims 1-12, wherein R^1 or R^4 is the point of covalent attachment to L.

18. The ADC of any one of claims 1-17, wherein R^1 selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, phenyl, and 5-10 membered heteroaryl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxythiocarbonyl, C_1-C_6 carbamoyl, phenyl, or 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,–NR^AR^B, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, acylated C_5-C_9 monosaccharide, C_{10}-C_{18} disaccharide, acylated C_{10}-C_{18} disaccharide, C_{15}-C_{27} trisaccharide, and acylated C_{15}-C_{27} trisaccharide.

19. The ADC of any one of claims 1-18, wherein R^1 selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6

alkanoyl, C_1-C_6 alkoxycarbonyl, or phenyl is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, C_1-C_6 alkoxy, $-NR^AR^B$, phosphoryl, sulfuryl, nitro, C_5-C_9 monosaccharide, and acylated C_5-C_9 monosaccharide.

20. The ADC of any one of claims 1-19, wherein R^1 is hydrogen or C_1-C_3 alkyl optionally substituted with a substituent selected from the group consisting of hydroxyl, halogen, and $-NH_2$.

21. The ADC of any one of claims 1-20, wherein R^1 is hydrogen or C_1-C_3 alkyl.

22. The ADC of any one of claims 1-21, wherein R^1 is hydrogen.

23. The ADC of any one of claims 1-12 or 15-22, wherein R^2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and phenyl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, or phenyl 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 $-NR^AR^B$.

24. The ADC of any one of claims 1-12 or 15-23, wherein R^2 is selected from the group consisting of hydrogen and C_1-C_3 alkyl, wherein the of C_1-C_3 alkyl 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 $-NR^AR^B$.

25. The ADC of any one of claims 1-12 or 15-24, wherein R^2 is hydrogen or C_1-C_3 alkyl.

26. The ADC of any one of claims 1-12 or 15-25, wherein R^2 is hydrogen.

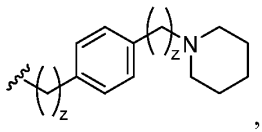
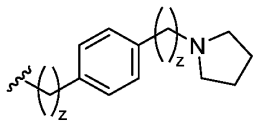
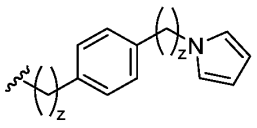
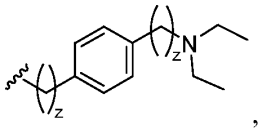
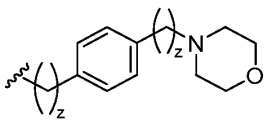
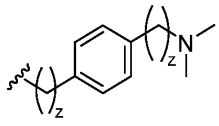
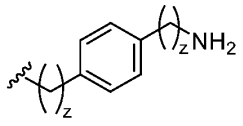
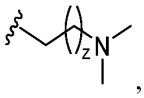
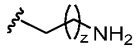
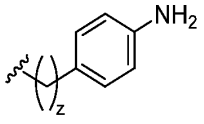
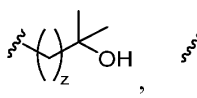
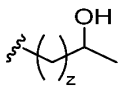
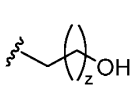
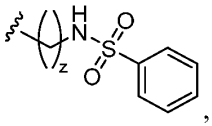
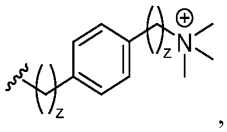
27. The ADC of any one of claims 1-26, wherein R^3 is selected from the group consisting of $-NR^AR^B$, $-C(=O)NR^AR^B$, C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl, and 5-10 membered heteroaryl; wherein the C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl, or 5-10 membered heteroaryl 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 $-NR^AR^B$.

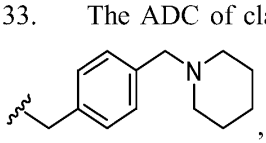
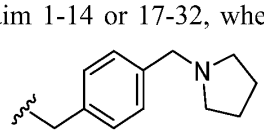
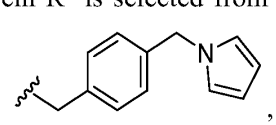
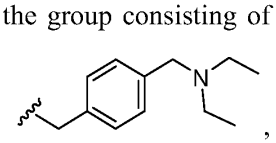
28. The ADC of any one of claims 1-27, wherein R^3 is C_1-C_5 alkyl optionally substituted with 1 substituent selected from the group consisting of hydroxyl, halogen, cyano, oxo, C_1-C_3 alkoxy, C_1-C_3 alkylthio, and $-NR^AR^B$.

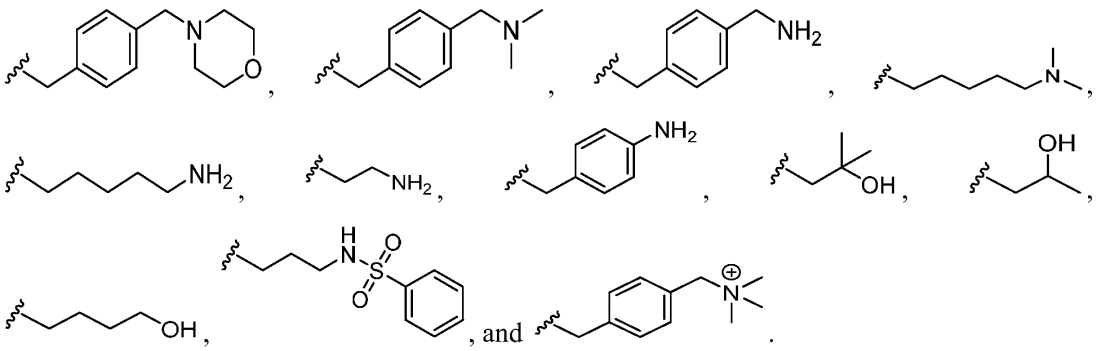
29. The ADC of any one of claims 1-28, wherein R^3 is selected from the group consisting of butyl, $-CH_2-O-CH_2CH_3$, $-CH_2-CH_2-O-CH_3$, and $-CH_2-NH-CH_2CH_3$.

30. The ADC of any one of claims 1-14 or 17-29, wherein R^4 is hydrogen; $-C(=O)NR^DR^E$; $-C(=O)OR^C$; $-C(=O)SR^C$; $-C(=S)R^C$; or C_1-C_6 alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) $-O(C_1$-C_6 alkyl); (iii) $-S(C_1$-C_6 alkyl); (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) $-NR^DR^E$, wherein the R^D of $-NR^DR^E$ is C_1-C_6 alkyl; (x) $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$; (xi) -(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, 5-10 membered heterocycle, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$, or 1-3 independently selected halogen; or (xii) phenyl substituted with halogen, hydroxyl, C_1-C_6 alkoxy, $-NR^DR^E$, $-C(=O)NR^DR^E$ or $-CO_2H$.

31. The ADC of any one of claims 1-14 or 17-30, wherein R^4 is hydrogen or C_1-C_6 alkyl substituted with: (ix) $-NR^DR^E$, wherein the R^D of $-NR^DR^E$ is C_1-C_6 alkyl; or (xi) -(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, 5-10 membered heterocycle, $-[N(C_1$-C_6 alkyl)$R^DR^E]^+$.

32. The ADC of any one of claims 1-14 or 17-31, wherein R^4 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , wherein each instance of subscript z is independently 1, 2, or 3.

33. The ADC of claim 1-14 or 17-32, wherein R^4 is selected from the group consisting of  ,  ,  ,  ,



34. The ADC of any one of claims 1-13, 15, or 17-33, wherein R^5 is -C(=O)OH or -C(=O)O(C_1-C_3 alkyl); and each R^6 is independently selected from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6 alkyl, and $-NR^AR^B$.

35. The ADC of any one of claims 1-13, 15, or 17-34, wherein R^5 is -C(=O)OH or -C(=O)O(C_1-C_3 alkyl); and subscript m is zero.

36. The ADC of any one of claims 1-13, 15, or 17-35, 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).

37. The ADC of any one of claims 1-12 or 17-33, wherein each R^X is independently selected from the group consisting of hydrogen, $-C(=O)OR^F$, $-C(=O)NR^GR^H$, $-S(O_2)NR^GR^H$, $-N(R^I)$-$C(=O)R^J$, $-N(R^I)$-$S(O_2)R^K$, $-S(O_3)R^K$, 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 $-NR^AR^B$.

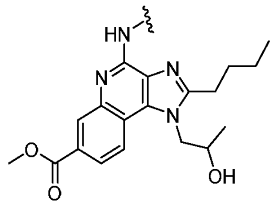
38. The ADC of any one of claims 1-12, 17-33 or 37, wherein subscript n is 1.

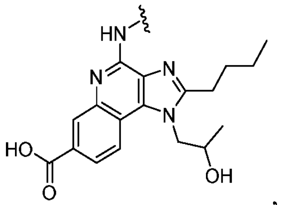
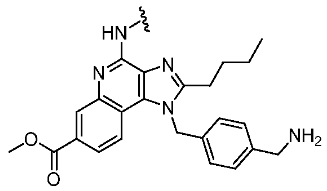
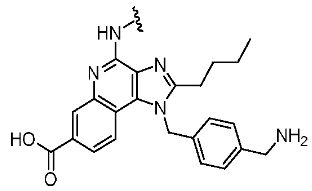
39. The ADC of any one of claims 1-38, wherein each instance of R^A and R^B is independently selected from the group consisting of hydrogen and C_1-C_3 alkyl.

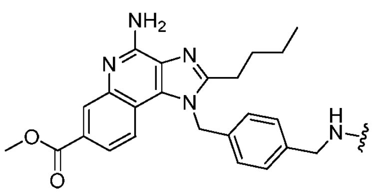
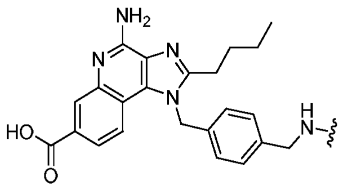
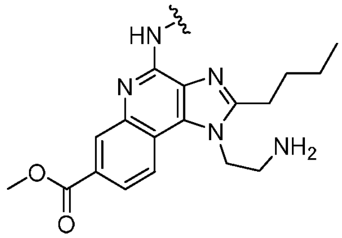
40. The ADC of any one of claims 1-39, wherein each instance of R^C is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl.

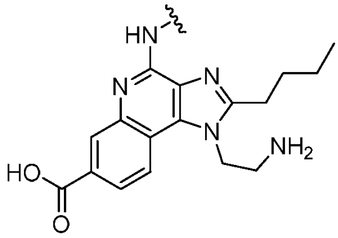
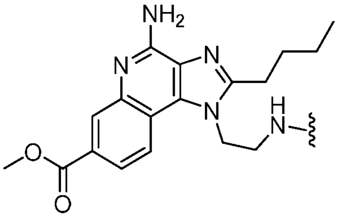
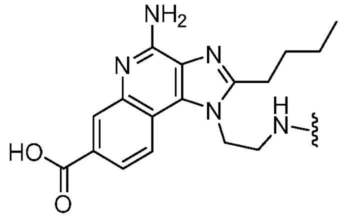
41. The ADC of any one of claims 1-40, wherein each instance of R^D, R^E, R^G, and R^H is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, C_4-C_6 cycloalkyl(C_1-C_3 alkyl)-, aryl, and aryl(C_1-C_3 alkyl).

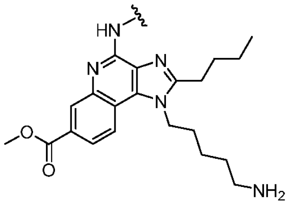
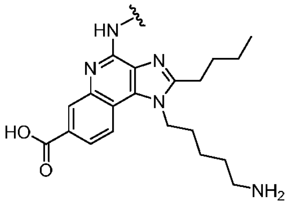
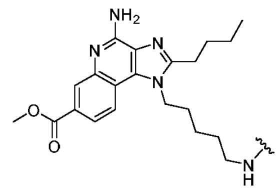
42. The ADC of any one of claims 1-41, wherein each instance of R^F is independently selected from the group consisting of hydrogen, trifluoromethyl, and C_1-C_6 alkyl.

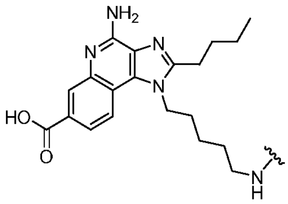
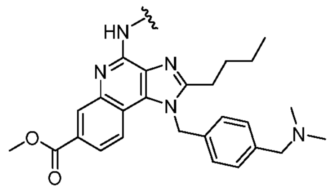
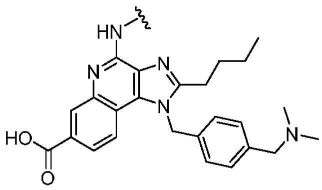
43. The ADC of any one of claims 1-42, wherein each D is  ,

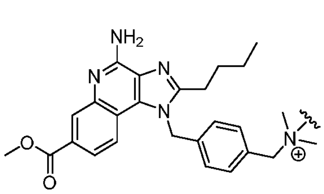
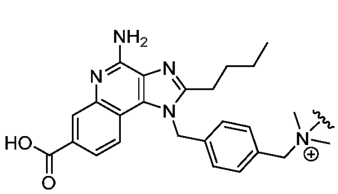
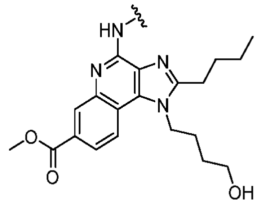
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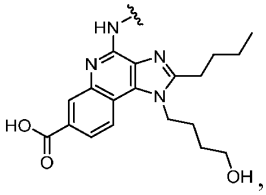
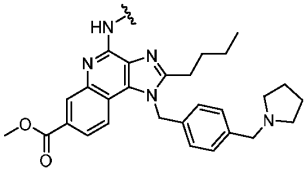
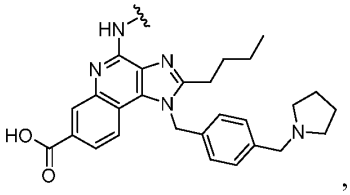
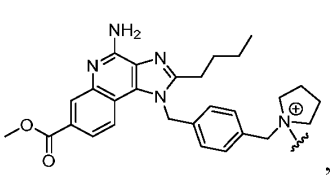
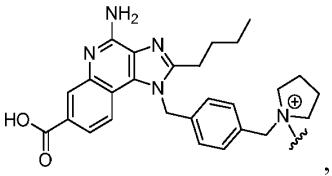
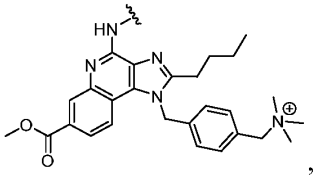
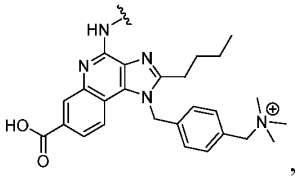
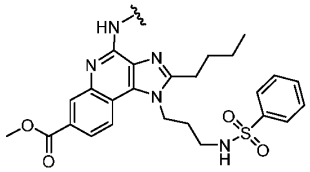
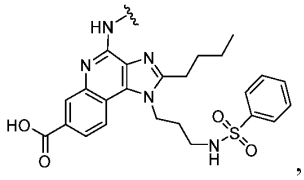
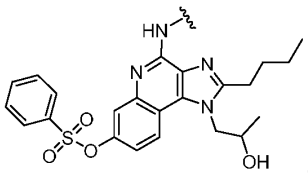
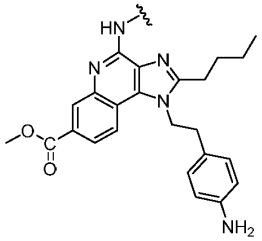
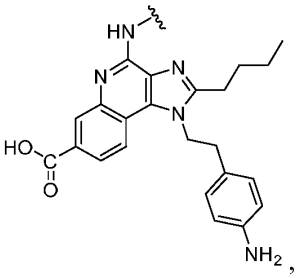
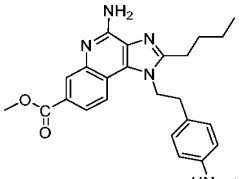
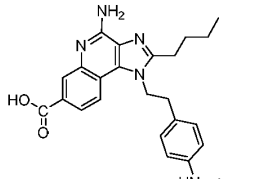
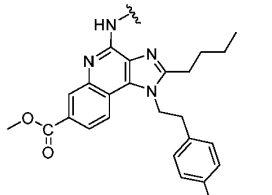
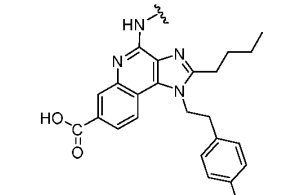
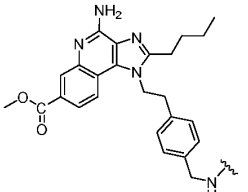
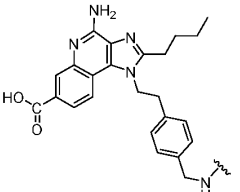
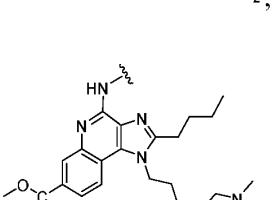
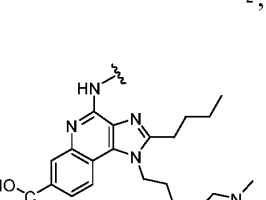
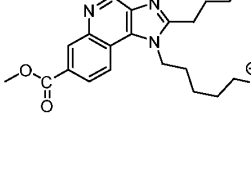
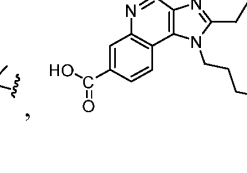
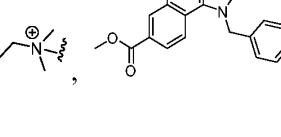
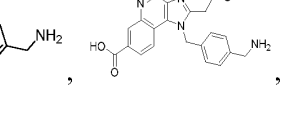
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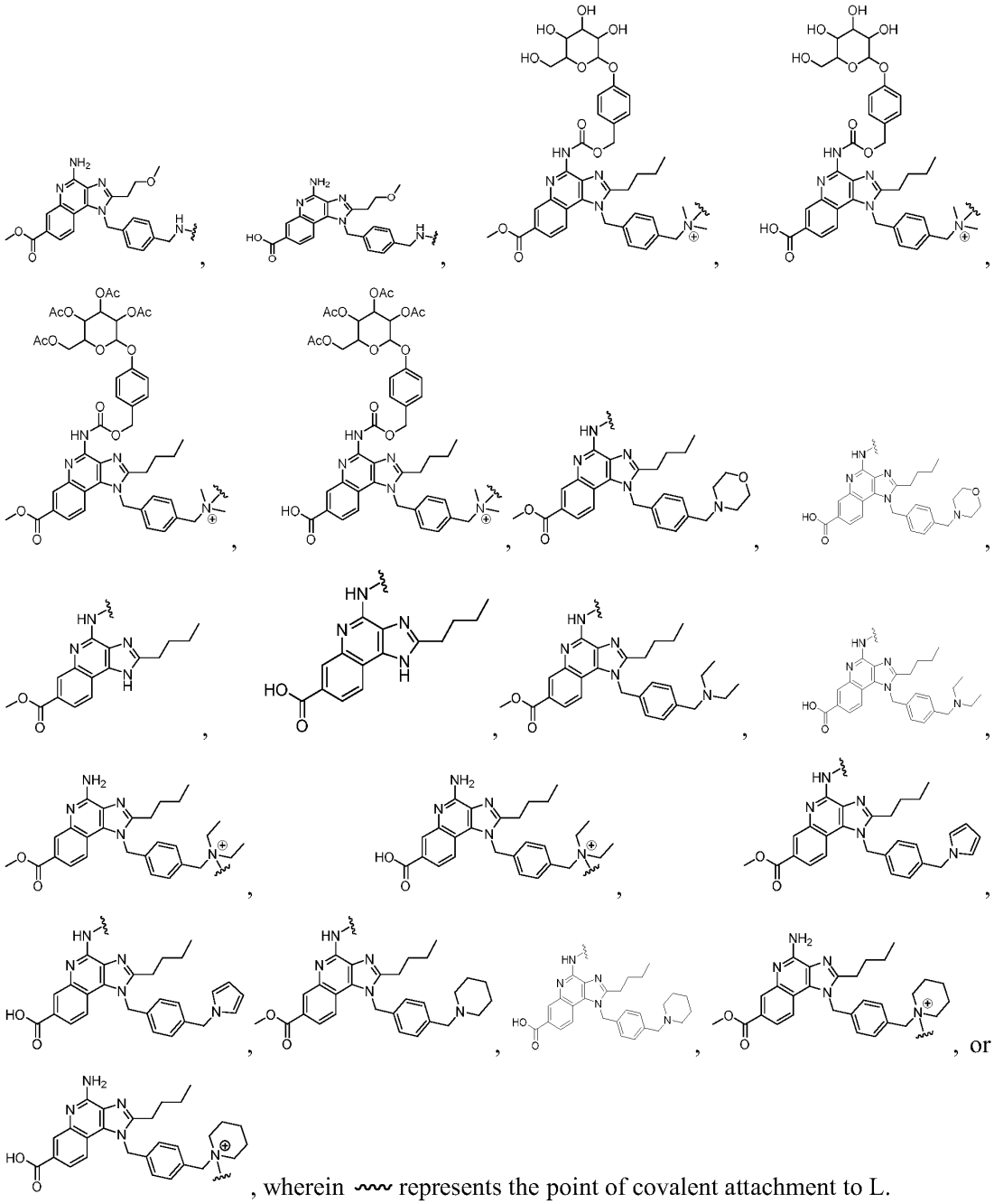

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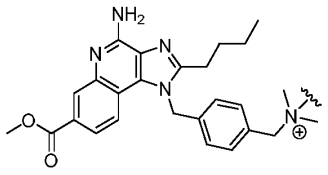
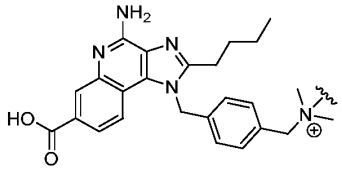
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, wherein ~~~ represents the point of covalent attachment to L.

44. The ADC of any one of claims 1-43, wherein each D is  or  , wherein ~~~ represents the point of covalent attachment to L.

45. The ADC of claim 43 or 44, wherein Ab comprises a heavy chain with at least 80% sequence identity to SEQ ID NO: 3 and a light chain with at least 80% sequence identity to SEQ ID NO: 5.

46. The ADC of any one of claims 1-45, wherein the linker comprises a length of between 10 and 40 atoms as defined by the pathway between D and Ab through the fewest number of bonds.

47. The ADC of any one of claims 1-46, wherein the linker comprises a length of between 15 and 30 atoms as defined by the pathway between D and Ab through the fewest number of bonds.

48. The ADC of any one of claims 1-47, wherein the linker comprises a PEG Unit from PEG1 to PEG72, a monosaccharide, a disaccharide, a trisaccharide, an oligopeptide, or a combination thereof.

49. The ADC of any one of claims 1-48, wherein 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, a disulfide, a dihydropyridazine, or a triazole;

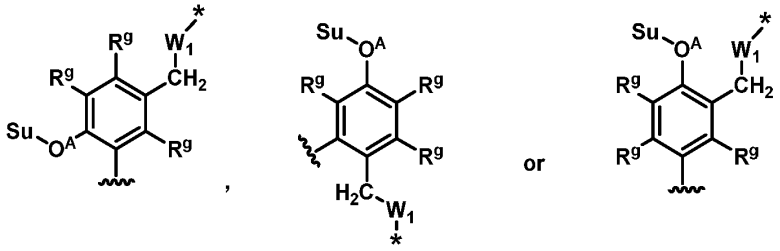
A is a C_{2-20} alkylene optionally substituted with 1-4 R^{a1}; or a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1};

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.

50. The ADC of claim 49, wherein subscript x is 1.

51. The ADC of claim 49 or 50 wherein X is a C_1-C_6 alkylene.

52. The ADC of any one of claims 49-51, wherein X is a C_1-C_3 alkylene.

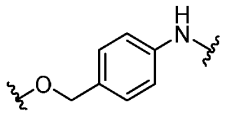
53. The ADC of claim 49 or 50, wherein X is a 3-6 membered heteroalkylene.

54. The ADC of any one of claims 49, 50, or 53, wherein X is a 3-4 membered heteroalkylene.

55. The ADC of claim 49, wherein subscript x is 0.

56. The ADC of any one of claims 49-55, wherein subscript y is 1.

57. The ADC of any one of claims 49-56, wherein Y is a self-immolative moiety.

58. The ADC of any one of claims 49-57, wherein Y is  .

59. The ADC of any one of claims 49-55, wherein Y is a non-cleavable moiety.

60. The ADC of any one of claims 49-55 or 59, wherein Y is a cyclohexanecarboxyl, undecanoyl, caproyl, hexanoyl, butanoyl or propionyl group.

61. The ADC of any one of claims 49-56, wherein Y is PEG4 to PEG12.

62. The ADC of any one of claims 49-55, wherein subscript y is 0.

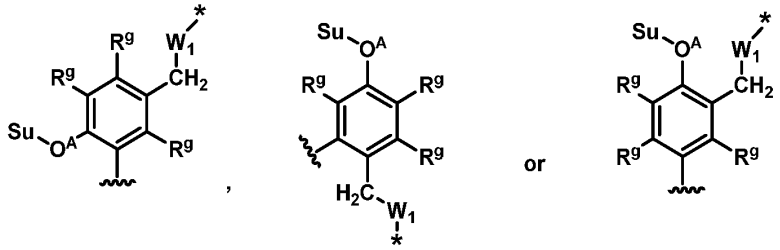
63. The ADC of any one of claims 49-62, wherein subscript w is 1.

64. The ADC of any one of claims 49-63, wherein W is from 6-12 amino acids.

65. The ADC of any one of claims 49-64, wherein W is from 6-9 amino acids.

66. The ADC of any one of claims 49-65, 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.

67. The ADC of any one of claims 49-63, wherein W has the structure:



wherein Su is a Sugar moiety;

-OA- 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.

68. The ADC of claim 67, wherein W^1 is absent.

69. The ADC of claim 67, wherein W^1 is *-C(=O)-O-.

70. The ADC of claim 67, wherein W^1 is *-O-C(=O)-.

71. The ADC of any one of claims 67-70, 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.

72. The ADC of any one of claims 67-71, wherein each R^g is hydrogen.

73. The ADC of any one of claims 49-62, wherein subscript w is 0.

74. The ADC of any one of claims 49-73, wherein subscript a is 1.

75. The ADC of any one of claims 49-74, wherein A is C_{2-20} alkylene optionally substituted with 1-4 R^{a1}.

76. The ADC of any one of claims 49-75, wherein A is C_{4-10} alkylene optionally substituted with 1-4 R^{a1}.

77. The ADC of any one of claims 49-75, wherein A is C_{2-20} alkylene substituted with one R^{a1}.

78. The ADC of any one of claims 49-77, wherein A is C_{4-10} alkylene substituted with one R^{a1}.

79. The ADC of any one of claims 49-74, wherein A is C_{2-20} alkylene.

80. The ADC of any one of claims 49-74 or 79, wherein A is C_{4-10} alkylene.

81. The ADC of any one of claims 49-74, wherein A is a 2 to 40 membered heteroalkylene optionally substituted with 1-4 R^{b1}.

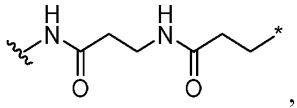
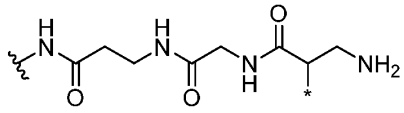
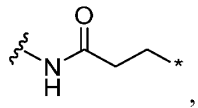
82. The ADC of any one of claims 49-74 or 81, wherein A is a 4 to 12 membered heteroalkylene optionally substituted with 1-4 R^{b1}.

83. The ADC of any one of claims 49-74 or 81, wherein A is a 2 to 40 membered heteroalkylene optionally substituted with one R^{b1}.

84. The ADC of any one of claims 49-74 or 81-83, wherein A is a 4 to 12 membered heteroalkylene optionally substituted with one R^{b1}.

85. The ADC of any one of claims 49-74, wherein A is a 2 to 40 membered heteroalkylene.

86. The ADC of any one of claims 49-74 or 85, wherein A is a 4 to 12 membered heteroalkylene.

87. The ADC of any one of claims 49-74, wherein A is  ,  , or  , wherein represents covalent attachment to W, and * represents covalent linkage to M.

88. The ADC of any one of claims 49-73, wherein subscript a is 0.

89. The ADC of any one of claims 49-88, wherein L is substituted with a PEG Unit from PEG1 to PEG72.

90. The ADC of any one of claims 49-87, wherein A is substituted with a PEG Unit from PEG1 to PEG72.

91. The ADC of any one of 49-90, wherein M is a succinimide, a hydrolyzed succinimide, an amide, a methyl ketone, a disulfide, a dihydropyridazine, or a triazole.

92. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the ADC of any one of claims 1-91, or a pharmaceutically acceptable salt thereof.

93. The method of claim 92, wherein the ADC is configured to internalize within a cell.

94. The method of claim 92 or 93, wherein the ADC targets a cancer-associated antigen.

95. The method of any one of claims 92-94, wherein the cell expresses the cancer-associated antigen.

96. The method of any one of claims 92-95, wherein the cell does not express the cancer-associated antigen.

97. The method of any one of claims 92-96, wherein the cell is an immune cell.

98. The method of claim 97, wherein the immune cell is a $CD8^+$ T-cell, a $CD4^+$ T-Cell, a T-regulatory cell, a macrophage, or a natural killer cell.

99. The method of claim 97 or 98, wherein the immune cell is a macrophage.

100. The method of any one of claims 97-99, wherein the immune cell expresses TLR7, TLR8, or TLR7 and TLR8.

101. The method of claim 97-100, wherein the cancer does not express TLR7 or TLR8.

102. The method of any one of claims 97-101, wherein the immune cell expresses a surface protein which binds to the cancer-associated antigen.

103. The method of any one of claims 93-102, wherein the internalizing comprises endocytosis or micropinocytosis.

104. The method of claim 92-103, 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.

105. The method of any one of claims 92-104, wherein the linker (L) of the ADC is configured to undergo cleavage subsequent to internalizing within the immune cell.

106. The method of any one of claims 92-105, wherein the cancer does not express CD4, CD8, an immune checkpoint, or a combination thereof.

107. The method of claim 106, wherein less than about 10%, less than about 7.5%, 5%, less than about 4.5%, less than about 4%, less than about 3.5%, less than about 3%, less than about 2.5%, less than about 2%, less than about 1.5%, less than about 1%, or less than about 0.5% of cancer cells of the cancer express the CD4, the CD8, the immune checkpoint, or the combination thereof.

108. The method of claim 106 or 107, wherein the CD4 expression, the CD8 expression, the immune checkpoint expression, or the combination thereof is membrane expression.

109. The method of any one of claims 106-108, wherein the immune checkpoint is PDL1, PD1, CTLA-4, B7H4, B7H3, TIGIT, TIM-3, VISTA, GITR/GITRL, CD80/CD86, CD155, PDL1, PDL2, galectin 9, CD40, OX40L, 4-1BB/4-1BBL, ICOS/ICOSL, CD70, or a combination thereof.

110. The method of any one of claims 106-109, wherein the immune checkpoint is PDL1.

111. The method of any one of claims 106-110, wherein the expression is in cancer cells derived from a tumor.

112. The method of claim 111, wherein the cancer cells derived from the tumor do not comprise tumor-associated immune cells.

113. The method of claim 111 or claim 112, wherein the cancer cells derived from the tumor comprise stromal cells from the tumor.

114. The method of any one of claims 106-113, wherein the determining comprises flow cytometry, immunohistochemistry, immunocytochemistry, immunofluorescence, immunoprecipitation, western blotting, ELISA, or mRNA analysis.

115. The method of claim 114, wherein the mRNA analysis comprises quantitative polymerase chain reaction (qPCR), reverse transcription qPCR (RT-qPCR), RNA sequencing, microarray analysis, in situ hybridization, or sequential gene expression analysis.