

FUNCTIONALIZED AURISTATINS, PHARMACEUTICAL COMPOSITIONS, AND THERAPEUTIC APPLICATIONS

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of the priority of International Application No. PCT/CN2023/106536, filed July 10, 2023, under 35 U.S.C. 119(a); the disclosure of which is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein are functionalized auristatins and pharmaceutical compositions thereof. Also provided herein are methods of their use for treating, preventing, or ameliorating one or more symptoms of a proliferative disease.

BACKGROUND

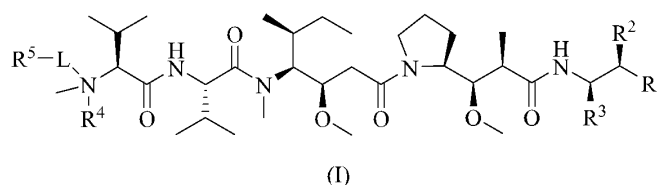
[0003] Glycosylation is an enzymatic process responsible for the attachment of a glycan to a glycosyl acceptor, *e.g.*, a cell surface protein. Reily *et al.*, *Nat. Rev. Nephrol.* **2019**, *15*, 346-66. Glycosylation is critical for physiological and pathological cellular functions. *Id.* Alternation in glycosylation has been identified almost in every type of cancer and has a major impact on cancer progression, tumor immunity, and clinical outcome. Hauselmann and Borsig, *Front. Oncol.* **2014**, *4*, 28; Stowell *et al.*, *Annu. Rev. Pathol.: Mech. Dis.* **2015**, *10*, 473-510; Pin and Reis, *Nat. Rev. Cancer* **2015**, *15*, 540-55; Munkley and Elliott, *Oncotarget* **2016**, *7*, 35478-89; Reily *et al.*, *Nat. Rev. Nephrol.* **2019**, *15*, 346-66.

[0004] Metabolic glycoengineering is a technique for introducing an unnatural sugar into a cellular glycan. Prescher *et al.*, *Nature* **2004**, *430*, 873-7; Agatemor *et al.*, *Nat. Rev. Chem.* **2019**, *3*, 605-20; Wang and Mooney, *Nat. Chem.* **2020**, *12*, 1102-14. Metabolic glycol-engineering takes advantage of cellular carbohydrate metabolism to tag a cell with a chemical reporter. *Id.* The chemical reporter (*e.g.*, azido) expressed on the cell surface can then be utilized for *in vivo* imaging or targeted drug delivery *via* bioorthogonal chemistry. Laughlin *et al.*, *Science* **2008**, *320*, 664-7; Sletten and Bertozzi, *Acc. Chem. Res.* **2011**, *44*, 666-76; Wang *et al.*, *Nat. Chem. Biol.* **2017**, *13*, 415; Wang and Mooney, *Nat. Chem.* **2020**, *12*, 1102-14.

[0005] Despite the advances in cancer diagnosis and treatment, cancer remains a major worldwide public health problem. Wang and Mooney, *Nat. Chem.* **2020**, *12*, 1102-14. It was estimated that there will be 1,958,310 new cancer cases diagnosed and 609,820 cancer deaths in the US alone in 2023. *Cancer Facts & Figures 2023*. Therefore, there is a need for an effective therapy for cancer treatment. Bargahi *et al.*, *Biol. Proced. Online* **2022**, *24*, 5.

SUMMARY OF THE DISCLOSURE

[0006] Provided herein is a compound of Formula (I):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

L is a self-immolative linker;

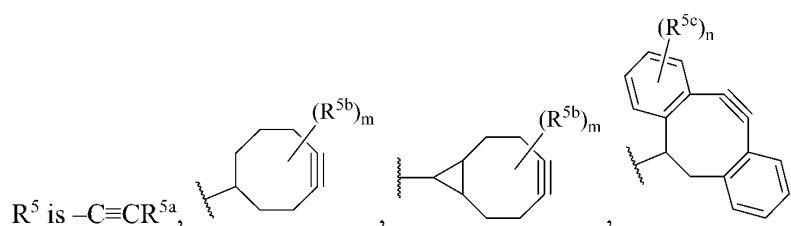
R¹ is C₆₋₁₄ aryl or heteroaryl;

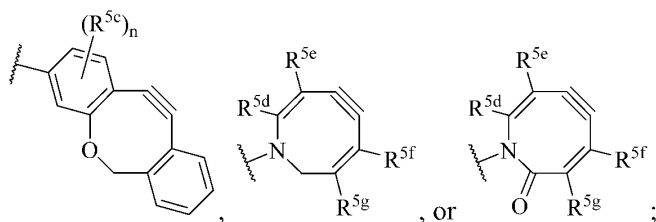
R² is hydrogen or -OR^{1a};

R³ is (i) hydrogen; (ii) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, or heteroaryl; or (iii)

-C(O)OR^{1a};

R⁴ is (i) absent; or (ii) C₁₋₆ alkyl or C₁₋₆ heteroalkyl, and the N atom to which R⁴ is attached is positively charged;





R^{5a} is hydrogen or deuterium;

each R^{5b} and R^{5c} is independently (i) deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)_2OR^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$;

each pair of R^{5d} and R^{5e} together with the carbon atoms to which they are attached independently forms C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene;

each pair of R^{5f} and R^{5g} together with the carbon atoms to which they are attached independently forms C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene;

each R^{1a} , R^{1b} , R^{1c} , and R^{1d} is independently hydrogen, deuterium, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and

each m and n is independently an integer of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q , wherein each Q is independently selected from: (a) deuterium, cyano, halo, nitro, and oxo; (b) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a ; and (c) $-C(O)R^a$, $-C(O)OR^a$,

$-C(O)NR^bR^c$, $-C(O)SR^a$, $-C(NR^a)NR^bR^c$, $-C(S)R^a$, $-C(S)OR^a$, $-C(S)NR^bR^c$, $-OR^a$, $-OC(O)R^a$,
 $-OC(O)OR^a$, $-OC(O)NR^bR^c$, $-OC(O)SR^a$, $-OC(NR^a)NR^bR^c$, $-OC(S)R^a$, $-OC(S)OR^a$,
 $-OC(S)NR^bR^c$, $-OP(O)(OR^b)OR^c$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-OS(O)NR^bR^c$, $-OS(O)_2NR^bR^c$,
 $-NR^bR^c$, $-NR^aC(O)R^d$, $-NR^aC(O)OR^d$, $-NR^aC(O)NR^bR^c$, $-NR^aC(O)SR^d$, $-NR^aC(NR^d)NR^bR^c$,
 $-NR^aC(S)R^d$, $-NR^aC(S)OR^d$, $-NR^aC(S)NR^bR^c$, $-NR^aS(O)R^d$, $-NR^aS(O)_2R^d$, $-NR^aS(O)NR^bR^c$,
 $-NR^aS(O)_2NR^bR^c$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)_2OR^a$, $-S(O)NR^bR^c$, and $-S(O)_2NR^bR^c$,
 wherein each R^a , R^b , R^c , and R^d is independently (i) hydrogen or deuterium; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a ; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a ;

wherein each Q^a is independently selected from: (a) deuterium, cyano, halo, nitro, and oxo; (b) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^fR^g$, $-C(O)SR^e$, $-C(NR^e)NR^fR^g$, $-C(S)R^e$, $-C(S)OR^e$, $-C(S)NR^fR^g$, $-OR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)NR^fR^g$, $-OC(O)SR^e$, $-OC(NR^e)NR^fR^g$, $-OC(S)R^e$, $-OC(S)OR^e$, $-OC(S)NR^fR^g$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^fR^g$, $-OS(O)_2NR^fR^g$, $-NR^fR^g$, $-NR^eC(O)R^h$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^fR^g$, $-NR^eC(O)SR^f$, $-NR^eC(NR^h)NR^fR^g$, $-NR^eC(S)R^h$, $-NR^eC(S)OR^f$, $-NR^eC(S)NR^fR^g$, $-NR^eS(O)R^h$, $-NR^eS(O)_2R^h$, $-NR^eS(O)NR^fR^g$, $-NR^eS(O)_2NR^fR^g$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)_2OR^e$, $-S(O)NR^fR^g$, and $-S(O)_2NR^fR^g$; wherein each R^e , R^f , R^g , and R^h is independently (i) hydrogen or deuterium; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl.

[0007] Also provided herein is a pharmaceutical composition comprising a compound of Formula (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and a pharmaceutically acceptable excipient.

[0008] Additionally, provided herein is a method of treating, treating, preventing, or

ameliorating one or more symptoms of a proliferative disease in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of Formula (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0009] Furthermore, provided herein is a method of inhibiting the growth of an cell, comprising contacting the cell with an effective amount of a compound of Formula (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 shows the anticancer effect of compound **A1** in a xenograft mouse model for ovarian cancer (OVCR3 cells), where compound **A1** (■) was administered intravenously at 20 mg/kg on Day 1; PBS (●) was used as a negative control; and each group had 6 mice.

[0011] FIG. 2 shows the effect of compound **A1** on body weight in a xenograft mouse model for ovarian cancer (OVCR3 cells), where compound **A1** (■) was administered at 20 mg/kg intravenously on Day 1; PBS (●) was used as a negative control; and each group had 6 mice.

[0012] FIG. 3 shows the anticancer effect of compound **A7** in a xenograft mouse model for ovarian cancer (SKOV3 cells), where AAM (tetraacetyl-*N*-azidoacetylmannosamine) was administered intratumorally at 10 mg/kg on Days 1, 2, 3, 15, 16, and 17 for azido labelling, coupled with administering compound **A7** intravenously at 5 mg/kg on Days 4 and 18 (◆); compound **A7** was administered alone intravenously at 5 mg/kg (▲) and 15 mg/kg (●) on Days 4 and 18; PBS (●) was used as a negative control; and each group had 6 mice.

[0013] FIG. 4 shows the effect of compound **A7** on body weight in a xenograft mouse model for ovarian cancer (SKOV3 cells), where AAM was administered intratumorally at 10 mg/kg on Days 1, 2, 3, 15, 16, and 17 for azido labelling, coupled with administering compound **A7** intravenously at 5 mg/kg on Days 4 and 18 (◆); compound **A7** was administered alone

intravenously at 5 mg/kg (▲) and 15 mg/kg (●) on Days 4 and 18; PBS (●) was used as a negative control; and each group had 6 mice.

[0014] FIG. 5 shows the anticancer effect of compound **B2** in a xenograft mouse model for ovarian cancer (SKOV3 cells), where compound **B2** (▼) was administered intravenously at 5 mg/kg on Day 1; cisplatin (■) and MMAE (▲) were used positive controls, and administered on Day 1 intravenously at 5 mg/kg and intratumorally at 2 mg/kg, respectively; PBS (●) was used as a negative control; and each group had 8 mice.

[0015] FIG. 6 shows the effect of compound **B2** on body weight in a xenograft mouse model for ovarian cancer (SKOV3 cells), where compound **B2** (▼) was administered intravenously at 5 mg/kg on Day 1; cisplatin (■) and MMAE (▲) were used positive controls and administered intratumorally on Day 1 at 5 mg/kg and 2 mg/kg, respectively; PBS (●) was used as a negative control; and each group had 8 mice.

[0016] FIG. 7 shows the anticancer effect of compound **A1** in a xenograft mouse model for ovarian cancer (A2780 cells), where AAM was administered intratumorally at 10 mg/kg on Days 1 to 3 for azido labelling, coupled with administering compound **A1** intravenously at 8 mg/kg on Day 4 (■); compound **A1** (▲) was administered alone intravenously at 8 mg/kg on Day 4; PBS (●) was used as a negative control; and each group had 8 mice.

[0017] FIG. 8 shows the effect of compound **A1** on body weight in a xenograft mouse model for ovarian cancer (A2780 cells), where AAM was administered intratumorally at 10 mg/kg on Days 1 to 3 for azido labelling, coupled with administering compound **A1** intravenously at 8 mg/kg on Day 4 (■); compound **A1** (▲) was administered alone intravenously at 8 mg/kg on Day 4; PBS (●) was used as a negative control; and each group had 8 mice.

DETAILED DESCRIPTION

[0018] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0019] Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, biochemistry, biology, and pharmacology described herein are

those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0020] The term “subject” refers to an animal, including, but not limited to, a primate (*e.g.*, human), cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject” and “patient” are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject. In one embodiment, the subject is a human.

[0021] The terms “treat,” “treating,” and “treatment” are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself.

[0022] The terms “prevent,” “preventing,” and “prevention” are meant to include a method of delaying and/or precluding the onset of a disorder, disease, or condition, and/or its attendant symptoms; barring a subject from acquiring a disorder, disease, or condition; or reducing a subject’s risk of acquiring a disorder, disease, or condition.

[0023] The terms “alleviate” and “alleviating” refer to easing or reducing one or more symptoms (*e.g.*, pain) of a disorder, disease, or condition. The terms can also refer to reducing adverse effects associated with an active ingredient. Sometimes, the beneficial effects that a subject derives from a prophylactic or therapeutic agent do not result in a cure of the disorder, disease, or condition.

[0024] The term “contacting” or “contact” is meant to refer to bringing together of a therapeutic agent and a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, or tissue such that a physiological and/or chemical effect takes place as a result of such contact. Contacting can take place *in vitro*, *ex vivo*, or *in vivo*. In one embodiment, a therapeutic agent is contacted with a biological molecule *in vitro* to determine the effect of the therapeutic agent on the biological molecule. In another embodiment, a therapeutic agent is contacted with a cell in cell culture (*in vitro*) to determine the effect of the therapeutic agent on the cell. In yet another embodiment, the contacting of a therapeutic agent with a biological molecule, cell, or tissue

includes the administration of a therapeutic agent to a subject having the biological molecule, cell, or tissue to be contacted.

[0025] The term “therapeutically effective amount” or “effective amount” is meant to include the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder, disease, or condition being treated. The term “therapeutically effective amount” or “effective amount” also refers to the amount of a compound that is sufficient to elicit a biological or medical response of a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0026] The term “pharmaceutically acceptable carrier,” “pharmaceutically acceptable excipient,” “physiologically acceptable carrier,” or “physiologically acceptable excipient” refers to a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In one embodiment, each component is “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of a subject (*e.g.*, a human) without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, and commensurate with a reasonable benefit/risk ratio. *See, e.g.*, *Remington: The Science and Practice of Pharmacy*, 23rd ed.; Adejare Ed.; Academic Press, 2020; *Handbook of Pharmaceutical Excipients*, 9th ed.; Sheskey *et al.*, Eds.; Pharmaceutical Press, 2020; *Handbook of Pharmaceutical Additives*, 3rd ed.; Ash and Ash Eds.; Synapse Information Resources, 2007; *Pharmaceutical Preformulation and Formulation*, 2nd ed.; Gibson Ed.; CRC Press, 2009.

[0027] The term “about” or “approximately” means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term “about” or “approximately” means within 1, 2, or 3 standard deviations. In certain embodiments, the term “about” or “approximately” means within 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

[0028] The term “alkyl” refers to a linear or branched saturated monovalent hydrocarbon

radical, wherein the alkyl is optionally substituted with one or more substituents Q as described herein. For example, C₁₋₆ alkyl refers to a linear saturated monovalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkyl is a linear saturated monovalent hydrocarbon radical that has 1 to 30 (C₁₋₃₀), 1 to 20 (C₁₋₂₀), 1 to 15 (C₁₋₁₅), 1 to 10 (C₁₋₁₀), or 1 to 6 (C₁₋₆) carbon atoms, or branched saturated monovalent hydrocarbon radical of 3 to 30 (C₃₋₃₀), 3 to 20 (C₃₋₂₀), 3 to 15 (C₃₋₁₅), 3 to 10 (C₃₋₁₀), or 3 to 6 (C₃₋₆) carbon atoms. As used herein, linear C₁₋₆ and branched C₃₋₆ alkyl groups are also referred to as “lower alkyl.” Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl (including all isomeric forms, *e.g.*, *n*-propyl and isopropyl), butyl (including all isomeric forms, *e.g.*, *n*-butyl, isobutyl, *sec*-butyl, and *t*-butyl), pentyl (including all isomeric forms, *e.g.*, *n*-pentyl, isopentyl, *sec*-pentyl, neopentyl, and *tert*-pentyl), and hexyl (including all isomeric forms, *e.g.*, *n*-hexyl, isohexyl, and *sec*-hexyl).

[0029] The terms “alkylene” and “alkanediyl” are used interchangeably herein in reference to a linear or branched saturated divalent hydrocarbon radical, wherein the alkanediyl is optionally substituted with one or more substituents Q as described herein. For example, C₁₋₆ alkanediyl refers to a linear saturated divalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated divalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkanediyl is a linear saturated divalent hydrocarbon radical that has 1 to 30 (C₁₋₃₀), 1 to 20 (C₁₋₂₀), 1 to 15 (C₁₋₁₅), 1 to 10 (C₁₋₁₀), or 1 to 6 (C₁₋₆) carbon atoms, or branched saturated divalent hydrocarbon radical of 3 to 30 (C₃₋₃₀), 3 to 20 (C₃₋₂₀), 3 to 15 (C₃₋₁₅), 3 to 10 (C₃₋₁₀), or 3 to 6 (C₃₋₆) carbon atoms. As used herein, linear C₁₋₆ and branched C₃₋₆ alkanediyl groups are also referred to as “lower alkanediyl.” Examples of alkanediyl groups include, but are not limited to, methanediyl, ethanediyl (including all isomeric forms, *e.g.*, ethane-1,1-diyl and ethane-1,2-diyl), propanediyl (including all isomeric forms, *e.g.*, propane-1,1-diyl, propane-1,2-diyl, and propane-1,3-diyl), butanediyl (including all isomeric forms, *e.g.*, butane-1,1-diyl, butane-1,2-diyl, butane-1,3-diyl, and butane-1,4-diyl), pentanediyl (including all isomeric forms, *e.g.*, pentane-1,1-diyl, pentane-1,2-diyl, pentane-1,3-diyl, and pentane-1,5-diyl), and hexanediyl (including all isomeric forms, *e.g.*, hexane-1,1-diyl, hexane-1,2-diyl, hexane-1,3-diyl, and hexane-1,6-diyl). Examples of substituted alkanediyl groups include, but are not limited to, -C(O)CH₂-, -C(O)(CH₂)₂-, -C(O)(CH₂)₃-, -C(O)(CH₂)₄-, -C(O)(CH₂)₅-, -C(O)(CH₂)₆-, -C(O)(CH₂)₇-, -C(O)(CH₂)₈-, -C(O)(CH₂)₉-, -C(O)(CH₂)₁₀-, -C(O)CH₂C(O)-, -C(O)(CH₂)₂C(O)-,

$-\text{C}(\text{O})(\text{CH}_2)_3\text{C}(\text{O})-$, $-\text{C}(\text{O})(\text{CH}_2)_4\text{C}(\text{O})-$, or $-\text{C}(\text{O})(\text{CH}_2)_5\text{C}(\text{O})-$.

[0030] The term “heteroalkyl” refers to a linear or branched saturated monovalent hydrocarbon radical that contains one or more heteroatoms on its main chain, each independently selected from O, S, and N. The heteroalkyl is optionally substituted with one or more substituents Q as described herein. For example, C_{1-6} heteroalkyl refers to a linear saturated monovalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the heteroalkyl is a linear saturated monovalent hydrocarbon radical that has 1 to 30 (C_{1-30}), 1 to 20 (C_{1-20}), 1 to 15 (C_{1-15}), 1 to 10 (C_{1-10}), or 1 to 6 (C_{1-6}) carbon atoms, or branched saturated monovalent hydrocarbon radical of 3 to 30 (C_{3-30}), 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. As used herein, linear C_{1-6} and branched C_{3-6} heteroalkyl groups are also referred as “lower heteroalkyl.” Examples of heteroalkyl groups include, but are not limited to, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{NHCH}_3$, $-\text{ONHCH}_3$, $-\text{NHOCH}_3$, $-\text{SCH}_3$, $-\text{CH}_2\text{NHCH}_2\text{CH}_3$, and $-\text{NHCH}_2\text{CH}_2\text{CH}_3$. Examples of substituted heteroalkyl groups include, but are not limited to, $-\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$ and $-\text{NHC}(\text{O})\text{CH}_2\text{CH}_3$.

[0031] The terms “heteroalkylene” and “heteroalkanediyl” are used interchangeably herein in reference to a linear or branched saturated divalent hydrocarbon radical that contains one or more heteroatoms in its main chain, each independently selected from O, S, and N. The heteroalkylene is optionally substituted with one or more substituents Q as described herein. For example, C_{1-6} heteroalkylene refers to a linear saturated divalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated divalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the heteroalkylene is a linear saturated divalent hydrocarbon radical that has 1 to 30 (C_{1-30}), 1 to 20 (C_{1-20}), 1 to 15 (C_{1-15}), 1 to 10 (C_{1-10}), or 1 to 6 (C_{1-6}) carbon atoms or branched saturated divalent hydrocarbon radical of 3 to 30 (C_{3-30}), 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. As used herein, linear C_{1-6} and branched C_{3-6} heteroalkylene groups are also referred as “lower heteroalkylene.” Examples of heteroalkylene groups include, but are not limited to, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{CH}_2\text{O}-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-$, $-(\text{CH}_2)_4\text{O}-$, $-(\text{CH}_2)_5\text{O}-$, $-(\text{CH}_2)_6\text{O}-$, $-(\text{CH}_2)_7\text{O}-$, $-(\text{CH}_2)_8\text{O}-$, $-(\text{CH}_2)_9\text{O}-$, $-(\text{CH}_2)_{10}\text{O}-$, $-\text{CH}_2\text{OCH}_2-$, $-\text{CH}_2\text{CH}_2\text{O}-$, $-(\text{CH}_2\text{CH}_2\text{O})_2-$, $-(\text{CH}_2\text{CH}_2\text{O})_3-$, $-(\text{CH}_2\text{CH}_2\text{O})_4-$, $-(\text{CH}_2\text{CH}_2\text{O})_5-$, $-\text{CH}_2\text{NH}-$, $-\text{CH}_2\text{NHCH}_2-$, $-\text{CH}_2\text{CH}_2\text{NH}-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}-$, $-(\text{CH}_2)_4\text{NH}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{SCH}_2-$, and

$-\text{CH}_2\text{CH}_2\text{S}-$. Examples of substituted heteroalkylene groups include, but are not limited to, $-\text{C}(\text{O})\text{CH}_2\text{O}-$, $-\text{C}(\text{O})(\text{CH}_2)_2\text{O}-$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-$, $-\text{C}(\text{O})(\text{CH}_2)_5\text{O}-$, $-\text{C}(\text{O})(\text{CH}_2)_6\text{O}-$, $-\text{C}(\text{O})(\text{CH}_2)_7\text{O}-$, $-\text{C}(\text{O})(\text{CH}_2)_8\text{O}-$, $-\text{C}(\text{O})(\text{CH}_2)_9\text{O}-$, $-\text{C}(\text{O})(\text{CH}_2)_{10}\text{O}-$, $-\text{C}(\text{O})\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}-$, $-\text{C}(\text{O})\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_2-$, $-\text{C}(\text{O})\text{CH}_2\text{O}-(\text{CH}_2\text{CH}_2\text{O})_3-$, $-\text{C}(\text{O})\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_4-$, $-\text{C}(\text{O})\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_5-$, $-\text{CH}_2\text{NHC}(\text{O})\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}-$, $-\text{CH}_2\text{N}(\text{CH}_3)-$, $-(\text{CH}_2)_2\text{N}(\text{CH}_3)-$, $-(\text{CH}_2)_3\text{N}(\text{CH}_3)-$, or $-(\text{CH}_2)_4\text{N}(\text{CH}_3)-$.

[0032] The term “alkenyl” refers to a linear or branched monovalent hydrocarbon radical, which contains one or more, in one embodiment, one, two, three, or four, in another embodiment, one, carbon-carbon double bond(s). The alkenyl is optionally substituted with one or more substituents Q as described herein. The term “alkenyl” embraces radicals having a “*cis*” or “*trans*” configuration or a mixture thereof, or alternatively, a “*Z*” or “*E*” configuration or a mixture thereof, as appreciated by those of ordinary skill in the art. For example, C₂₋₆ alkenyl refers to a linear unsaturated monovalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkenyl is a linear monovalent hydrocarbon radical of 2 to 30 (C₂₋₃₀), 2 to 20 (C₂₋₂₀), 2 to 15 (C₂₋₁₅), 2 to 10 (C₂₋₁₀), or 2 to 6 (C₂₋₆) carbon atoms, or a branched monovalent hydrocarbon radical of 3 to 30 (C₃₋₃₀), 3 to 20 (C₃₋₂₀), 3 to 15 (C₃₋₁₅), 3 to 10 (C₃₋₁₀), or 3 to 6 (C₃₋₆) carbon atoms. Examples of alkenyl groups include, but are not limited to, ethenyl, propenyl (including all isomeric forms, *e.g.*, propen-1-yl, propen-2-yl, and allyl), and butenyl (including all isomeric forms, *e.g.*, buten-1-yl, buten-2-yl, buten-3-yl, and 2-buten-1-yl).

[0033] The terms “alkenylene” and “alkenediyl” are used interchangeably herein in reference to a linear or branched divalent hydrocarbon radical, which contains one or more, in one embodiment, one, two, three, or four, in another embodiment, one, carbon-carbon double bond(s). The alkenediyl is optionally substituted with one or more substituents Q as described herein. The term “alkenediyl” embraces radicals having a “*cis*” or “*trans*” configuration or a mixture thereof, or alternatively, a “*Z*” or “*E*” configuration or a mixture thereof, as appreciated by those of ordinary skill in the art. For example, C₂₋₆ alkenediyl refers to a linear unsaturated divalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated divalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkenediyl is a linear divalent hydrocarbon radical of 2 to 30 (C₂₋₃₀), 2 to 20 (C₂₋₂₀), 2 to 15 (C₂₋₁₅), 2 to 10 (C₂₋₁₀), or 2

to 6 (C_{2-6}) carbon atoms, or a branched divalent hydrocarbon radical of 3 to 30 (C_{3-30}), 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. Examples of alkenediyl groups include, but are not limited to, ethenediyl (including all isomeric forms, *e.g.*, ethene-1,1-diyl and ethene-1,2-diyl), propenediyl (including all isomeric forms, *e.g.*, 1-propene-1,1-diyl, 1-propene-1,2-diyl, and 1-propene-1,3-diyl), butenediyl (including all isomeric forms, *e.g.*, 1-butene-1,1-diyl, 1-butene-1,2-diyl, and 1-butene-1,4-diyl), pentenediyl (including all isomeric forms, *e.g.*, 1-pentene-1,1-diyl, 1-pentene-1,2-diyl, and 1-pentene-1,5-diyl), and hexenediyl (including all isomeric forms, *e.g.*, 1-hexene-1,1-diyl, 1-hexene-1,2-diyl, 1-hexene-1,3-diyl, 1-hexene-1,4-diyl, 1-hexene-1,5-diyl, and 1-hexene-1,6-diyl).

[0034] The term “alkynyl” refers to a linear or branched monovalent hydrocarbon radical, which contains one or more, in one embodiment, one, two, three, or four, in another embodiment, one, carbon-carbon triple bond(s). An alkynyl group does not contain a carbon-carbon double bond. The alkynyl is optionally substituted with one or more substituents Q as described herein. For example, C_{2-6} alkynyl refers to a linear unsaturated monovalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated monovalent hydrocarbon radical of 4 to 6 carbon atoms. In certain embodiments, the alkynyl is a linear monovalent hydrocarbon radical of 2 to 30 (C_{2-30}), 2 to 20 (C_{2-20}), 2 to 15 (C_{2-15}), 2 to 10 (C_{2-10}), or 2 to 6 (C_{2-6}) carbon atoms, or a branched monovalent hydrocarbon radical of 4 to 30 (C_{4-30}), 4 to 20 (C_{4-20}), 4 to 15 (C_{4-15}), 4 to 10 (C_{4-10}), or 4 to 6 (C_{4-6}) carbon atoms. Examples of alkynyl groups include, but are not limited to, ethynyl ($-C\equiv CH$), propynyl (including all isomeric forms, *e.g.*, 1-propynyl ($-C\equiv CCH_3$) and propargyl ($-CH_2C\equiv CH$)), butynyl (including all isomeric forms, *e.g.*, 1-butyn-1-yl and 2-butyn-1-yl), pentynyl (including all isomeric forms, *e.g.*, 1-pentyn-1-yl and 1-methyl-2-butyn-1-yl), and hexynyl (including all isomeric forms, *e.g.*, 1-hexyn-1-yl and 2-hexyn-1-yl).

[0035] The terms “alkynylene” and “alkynediyl” are used interchangeably herein in reference to a linear or branched divalent hydrocarbon radical, which contains one or more, in one embodiment, one, two, three, or four, in another embodiment, one, carbon-carbon triple bond(s). An alkynylene group does not contain a carbon-carbon double bond. The alkynediyl is optionally substituted with one or more substituents Q as described herein. For example, C_{2-6} alkynediyl refers to a linear unsaturated divalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated divalent hydrocarbon radical of 4 to 6 carbon atoms. In certain

embodiments, the alkynediyl is a linear divalent hydrocarbon radical of 2 to 30 (C₂₋₃₀), 2 to 20 (C₂₋₂₀), 2 to 15 (C₂₋₁₅), 2 to 10 (C₂₋₁₀), or 2 to 6 (C₂₋₆) carbon atoms, or a branched divalent hydrocarbon radical of 4 to 30 (C₄₋₃₀), 4 to 20 (C₄₋₂₀), 4 to 15 (C₄₋₁₅), 4 to 10 (C₄₋₁₀), or 4 to 6 (C₄₋₆) carbon atoms. Examples of alkynediyl groups include, but are not limited to, ethynediyl, propynediyl (including all isomeric forms, *e.g.*, 1-propyne-1,3-diyl and 1-propyne-3,3-diyl), butynediyl (including all isomeric forms, *e.g.*, 1-butyne-1,3-diyl, 1-butyne-1,4-diyl, and 2-butyne-1,1-diyl), pentynediyl (including all isomeric forms, *e.g.*, 1-pentyne-1,3-diyl, 1-pentyne-1,4-diyl, and 2-pentyne-1,1-diyl), and hexynediyl (including all isomeric forms, *e.g.*, 1-hexyne-1,3-diyl, 1-hexyne-1,4-diyl, and 2-hexyne-1,1-diyl).

[0036] The term “cycloalkyl” refers to a cyclic monovalent hydrocarbon radical, which is optionally substituted with one or more substituents Q as described herein. In one embodiment, the cycloalkyl is a saturated or unsaturated but non-aromatic, and/or bridged or non-bridged, and/or fused bicyclic group. In certain embodiments, the cycloalkyl has from 3 to 20 (C₃₋₂₀), from 3 to 15 (C₃₋₁₅), from 3 to 10 (C₃₋₁₀), or from 3 to 7 (C₃₋₇) carbon atoms. In one embodiment, the cycloalkyl is monocyclic. In another embodiment, the cycloalkyl is bicyclic. In yet another embodiment, the cycloalkyl is tricyclic. In still another embodiment, the cycloalkyl is polycyclic. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptenyl, bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, decalinyl, and adamantyl.

[0037] The terms “cycloalkylene” and “cycloalkanediyl” are used interchangeably herein in reference to a cyclic divalent hydrocarbon radical, which may be optionally substituted with one or more substituents Q as described herein. In one embodiment, cycloalkanediyl groups may be saturated or unsaturated but non-aromatic, and/or bridged, and/or non-bridged, and/or fused bicyclic groups. In certain embodiments, the cycloalkanediyl has from 3 to 30 (C₃₋₃₀), 3 to 20 (C₃₋₂₀), from 3 to 15 (C₃₋₁₅), from 3 to 10 (C₃₋₁₀), or from 3 to 7 (C₃₋₇) carbon atoms. Examples of cycloalkanediyl groups include, but are not limited to, cyclopropanediyl (including all isomeric forms, *e.g.*, cyclopropane-1,1-diyl and cyclopropane-1,2-diyl), cyclobutanediyl (including all isomeric forms, *e.g.*, cyclobutane-1,1-diyl, cyclobutane-1,2-diyl, and cyclobutane-1,3-diyl), cyclopentane-1,1-diyl, cyclopentane-1,2-diyl, cyclopentane-1,3-diyl, cyclopentane-1,4-diyl, and cyclopentane-2,2-diyl.

cyclopentane-1,2-diyl, and cyclopentane-1,3-diyl), cyclohexanediyl (including all isomeric forms, *e.g.*, cyclohexane-1,1-diyl, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl, and cyclohex-1,4-diyl), cycloheptanediyl (including all isomeric forms, *e.g.*, cycloheptane-1,1-diyl, cycloheptane-1,2-diyl, cycloheptane-1,3-diyl, and cycloheptane-1,4-diyl), decalinediyl (including all isomeric forms, *e.g.*, decaline-1,1-diyl, decaline-1,2-diyl, and decaline-1,8-diyl), and adamantdiyl (including all isomeric forms, *e.g.*, adamant-1,2-diyl, adamant-1,3-diyl, and adamant-1,8-diyl).

[0038] The term “aryl” refers to a monovalent monocyclic aromatic hydrocarbon radical and/or monovalent polycyclic aromatic hydrocarbon radical that contain at least one aromatic carbon ring. In certain embodiments, the aryl has from 6 to 30 (C_{6-30}), from 6 to 20 (C_{6-20}), from 6 to 15 (C_{6-15}), or from 6 to 10 (C_{6-10}) ring carbon atoms. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, fluorenyl, azulenyl, anthryl, phenanthryl, pyrenyl, biphenyl, and terphenyl. The aryl also refers to bicyclic or tricyclic carbon rings, where one of the rings is aromatic and the others of which may be saturated, partially unsaturated, or aromatic, for example, dihydronaphthyl, indenyl, indanyl, or tetrahydronaphthyl (tetralinyl). In one embodiment, the aryl is monocyclic. In another embodiment, the aryl is bicyclic. In yet another embodiment, the aryl is tricyclic. In still another embodiment, the aryl is polycyclic. In certain embodiments, the aryl is optionally substituted with one or more substituents Q as described herein.

[0039] The terms “arylene” and “arenediyl” are used interchangeably herein in reference to a divalent monocyclic aromatic hydrocarbon radical or divalent polycyclic aromatic hydrocarbon radical that contains at least one aromatic hydrocarbon ring. In certain embodiments, the arylene has from 6 to 30 (C_{6-30}), from 6 to 20 (C_{6-20}), from 6 to 15 (C_{6-15}), or from 6 to 10 (C_{6-10}) ring atoms. Examples of arylene groups include, but are not limited to, phenylene (including all isomeric forms, *e.g.*, phen-1,2-diyl, phen-1,3-diyl, and phen-1,4-diyl), naphthylene (including all isomeric forms, *e.g.*, naphth-1,2-diyl, naphth-1,3-diyl, and naphth-1,8-diyl), fluorenylene (including all isomeric forms, *e.g.*, fluoren-1,2-diyl, fluoren-1,3-diyl, and fluoren-1,8-diyl), azulenylene (including all isomeric forms, *e.g.*, azulen-1,2-diyl, azulen-1,3-diyl, and azulen-1,8-diyl), anthrylene (including all isomeric forms, *e.g.*, anthr-1,2-diyl, anthr-1,3-diyl, and anthr-1,8-diyl), phenanthrylene (including all isomeric forms, *e.g.*, phenanthr-1,2-diyl, phenanthr-1,3-diyl, and phenanthr-1,8-diyl), pyrenylene (including all isomeric forms, *e.g.*,

pyren-1,2-diyl, pyren-1,3-diyl, and pyren-1,8-diyl), biphenylene (including all isomeric forms, *e.g.*, biphen-2,3-diyl, biphen-3,4'-diyl, and biphen-4,4'-diyl), and terphenylene (including all isomeric forms, *e.g.*, terphen-2,3-diyl, terphen-3,4'-diyl, and terphen-4,4'-diyl). Arylene also refers to bicyclic or tricyclic carbon rings, where one of the rings is aromatic and the others of which may be saturated, partially unsaturated, or aromatic, for example, dihydronaphthylene (including all isomeric forms, *e.g.*, dihydronaphth-1,2-diyl and dihydronaphth-1,8-diyl), indenylene (including all isomeric forms, *e.g.*, inden-1,2-diyl, inden-1,5-diyl, and inden-1,7-diyl), indanylene (including all isomeric forms, *e.g.*, indan-1,2-diyl, indan-1,5-diyl, and indan-1,7-diyl), or tetrahydronaphthylene (tetralinylene) (including all isomeric forms, *e.g.*, tetrahydronaphth-1,2-diyl, tetrahydronaphth-1,5-diyl, and tetrahydronaphth-1,8-diyl). In certain embodiments, arylene is optionally substituted with one or more substituents Q as described herein.

[0040] The term “aralkyl” or “arylalkyl” refers to a monovalent alkyl group substituted with one or more aryl groups. In certain embodiments, the aralkyl has from 7 to 30 (C_{7-30}), from 7 to 20 (C_{7-20}), or from 7 to 16 (C_{7-16}) carbon atoms. Examples of aralkyl groups include, but are not limited to, benzyl, phenylethyl (including all isomeric forms, *e.g.*, 1-phenylethyl and 2-phenylethyl), and phenylpropyl (including all isomeric forms, *e.g.*, 1-phenylpropyl, 2-phenylpropyl, and 3-phenylpropyl). In certain embodiments, the aralkyl is optionally substituted with one or more substituents Q as described herein.

[0041] The term “aralkylene” or “arylalkylene” refers to a divalent alkyl group substituted with one or more aryl groups. In certain embodiments, the aralkylene has from 7 to 30 (C_{7-30}), from 7 to 20 (C_{7-20}), or from 7 to 16 (C_{7-16}) carbon atoms. Examples of aralkylene groups include, but are not limited to, benzylene (including all isomeric forms, *e.g.*, phenylmethdiyl), phenylethylene (including all isomeric forms, *e.g.*, 2-phenyl-ethan-1,1-diyl and 2-phenyl-ethan-1,2-diyl), and phenylpropylene (including all isomeric forms, *e.g.*, 3-phenyl-propan-1,1-diyl, 3-phenyl-propan-1,2-diyl, and 3-phenyl-propan-1,3-diyl). In certain embodiments, the aralkylene is optionally substituted with one or more substituents Q as described herein.

[0042] The term “heteroaryl” refers to a monovalent monocyclic aromatic group or monovalent polycyclic aromatic group that contain at least one aromatic ring, wherein at least

one aromatic ring contains one or more heteroatoms, each independently selected from O, S, and N, in the ring. For a heteroaryl group containing a heteroaromatic ring and a nonaromatic heterocyclic ring, the heteroaryl group is not bonded to the rest of a molecule through its nonaromatic heterocyclic ring. Each ring of a heteroaryl group can contain one or two O atoms, one or two S atoms, and/or one to four N atoms; provided that the total number of heteroatoms in each ring is four or less and each ring contains at least one carbon atom. In certain embodiments, the heteroaryl has from 5 to 20, from 5 to 15, or from 5 to 10 ring atoms. In one embodiment, the heteroaryl is monocyclic. Examples of monocyclic heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl, and triazolyl. In another embodiment, the heteroaryl is bicyclic. Examples of bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzimidazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzotriazolyl, benzoxazolyl, furopyrindyl (including all isomeric forms, *e.g.*, furo[2,3-*b*]pyridinyl, furo[2,3-*c*]pyridinyl, furo[3,2-*b*]pyridinyl, furo[3,2-*c*]pyridinyl, furo[3,4-*b*]pyridinyl, and furo[3,4-*c*]pyridinyl), imidazopyridinyl (including all isomeric forms, *e.g.*, imidazo[1,2-*a*]pyridinyl, imidazo[4,5-*b*]pyridinyl, and imidazo[4,5-*c*]pyridinyl), imidazothiazolyl (including all isomeric forms, *e.g.*, imidazo[2,1-*b*]thiazolyl and imidazo[4,5-*d*]thiazolyl), indazolyl, indoliziny, indolyl, isobenzofuranyl, isobenzothienyl (*i.e.*, benzo[*c*]thienyl), isoindolyl, isoquinoliny, naphthyridinyl (including all isomeric forms, *e.g.*, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, and 1,8-naphthyridinyl), oxazolopyridinyl (including all isomeric forms, *e.g.*, oxazolo[4,5-*b*]pyridinyl, oxazolo[4,5-*c*]pyridinyl, oxazolo[5,4-*b*]pyridinyl, and oxazolo[5,4-*c*]pyridinyl), phthalazinyl, pteridinyl, purinyl, pyrrolopyridyl (including all isomeric forms, *e.g.*, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[2,3-*c*]pyridinyl, pyrrolo[3,2-*b*]pyridinyl, and pyrrolo[3,2-*c*]pyridinyl), quinoliny, quinoxaliny, quinazolinyl, thiadiazolopyrimidyl (including all isomeric forms, *e.g.*, [1,2,5]thiadiazolo[3,4-*d*]pyrimidinyl and [1,2,3]thiadiazolo[4,5-*d*]pyrimidinyl), and thienopyridyl (including all isomeric forms, *e.g.*, thieno[2,3-*b*]pyridinyl, thieno[2,3-*c*]pyridinyl, thieno[3,2-*b*]pyridinyl, and thieno[3,2-*c*]pyridinyl). In yet another embodiment, the heteroaryl is tricyclic. Examples of tricyclic heteroaryl groups include, but are not limited to, acridinyl, benzindolyl, carbazolyl, dibenzofuranyl, perimidinyl, phenanthrolinyl, phenanthridinyl (including all isomeric forms, *e.g.*, 1,5-phenanthrolinyl, 1,6-phenanthrolinyl, 1,7-phenanthrolinyl, 1,9-phen-

anthrolinyl, and 2,10-phenanthrolinyl), phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, and xanthenyl. In certain embodiments, the heteroaryl is optionally substituted with one or more substituents Q as described herein.

[0043] The terms “heteroarylene” and “heteroarenediyl” are used interchangeably herein in reference to a divalent monocyclic aromatic group or divalent polycyclic aromatic group that contains at least one aromatic ring, wherein at least one aromatic ring contains one or more heteroatoms in the ring, each of which is independently selected from O, S, and N. For a heteroarylene group containing a heteroaromatic ring and a nonaromatic heterocyclic ring, the heteroarylene group is not bonded to the rest of a molecule *via* its nonaromatic heterocyclic ring. Each ring of a heteroarylene group can contain one or two O atoms, one or two S atoms, and/or one to four N atoms, provided that the total number of heteroatoms in each ring is four or less and each ring contains at least one carbon atom. In certain embodiments, the heteroarylene has from 5 to 20, from 5 to 15, or from 5 to 10 ring atoms. Examples of monocyclic heteroarylene groups include, but are not limited to, furandiyl, imidazoldiyl, isothiazoldiyl, isoxazoldiyl, oxadiazoldiyl, oxazoldiyl, pyrazindiyl, pyrazoldiyl, pyridazindiyl, pyridindiyl, pyrimidindiyl, pyrroldiyl, thiadiazoldiyl, thiazoldiyl, thiendiyl, tetrazoldiyl, triazinediyl, and triazoldiyl. Examples of bicyclic heteroarylene groups include, but are not limited to, benzofurandiyl, benzimidazoldiyl, benzoisoxazoldiyl, benzopyrandiyl, benzothiadiazoldiyl, benzothiazoldiyl, benzothiendiyl, benzotriazoldiyl, benzoxazoldiyl, furopyridindiyl (including all isomeric forms, *e.g.*, furo[2,3-*b*]pyridindiyl, furo[2,3-*c*]pyridindiyl, furo[3,2-*b*]pyridindiyl, furo[3,2-*c*]pyridindiyl, furo[3,4-*b*]pyridindiyl, and furo[3,4-*c*]pyridindiyl), imidazopyridindiyl (including all isomeric forms, *e.g.*, imidazo[1,2-*a*]pyridindiyl, imidazo[4,5-*b*]pyridindiyl, and imidazo[4,5-*c*]pyridindiyl), imidazothiazoldiyl (including all isomeric forms, *e.g.*, imidazo[2,1-*b*]thiazoldiyl and imidazo[4,5-*d*]thiazoldiyl), indazoldiyl, indolizindiyl, indoldiyl, isobenzofurandiyl, isobenzothiendiyl (*i.e.*, benzo[*c*]thiendiyl), isoindoldiyl, isoquinolindiyl, naphthyridindiyl (including all isomeric forms, *e.g.*, 1,5-naphthyridindiyl, 1,6-naphthyridindiyl, 1,7-naphthyridindiyl, and 1,8-naphthyridindiyl), oxazolopyridindiyl (including all isomeric forms, *e.g.*, oxazolo[4,5-*b*]pyridindiyl, oxazolo[4,5-*c*]pyridindiyl, oxazolo[5,4-*b*]pyridindiyl, and oxazolo[5,4-*c*]pyridindiyl), phthalazindiyl, pteridindiyl, purindiyl, pyrrolopyridindiyl (including all isomeric forms, *e.g.*, pyrrolo[2,3-*b*]pyridindiyl, pyrrolo[2,3-*c*]pyridindiyl, pyrrolo[3,2-*b*]pyridindiyl, and pyrrolo[3,2-*c*]pyridindiyl), quinolindiyl, quinoxalindiyl, quinazolindiyl,

thiadiazolopyrimidindiyl (including all isomeric forms, *e.g.*, [1,2,5]thiadiazolo[3,4-*d*]-pyrimidindiyl and [1,2,3]thiadiazolo[4,5-*d*]pyrimidindiyl), and thienopyridindiyl (including all isomeric forms, *e.g.*, thieno[2,3-*b*]pyridindiyl, thieno[2,3-*c*]pyridindiyl, thieno[3,2-*b*]pyridindiyl, and thieno[3,2-*c*]pyridindiyl). Examples of tricyclic heteroarylene groups include, but are not limited to, acridindiyl, benzindoldiyl, carbazoldiyl, dibenzofurandiyl, perimidindiyl, phenanthrolindiyl (including all isomeric forms, *e.g.*, 1,5-phenanthrolindiyl, 1,6-phenanthrolindiyl, 1,7-phenanthrolindiyl, 1,9-phenanthrolindiyl, and 2,10-phenanthrolindiyl), phenanthridindiyl, phenarsazindiyl, phenazindiyl, phenothiazindiyl, phenoxazindiyl, and xanthendiyl. In certain embodiments, heteroarylene is optionally substituted with one or more substituents Q as described herein.

[0044] The term “heterocyclyl” or “heterocyclic” refers to a monovalent monocyclic non-aromatic ring system or monovalent polycyclic ring system that contains at least one non-aromatic ring, wherein one or more of the non-aromatic ring atoms are heteroatoms, each independently selected from O, S, and N; and the remaining ring atoms are carbon atoms. For a heterocyclyl group containing a heteroaromatic ring and a nonaromatic heterocyclic ring, the heterocyclyl group is not bonded to the rest of a molecule through the heteroaromatic ring. In certain embodiments, the heterocyclyl or heterocyclic group has from 3 to 20, from 3 to 15, from 3 to 10, from 3 to 8, from 4 to 7, or from 5 to 6 ring atoms. In certain embodiments, the heterocyclyl is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may be fused or bridged, and in which nitrogen or sulfur atoms may be optionally oxidized, nitrogen atoms may be optionally quaternized, and some rings may be partially or fully saturated, or aromatic. The heterocyclyl may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of heterocyclyls and heterocyclic groups include, but are not limited to, azepinyl, benzodioxanyl, benzodioxolyl, benzofuranonyl, chromanyl, decahydroisoquinolinyl, dihydrobenzofuranyl, dihydrobenzothiazolyl, dihydrobenzoxazinyl (including all isomeric forms, *e.g.*, 1,4-dihydrobenzo[*d*][1,3]oxazinyl, 3,4-dihydrobenzo[*c*][1,2]-oxazinyl, and 3,4-dihydrobenzo[*d*][1,2]oxazinyl), dihydrobenzothienyl, dihydroisobenzofuranyl, dihydrobenzo[*c*]thienyl, dihydrofuryl, dihydroisoindolyl, dihydropyranyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, imidazolidinyl, imidazolynyl, indolynyl, isochromanyl, isoindolynyl, isothiazolidinyl, isoxazolidinyl, morpholynyl, octahydroindolyl,

octahydroisoindolyl, oxazolidinonyl, oxazolidinyl, oxiranyl, piperazinyl, piperidinyl, 4-piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydropyranyl, tetrahydrothienyl, thiamorpholinyl, thiazolidinyl, thiochromanyl, tetrahydroquinolyl, and 1,3,5-trithianyl. In certain embodiments, the heterocyclyl is optionally substituted with one or more substituents Q as described herein.

[0045] The term “heterocyclylene” refers to a divalent monocyclic non-aromatic ring system or divalent polycyclic ring system that contains at least one non-aromatic ring, wherein one or more of the non-aromatic ring atoms are heteroatoms independently selected from O, S, and N; and the remaining ring atoms are carbon atoms. For a heterocyclylene group containing a heteroaromatic ring and a nonaromatic heterocyclic ring, the heterocyclylene group has at least one bond to the rest of a molecule *via* its nonaromatic heterocyclic ring. In certain embodiments, the heterocyclylene group has from 3 to 20, from 3 to 15, from 3 to 10, from 3 to 8, from 4 to 7, or from 5 to 6 ring atoms. In certain embodiments, the heterocyclylene is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may be fused or bridged, and in which nitrogen or sulfur atoms may be optionally oxidized, nitrogen atoms may be optionally quaternized, and some rings may be partially or fully saturated, or aromatic. The heterocyclylene may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclylene groups include, but are not limited to, azepindiyl, benzodioxandiyl, benzodioxoldiyl, benzofuranondiyl, chromandiyl, decahydroisoquinolindiyl, dihydrobenzofurandiyl, dihydrobenzothiazoldiyl, dihydrobenzisoxazindiyl (including all isomeric forms, *e.g.*, 1,4-dihydrobenzo[*d*][1,3]oxazindiyl, 3,4-dihydrobenzo[*c*][1,2]oxazindiyl, and 3,4-dihydrobenzo[*d*][1,2]oxazindiyl), dihydrobenzothiendiyl, dihydroisobenzofurandiyl, dihydrobenzo[*c*]thiendiyl, dihydrofurdyl, dihydroisoindoldiyl, dihydropyrandiyl, dihydropyrazoldiyl, dihydropyrazindiyl, dihydropyridindiyl, dihydropyrimidindiyl, dihydropyrroldiyl, dioxolandiyl, 1,4-dithiandiyl, furanondiyl, imidazolidindiyl, imidazolindiyl, indolindiyl, isochromandiyl, isoindolindiyl, isothiazolidindiyl, isoxazolidindiyl, morpholindiyl, octahydroindoldiyl, octahydroisoindoldiyl, oxazolidinondiyl, oxazolidindiyl, oxirandiyl, piperazindiyl, piperidindiyl, 4-piperidondiyl, pyrazolidindiyl, pyrazolindiyl, pyrrolidindiyl, pyrrolindiyl, quinuclidindiyl, tetrahydrofurdyl, tetrahydroisoquinolindiyl, tetrahydropyrandiyl, tetrahydrothiendiyl, thiamorpholindiyl, thiazolidindiyl, thiochromandiyl, tetrahydroquinolindiyl, and 1,3,5-trithiandiyl. In certain embodiments, the heterocyclylene is optionally substituted with one or

more substituents Q as described herein.

[0046] The term “halogen,” “halide,” or “halo” refers to fluoro, chloro, bromo, and/or iodo.

[0047] The term “optionally substituted” is intended to mean that a group or substituent, such as an alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkenylene, alkynyl, alkynylene, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, aralkylene, heteroaryl, heteroarylene, heterocyclyl, or heterocyclylene group, may be substituted with one or more, in one embodiment, one, two, three, or four, substituents Q, each of which is independently selected from, *e.g.*, (a) deuterium (–D), cyano (–CN), halo, nitro (–NO₂), and oxo (=O); (b) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and (c) –C(O)R^a, –C(O)OR^a, –C(O)NR^bR^c, –C(O)SR^a, –C(NR^a)NR^bR^c, –C(S)R^a, –C(S)OR^a, –C(S)NR^bR^c, –OR^a, –OC(O)R^a, –OC(O)OR^a, –OC(O)NR^bR^c, –OC(O)SR^a, –OC(NR^a)NR^bR^c, –OC(S)R^a, –OC(S)OR^a, –OC(S)NR^bR^c, –OP(O)(OR^b)OR^c, –OS(O)R^a, –OS(O)₂R^a, –OS(O)NR^bR^c, –OS(O)₂NR^bR^c, –NR^bR^c, –NR^aC(O)R^d, –NR^aC(O)OR^d, –NR^aC(O)NR^bR^c, –NR^aC(O)SR^d, –NR^aC(NR^d)NR^bR^c, –NR^aC(S)R^d, –NR^aC(S)OR^d, –NR^aC(S)NR^bR^c, –NR^aS(O)R^d, –NR^aS(O)₂R^d, –NR^aS(O)NR^bR^c, –NR^aS(O)₂NR^bR^c, –SR^a, –S(O)R^a, –S(O)₂R^a, –S(O)₂OR^a, –S(O)NR^bR^c, and –S(O)₂NR^bR^c, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen or deuterium; (ii) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a. As used herein, all groups that can be substituted are “optionally substituted.”

[0048] In one embodiment, each Q^a is independently selected from: (a) deuterium, cyano, halo, nitro, and oxo; (b) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, and heterocyclyl; and (c) –C(O)R^e, –C(O)OR^e, –C(O)NR^fR^g, –C(O)SR^e, –C(NR^e)NR^fR^g, –C(S)R^e, –C(S)OR^e, –C(S)NR^fR^g, –OR^e, –OC(O)R^e, –OC(O)OR^e,

$-\text{OC}(\text{O})\text{NR}^{\text{f}}\text{R}^{\text{g}}, -\text{OC}(\text{O})\text{SR}^{\text{e}}, -\text{OC}(\text{NR}^{\text{e}})\text{NR}^{\text{f}}\text{R}^{\text{g}}, -\text{OC}(\text{S})\text{R}^{\text{e}}, -\text{OC}(\text{S})\text{OR}^{\text{e}}, -\text{OC}(\text{S})\text{NR}^{\text{f}}\text{R}^{\text{g}},$
 $-\text{OP}(\text{O})(\text{OR}^{\text{f}})\text{OR}^{\text{g}}, -\text{OS}(\text{O})\text{R}^{\text{e}}, -\text{OS}(\text{O})_2\text{R}^{\text{e}}, -\text{OS}(\text{O})\text{NR}^{\text{f}}\text{R}^{\text{g}}, -\text{OS}(\text{O})_2\text{NR}^{\text{f}}\text{R}^{\text{g}}, -\text{NR}^{\text{f}}\text{R}^{\text{g}},$
 $-\text{NR}^{\text{e}}\text{C}(\text{O})\text{R}^{\text{h}}, -\text{NR}^{\text{e}}\text{C}(\text{O})\text{OR}^{\text{f}}, -\text{NR}^{\text{e}}\text{C}(\text{O})\text{NR}^{\text{f}}\text{R}^{\text{g}}, -\text{NR}^{\text{e}}\text{C}(\text{O})\text{SR}^{\text{f}}, -\text{NR}^{\text{e}}\text{C}(\text{NR}^{\text{h}})\text{NR}^{\text{f}}\text{R}^{\text{g}},$
 $-\text{NR}^{\text{e}}\text{C}(\text{S})\text{R}^{\text{h}}, -\text{NR}^{\text{e}}\text{C}(\text{S})\text{OR}^{\text{f}}, -\text{NR}^{\text{e}}\text{C}(\text{S})\text{NR}^{\text{f}}\text{R}^{\text{g}}, -\text{NR}^{\text{e}}\text{S}(\text{O})\text{R}^{\text{h}}, -\text{NR}^{\text{e}}\text{S}(\text{O})_2\text{R}^{\text{h}}, -\text{NR}^{\text{e}}\text{S}(\text{O})\text{NR}^{\text{f}}\text{R}^{\text{g}},$
 $-\text{NR}^{\text{e}}\text{S}(\text{O})_2\text{NR}^{\text{f}}\text{R}^{\text{g}}, -\text{SR}^{\text{e}}, -\text{S}(\text{O})\text{R}^{\text{e}}, -\text{S}(\text{O})_2\text{R}^{\text{e}}, -\text{S}(\text{O})_2\text{OR}^{\text{e}}, -\text{S}(\text{O})\text{NR}^{\text{f}}\text{R}^{\text{g}}, \text{ and } -\text{S}(\text{O})_2\text{NR}^{\text{f}}\text{R}^{\text{g}};$
 wherein each $\text{R}^{\text{e}}, \text{R}^{\text{f}}, \text{R}^{\text{g}},$ and R^{h} is independently (i) hydrogen or deuterium; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^{f} and R^{g} together with the N atom to which they are attached form heterocyclyl.

[0049] In certain embodiments, “optically active” and “enantiomerically active” refer to a collection of molecules, which has an enantiomeric excess of no less than about 80%, no less than about 90%, no less than about 91%, no less than about 92%, no less than about 93%, no less than about 94%, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%. In certain embodiments, an optically active compound comprises about 95% or more of one enantiomer and about 5% or less of the other enantiomer based on the total weight of the enantiomeric mixture in question. In certain embodiments, an optically active compound comprises about 98% or more of one enantiomer and about 2% or less of the other enantiomer based on the total weight of the enantiomeric mixture in question. In certain embodiments, an optically active compound comprises about 99% or more of one enantiomer and about 1% or less of the other enantiomer based on the total weight of the enantiomeric mixture in question.

[0050] In describing an optically active compound, the prefixes *R* and *S* are used to denote the absolute configuration of the compound about its chiral center(s). The (+) and (-) are used to denote the optical rotation of the compound, that is, the direction in which a plane of polarized light is rotated by the optically active compound. The (-) prefix indicates that the compound is levorotatory, that is, the compound rotates the plane of polarized light to the left or counterclockwise. The (+) prefix indicates that the compound is dextrorotatory, that is, the compound rotates the plane of polarized light to the right or clockwise. However, the sign of optical rotation, (+) and (-), is not related to the absolute configuration of the compound, *R* and *S*.

[0051] The term “isotopically enriched” refers to a compound that contains an unnatural

proportion of an isotope at one or more of the atoms that constitute such a compound. In certain embodiments, an isotopically enriched compound contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (^1H), deuterium (^2H), tritium (^3H), carbon-11 (^{11}C), carbon-12 (^{12}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), fluorine-18 (^{18}F), phosphorus-31 (^{31}P), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-35 (^{35}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-36 (^{36}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-127 (^{127}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). In certain embodiments, an isotopically enriched compound is in a stable form, that is, non-radioactive. In certain embodiments, an isotopically enriched compound contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (^1H), deuterium (^2H), carbon-12 (^{12}C), carbon-13 (^{13}C), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), phosphorus-31 (^{31}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), and iodine-127 (^{127}I). In certain embodiments, an isotopically enriched compound is in an unstable form, that is, radioactive. In certain embodiments, an isotopically enriched compound contains unnatural proportions of one or more isotopes, including, but not limited to, tritium (^3H), carbon-11 (^{11}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), fluorine-18 (^{18}F), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-35 (^{35}S), chlorine-36 (^{36}Cl), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). It will be understood that, in a compound as provided herein, any hydrogen can be ^2H , as example, or any carbon can be ^{13}C , as example, or any nitrogen can be ^{15}N , as example, or any oxygen can be ^{18}O , as example, where feasible according to the judgment of one of ordinary skill in the art.

[0052] The term “isotopic enrichment” refers to the percentage of incorporation of a less prevalent isotope (*e.g.*, D for deuterium or hydrogen-2) of an element at a given position in a molecule in the place of a more prevalent isotope (*e.g.*, ^1H for protium or hydrogen-1) of the element. As used herein, when an atom at a particular position in a molecule is designated as a particular less prevalent isotope, it is understood that the abundance of that isotope at that position is substantially greater than its natural abundance.

[0053] The term “isotopic enrichment factor” refers to the ratio between the isotopic abundance in an isotopically enriched compound and the natural abundance of a specific isotope.

[0054] The term “hydrogen” or the symbol “H” refers to the composition of naturally occurring hydrogen isotopes, which include protium (^1H), deuterium (^2H or D), and tritium (^3H), in their natural abundances. Protium is the most common hydrogen isotope having a natural abundance of more than 99.98%. Deuterium is a less prevalent hydrogen isotope having a natural abundance of about 0.0156%.

[0055] The term “deuterium enrichment” refers to the percentage of incorporation of deuterium at a given position in a molecule in the place of hydrogen. For example, deuterium enrichment of 1% at a given position means that 1% of molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156% on average, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156% on average. As used herein, when a particular position in an isotopically enriched compound is designated as having deuterium, it is understood that the abundance of deuterium at that position in the compound is substantially greater than its natural abundance (0.0156%).

[0056] The term “carbon” or the symbol “C” refers to the composition of naturally occurring carbon isotopes, which include carbon-12 (^{12}C) and carbon-13 (^{13}C) in their natural abundances. Carbon-12 is the most common carbon isotope having a natural abundance of more than 98.89%. Carbon-13 is a less prevalent carbon isotope having a natural abundance of about 1.11%.

[0057] The term “carbon-13 enrichment” or “ ^{13}C enrichment” refers to the percentage of incorporation of carbon-13 at a given position in a molecule in the place of carbon. For example, carbon-13 enrichment of 10% at a given position means that 10% of molecules in a given sample contain carbon-13 at the specified position. Because the naturally occurring distribution of carbon-13 is about 1.11% on average, carbon-13 enrichment at any position in a compound synthesized using non-enriched starting materials is about 1.11% on average. As used herein, when a particular position in an isotopically enriched compound is designated as having carbon-13, it is understood that the abundance of carbon-13 at that position in the compound is

substantially greater than its natural abundance (1.11%).

[0058] The terms “substantially pure” and “substantially homogeneous” mean, when referred to a substance, sufficiently homogeneous to appear free of readily detectable impurities as determined by a standard analytical method used by one of ordinary skill in the art, including, but not limited to, thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC), gas chromatography (GC), nuclear magnetic resonance (NMR), and mass spectrometry (MS); or sufficiently pure such that further purification would not detectably alter the physical, chemical, biological, and/or pharmacological properties, such as enzymatic and biological activities, of the substance. In certain embodiments, “substantially pure” or “substantially homogeneous” refers to a collection of molecules, wherein at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 99.5% by weight of the molecules are a single compound, including a single enantiomer, a racemic mixture, or a mixture of enantiomers, as determined by standard analytical methods. As used herein, when an atom at a particular position in an isotopically enriched molecule is designated as a particular less prevalent isotope, a molecule that contains other than the designated isotope at the specified position is an impurity with respect to the isotopically enriched compound. Thus, for a deuterated compound that has an atom at a particular position designated as deuterium, a compound that contains a protium at the same position is an impurity.

[0059] The term “solvate” refers to a complex or aggregate formed by one or more molecules of a solute, *e.g.*, a compound provided herein, and one or more molecules of a solvent, which are present in a stoichiometric or non-stoichiometric amount. Suitable solvents include, but are not limited to, water, methanol, ethanol, *n*-propanol, isopropanol, and acetic acid. In certain embodiments, the solvent is pharmaceutically acceptable. In one embodiment, the complex or aggregate is in a crystalline form. In another embodiment, the complex or aggregate is in a noncrystalline form. Where the solvent is water, the solvate is a hydrate. Examples of hydrates include, but are not limited to, a hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate, and pentahydrate.

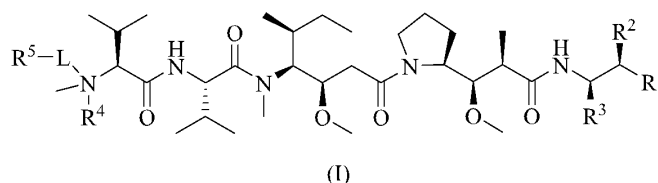
[0060] For a divalent group described herein, no orientation is implied by the direction in which the divalent group is presented. For example, unless a particular orientation is specified,

the formula $-\text{C}(\text{O})\text{NH}-$ represents both $-\text{C}(\text{O})\text{NH}-$ and $-\text{NHC}(\text{O})-$.

[0061] The phrase “an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof” has the same meaning as the phrase “(i) an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant of the compound referenced therein; (ii) a pharmaceutically acceptable salt, solvate, hydrate, or prodrug of the compound referenced therein; or (iii) a pharmaceutically acceptable salt, solvate, hydrate, or prodrug of an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant of the compound referenced therein.”

Compounds

[0062] In one embodiment, provided herein is a compound of Formula (I):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

L is a self-immolative linker;

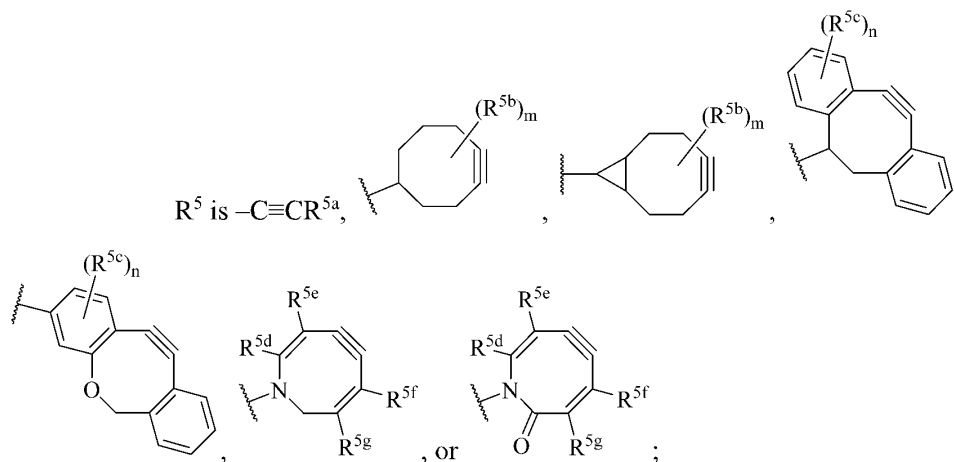
R^1 is C_{6-14} aryl or heteroaryl;

R^2 is hydrogen or $-\text{OR}^{1a}$;

R^3 is (i) hydrogen; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, or heteroaryl; or (iii)

$-\text{C}(\text{O})\text{OR}^{1a}$;

R^4 is (i) absent; or (ii) C_{1-6} alkyl or C_{1-6} heteroalkyl, and the N atom to which R^4 is attached is positively charged;



R^{5a} is hydrogen or deuterium;

each R^{5b} and R^{5c} is independently (i) deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)_2OR^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$;

each pair of R^{5d} and R^{5e} together with the carbon atoms to which they are attached independently forms C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene;

each pair of R^{5f} and R^{5g} together with the carbon atoms to which they are attached independently forms C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene;

each R^{1a} , R^{1b} , R^{1c} , and R^{1d} is independently hydrogen, deuterium, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and

each m and n is independently an integer of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally

substituted with one or more, in one embodiment, one, two, three, or four, substituents Q, wherein each Q is independently selected from: (a) deuterium, cyano, halo, nitro, and oxo; (b) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and (c) -C(O)R^a, -C(O)OR^a, -C(O)NR^bR^c, -C(O)SR^a, -C(NR^a)NR^bR^c, -C(S)R^a, -C(S)OR^a, -C(S)NR^bR^c, -OR^a, -OC(O)R^a, -OC(O)OR^a, -OC(O)NR^bR^c, -OC(O)SR^a, -OC(NR^a)NR^bR^c, -OC(S)R^a, -OC(S)OR^a, -OC(S)NR^bR^c, -OP(O)(OR^b)OR^c, -OS(O)R^a, -OS(O)₂R^a, -OS(O)NR^bR^c, -OS(O)₂NR^bR^c, -NR^bR^c, -NR^aC(O)R^d, -NR^aC(O)OR^d, -NR^aC(O)NR^bR^c, -NR^aC(O)SR^d, -NR^aC(NR^d)NR^bR^c, -NR^aC(S)R^d, -NR^aC(S)OR^d, -NR^aC(S)NR^bR^c, -NR^aS(O)R^d, -NR^aS(O)₂R^d, -NR^aS(O)NR^bR^c, -NR^aS(O)₂NR^bR^c, -SR^a, -S(O)R^a, -S(O)₂R^a, -S(O)₂OR^a, -S(O)NR^bR^c, and -S(O)₂NR^bR^c, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen or deuterium; (ii) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a;

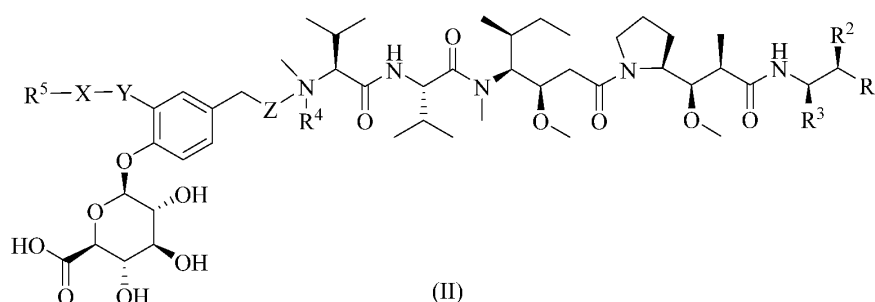
wherein each Q^a is independently selected from: (a) deuterium, cyano, halo, nitro, and oxo; (b) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, and heterocyclyl; and (c) -C(O)R^e, -C(O)OR^e, -C(O)NR^fR^g, -C(O)SR^e, -C(NR^e)NR^fR^g, -C(S)R^e, -C(S)OR^e, -C(S)NR^fR^g, -OR^e, -OC(O)R^e, -OC(O)OR^e, -OC(O)NR^fR^g, -OC(O)SR^e, -OC(NR^e)NR^fR^g, -OC(S)R^e, -OC(S)OR^e, -OC(S)NR^fR^g, -OS(O)R^e, -OS(O)₂R^e, -OS(O)NR^fR^g, -OS(O)₂NR^fR^g, -NR^fR^g, -NR^eC(O)R^h, -NR^eC(O)OR^f, -NR^eC(O)NR^fR^g, -NR^eC(O)SR^f, -NR^eC(NR^h)NR^fR^g, -NR^eC(S)R^h, -NR^eC(S)OR^f, -NR^eC(S)NR^fR^g, -NR^eS(O)R^h, -NR^eS(O)₂R^h, -NR^eS(O)NR^fR^g, -NR^eS(O)₂NR^fR^g, -SR^e, -S(O)R^e, -S(O)₂R^e, -S(O)₂OR^e, -S(O)NR^fR^g, and -S(O)₂NR^fR^g; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen or deuterium; (ii) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl.

[0063] In certain embodiments, in Formula (I), L is a self-immolative linker that is sensitive to an acidic pH. In certain embodiments, in Formula (I), L is a self-immolative linker

comprising a reducible disulfide. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by glutathione. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by an enzyme. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by a protease. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by a lysosomal protease. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by a cathepsin. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by cathepsin B. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by a glycosidase. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by a β -glycosidase. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by a galactosidase. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by a β -galactosidase. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by a glucuronidase. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by a β -glucuronidase. In certain embodiments, in Formula (I), L is a self-immolative linker cleavable by a phosphatase. Exemplary linkers suitable for a compound provided herein include, but are not limited to, those disclosed in Beck *et al.*, *Nat. Rev. Drug Discov.* **2017**, 16, 317-37; Bargh *et al.*, *Chem. Soc. Rev.* **2019**, 48, 4361-74; the disclosure of each of which is incorporated herein by reference in its entirety.

[0064] In certain embodiments, in Formula (I), L is a self-immolative linker comprising sulfo ($-\text{SO}_3\text{H}$).

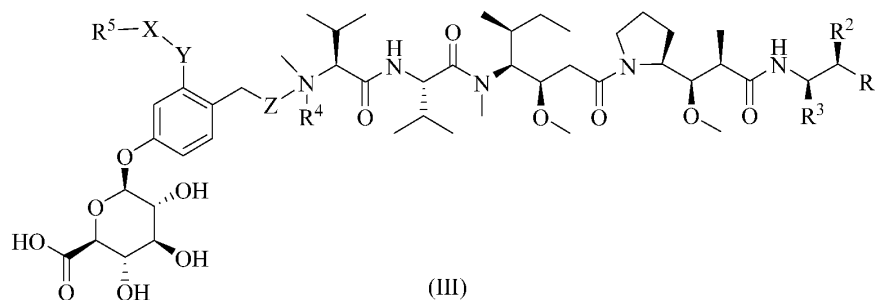
[0065] In another embodiment, provided herein is a compound of Formula (II):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein X is a divalent

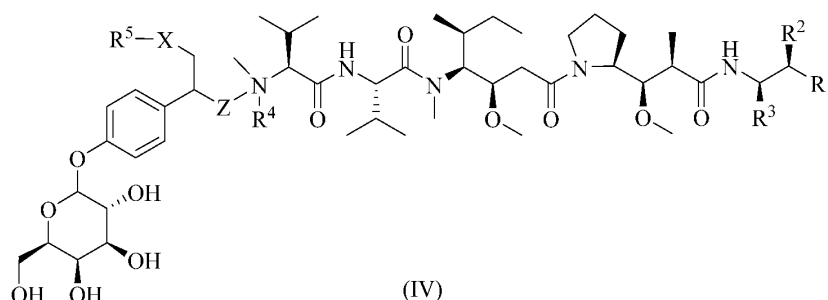
linker; Y is a bond, $-O-$, or $-N(R^{1b})-$; Z is a bond or $-OC(O)-$; and R^1 , R^2 , R^3 , R^4 , R^5 , and R^{1b} are each as defined herein.

[0066] In yet another embodiment, provided herein is a compound of Formula (III):



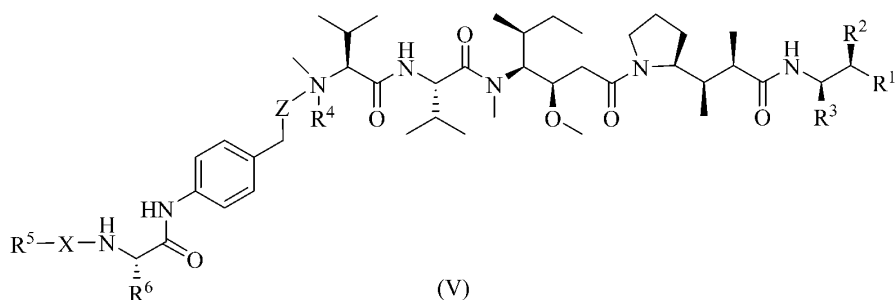
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^5 , X, Y, and Z are each as defined herein.

[0067] In yet another embodiment, provided herein is a compound of Formula (IV):



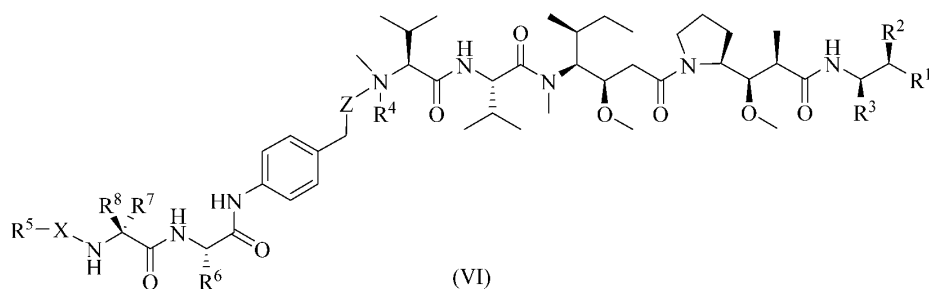
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^5 , X, and Z are each as defined herein.

[0068] In yet another embodiment, provided herein is a compound of Formula (V):



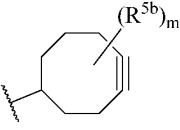
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^6 is (i) hydrogen or deuterium; or (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents Q; and R^1 , R^2 , R^3 , R^4 , R^5 , X, and Z are each as defined herein.

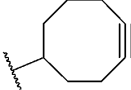
[0069] In still another embodiment, provided herein is a compound of Formula (VI):

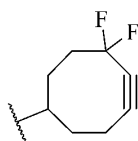


or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^7 and R^8 are each independently (i) hydrogen or deuterium; or (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents Q; or R^7 and R^8 together with the carbon atom to which they are attached form C_{3-10} cycloalkylene or heterocyclylene, each optionally substituted with one or more substituents Q; and R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , X, and Z are each as defined herein.

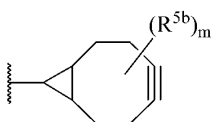
[0070] In certain embodiments, in any one of Formulae (I) to (VI), R^5 is $-C\equiv CR^{5a}$, wherein R^{5a} is as defined herein. In certain embodiments, in any one of Formulae (I) to (VI), R^5

is ethynyl. In certain embodiments, in any one of Formulae (I) to (VI), R^5 is , wherein each R^{5b} and m is as defined herein. In certain embodiments, in any one of Formulae (I)

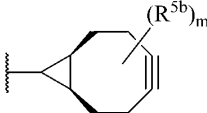
to (VI), R^5 is . In certain embodiments, in any one of Formulae (I) to (VI), R^5 is

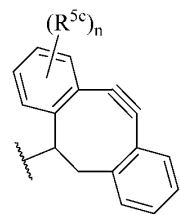


. In certain embodiments, in any one of Formulae (I) to (VI), R^5 is

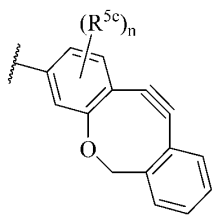


, wherein each R^{5b} and m is as defined herein. In certain embodiments, in any

one of Formulae (I) to (VI), R^5 is , wherein each R^{5b} and m is as defined



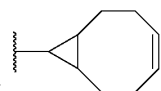
herein. In certain embodiments, in any one of Formulae (I) to (VI), R^5 is wherein each R^{5c} and n is as defined herein. In certain embodiments, in any one of Formulae (I)

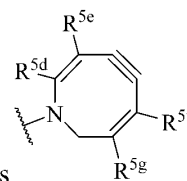


to (VI), R^5 is , wherein each R^{5c} and n is as defined herein.

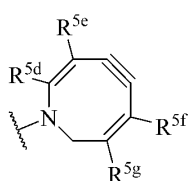
[0071]

In certain embodiments, in a compound provided herein, R^5 is not

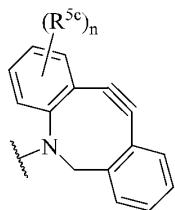




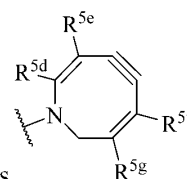
[0072] In certain embodiments, in any one of Formulae (I) to (VI), R^5 is , wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form C_{6-14} arylene, optionally substituted with one or more substituents Q; and R^{5f} and R^{5g} together with the carbon atoms to which they are attached form C_{6-14} arylene, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (VI), R^5 is



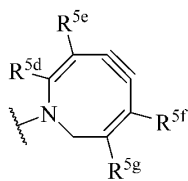
, wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form phenylene, optionally substituted with one or more substituents Q; and R^{5f} and R^{5g} together with the carbon atoms to which they are attached form phenylene, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (VI), R^5 is



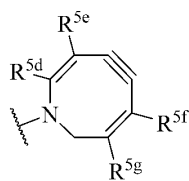
, wherein each R^{5c} and n is as defined herein.



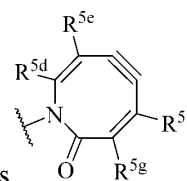
[0073] In certain embodiments, in any one of Formulae (I) to (VI), R^5 is , wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form heteroarylene, optionally substituted with one or more substituents Q; and R^{5f} and R^{5g} together with the carbon atoms to which they are attached form heteroarylene, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (VI), R^5 is



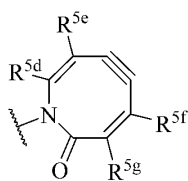
, wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form monocyclic heteroarylene, optionally substituted with one or more substituents Q; and R^{5f} and R^{5g} together with the carbon atoms to which they are attached form monocyclic heteroarylene, optionally substituted with one or more substituents Q. In certain embodiments,



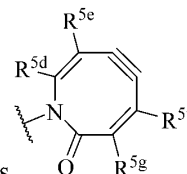
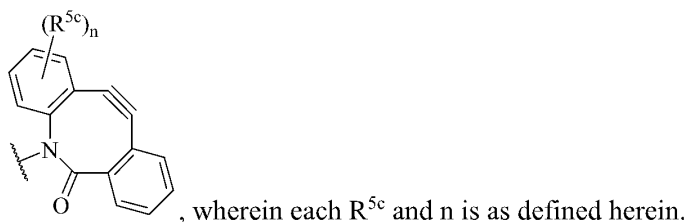
in any one of Formulae (I) to (VI), R⁵ is , wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form 5- or 6-membered heteroarylene, each optionally substituted with one or more substituents Q; and R^{5f} and R^{5g} together with the carbon atoms to which they are attached form 5- or 6-membered heteroarylene, each optionally substituted with one or more substituents Q.

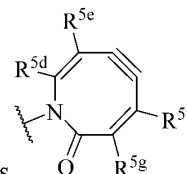


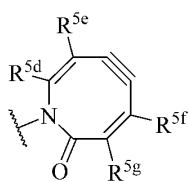
[0074] In certain embodiments, in any one of Formulae (I) to (VI), R⁵ is , wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form C₆₋₁₄ arylene, optionally substituted with one or more substituents Q; and R^{5f} and R^{5g} together with the carbon atoms to which they are attached form C₆₋₁₄ arylene, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (VI), R⁵ is



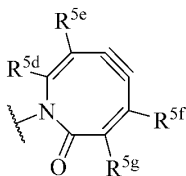
, wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form phenylene, optionally substituted with one or more substituents Q; and R^{5f} and R^{5g} together with the carbon atoms to which they are attached form phenylene, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (VI), R⁵ is

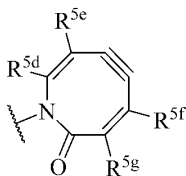


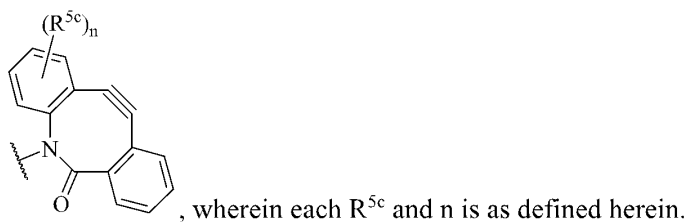
[0075] In certain embodiments, in any one of Formulae (I) to (VI), R^5 is , wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form heteroarylene, optionally substituted with one or more substituents Q ; and R^{5f} and R^{5g} together with the carbon atoms to which they are attached form heteroarylene, optionally substituted with one or more substituents Q . In certain embodiments, in any one of Formulae (I) to (VI), R^5 is



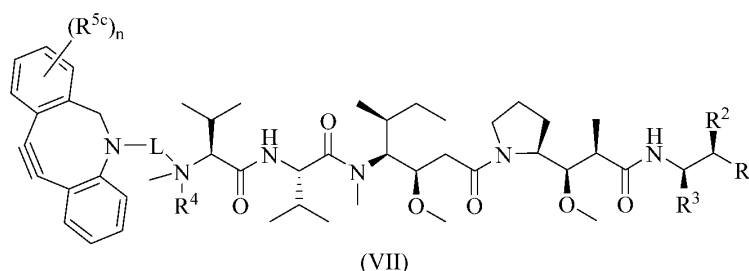
, wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form monocyclic heteroarylene, optionally substituted with one or more substituents Q ; and R^{5f} and R^{5g} together with the carbon atoms to which they are attached form monocyclic heteroarylene, optionally substituted with one or more substituents Q . In certain embodiments,



in any one of Formulae (I) to (VI), R^5 is , wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form 5- or 6-membered heteroarylene, each optionally substituted with one or more substituents Q ; and R^{5f} and R^{5g} together with the carbon atoms to which they are attached form 5- or 6-membered heteroarylene, each optionally substituted with one or more substituents Q . In certain embodiments, in any one of Formulae (I) to (VI), R^5 is



[0076] In one embodiment, provided herein is a compound of Formula (VII):



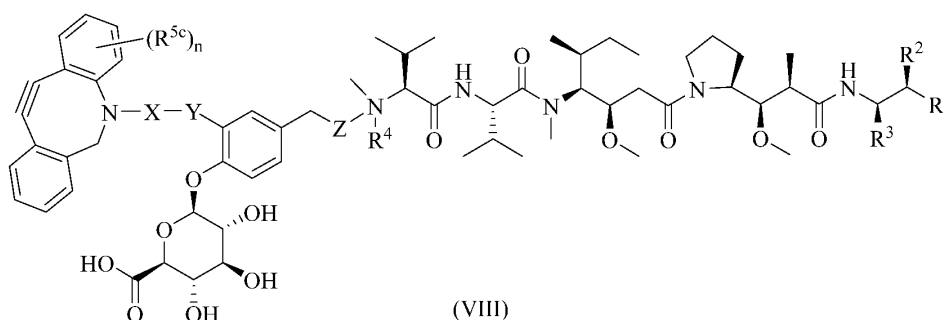
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^{5c} , L , and n are each as defined herein.

[0077] In certain embodiments, in Formula (VII), L is a self-immolative linker that is sensitive to an acidic pH. In certain embodiments, in Formula (VII), L is a self-immolative linker comprising a reducible disulfide. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by glutathione. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by an enzyme. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by a protease. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by a lysosomal protease. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by a cathepsin. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by cathepsin B. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by a glycosidase. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by a β -glycosidase. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by a galactosidase. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by a β -galactosidase. In certain embodiments, in Formula (VII), L is a self-immolative linker

cleavable by a glucuronidase. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by a β -glucuronidase. In certain embodiments, in Formula (VII), L is a self-immolative linker cleavable by a phosphatase. Exemplary linkers suitable for a compound provided herein include, but are not limited to, those disclosed in Beck *et al.*, *Nat. Rev. Drug Discov.* **2017**, *16*, 317-37; Bargh *et al.*, *Chem. Soc. Rev.* **2019**, *48*, 4361-74; the disclosure of each of which is incorporated herein by reference in its entirety.

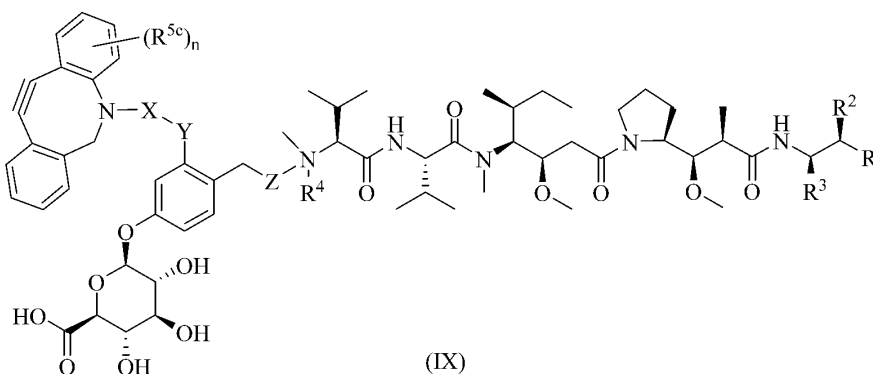
[0078] In certain embodiments, in Formula (VII), L is a self-immolative linker comprising sulfo ($-\text{SO}_3\text{H}$).

[0079] In another embodiment, provided herein is a compound of Formula (VIII):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^{5c} , X, Y, Z, and n are each as defined herein.

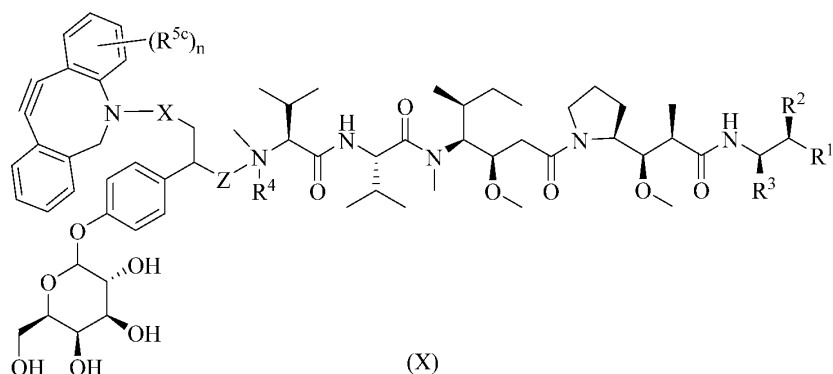
[0080] In yet another embodiment, provided herein is a compound of Formula (IX):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more

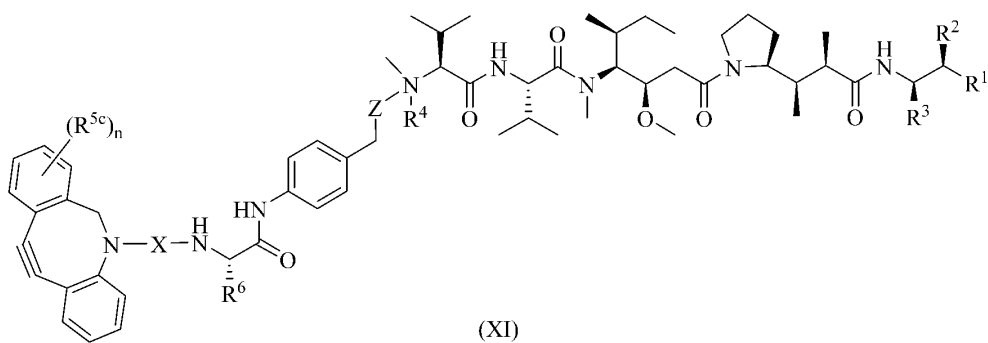
diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^{5c} , X, Y, Z, and n are each as defined herein.

[0081] In yet another embodiment, provided herein is a compound of Formula (X):



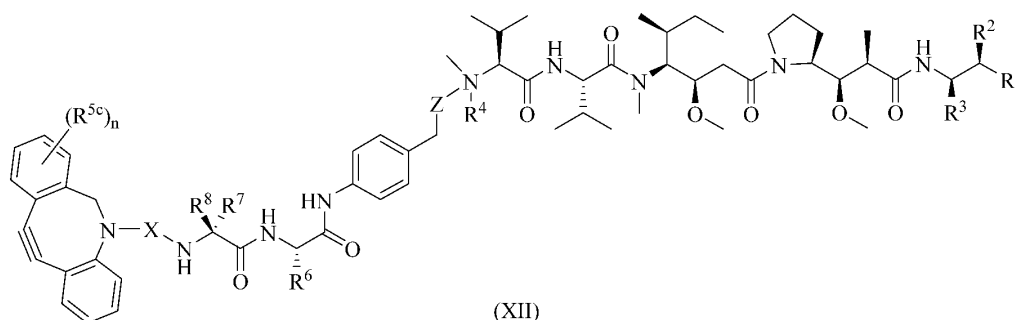
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^{5c} , X, Z, and n are each as defined herein.

[0082] In yet another embodiment, provided herein is a compound of Formula (XI):



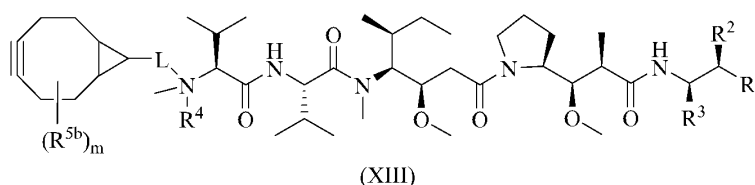
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^{5c} , X, Z, and n are each as defined herein.

[0083] In still another embodiment, provided herein is a compound of Formula (XII):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , R^{5c} , X , Z , and n are each as defined herein.

[0084] In one embodiment, provided herein is a compound of Formula (XIII):



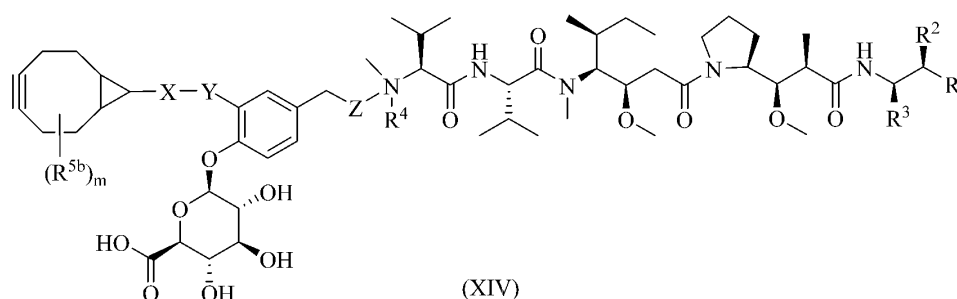
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^{5b} , L , and m are each as defined herein.

[0085] In certain embodiments, in Formula (XIII), L is a self-immolative linker that is sensitive to an acidic pH. In certain embodiments, in Formula (XIII), L is a self-immolative linker comprising a reducible disulfide. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by glutathione. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by an enzyme. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by a protease. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by a lysosomal protease. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by a cathepsin. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by cathepsin B. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by a glycosidase. In certain

embodiments, in Formula (XIII), L is a self-immolative linker cleavable by a β -glycosidase. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by a galactosidase. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by a β -galactosidase. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by a glucuronidase. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by a β -glucuronidase. In certain embodiments, in Formula (XIII), L is a self-immolative linker cleavable by a phosphatase. Exemplary linkers suitable for a compound provided herein include, but are not limited to, those disclosed in Beck *et al.*, *Nat. Rev. Drug Discov.* **2017**, *16*, 317-37; Bargh *et al.*, *Chem. Soc. Rev.* **2019**, *48*, 4361-74; the disclosure of each of which is incorporated herein by reference in its entirety.

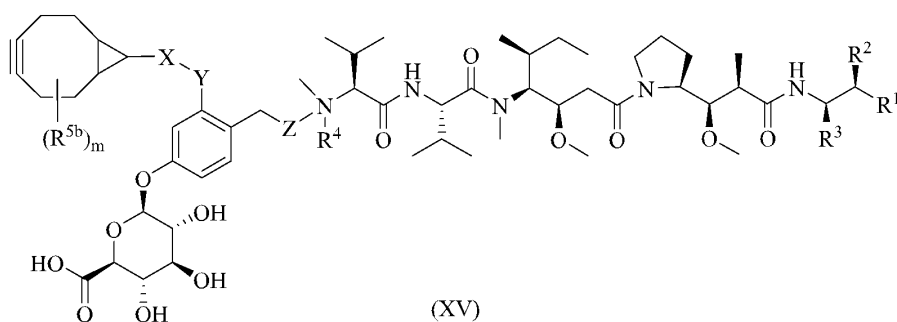
[0086] In certain embodiments, in Formula (XIII), L is a self-immolative linker comprising sulfo ($-\text{SO}_3\text{H}$).

[0087] In another embodiment, provided herein is a compound of Formula (XIV):



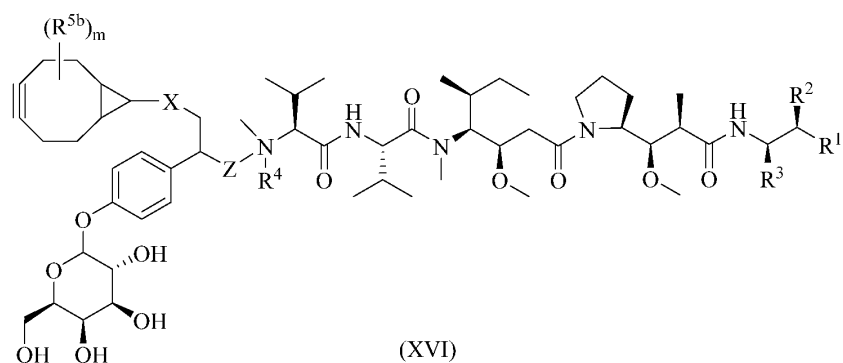
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^{5b} , X, Y, Z, and m are each as defined herein.

[0088] In yet another embodiment, provided herein is a compound of Formula (XV):



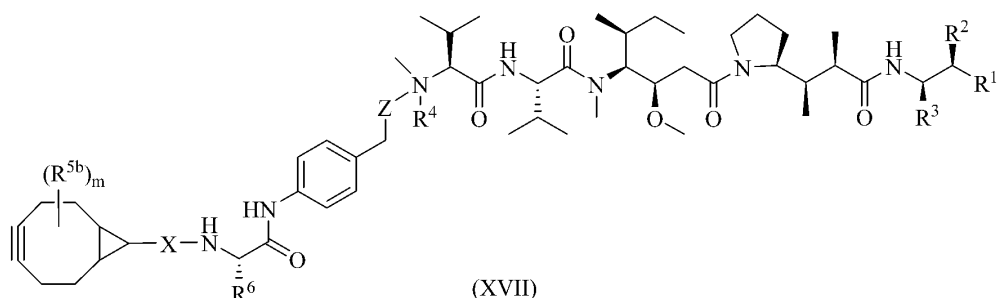
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^{5b} , X , Y , Z , and m are each as defined herein.

[0089] In yet another embodiment, provided herein is a compound of Formula (XVI):



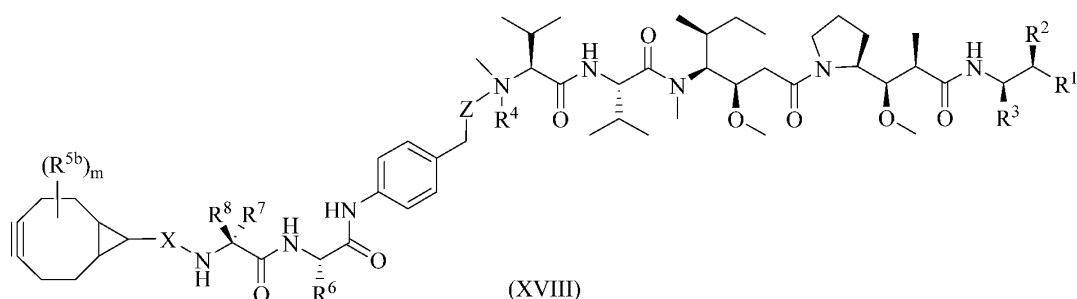
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^{5b} , X , Z , and m are each as defined herein.

[0090] In yet another embodiment, provided herein is a compound of Formula (XVII):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^{5b} , X, Z, and m are each as defined herein.

[0091] In still another embodiment, provided herein is a compound of Formula (XVIII):

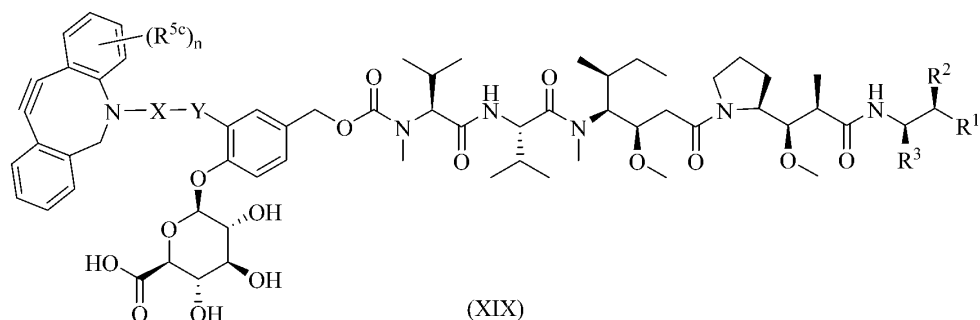


or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , R^{5b} , X, Z, and m are each as defined herein.

[0092] In certain embodiments, in any one of Formulae (I) to (XVIII), R^4 is absent. In certain embodiments, in any one of Formulae (I) to (XVIII), R^4 is C_{1-6} alkyl, optionally substituted with one or more substituents Q; and the N atom to which R^4 is attached is positively charged. In certain embodiments, in any one of Formulae (I) to (XVIII), R^4 is methyl; and the N atom to which R^4 is attached is positively charged.

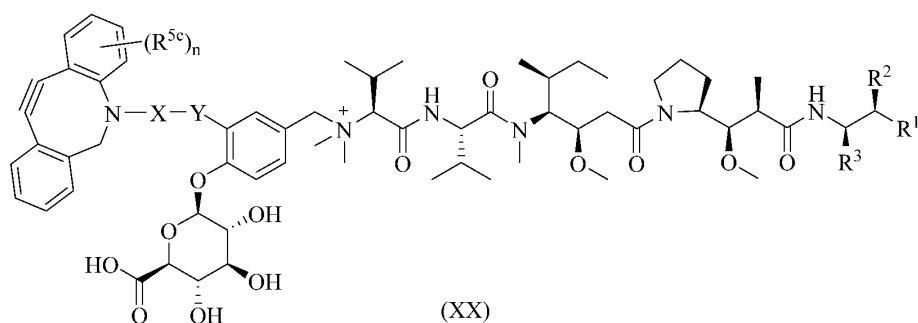
[0093] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XVIII), Z is a bond. In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XVIII), Z is $-OC(O)-$.

[0094] In one embodiment, provided herein is a compound of Formula (XIX):



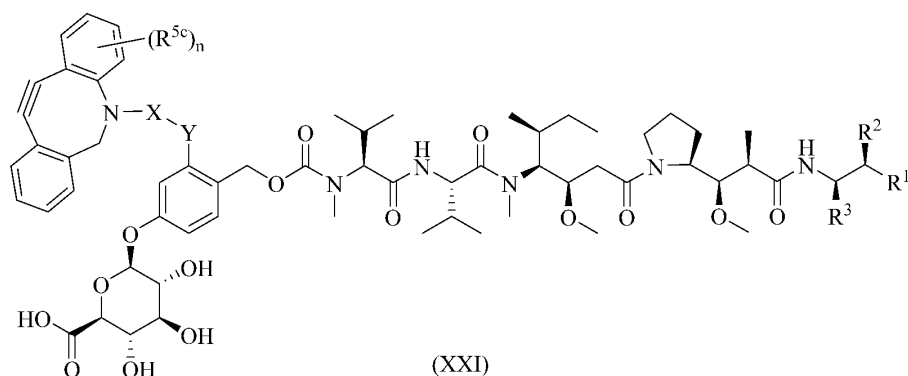
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5c} , X , Y , and n are each as defined herein.

[0095] In another embodiment, provided herein is a compound of Formula (XX):



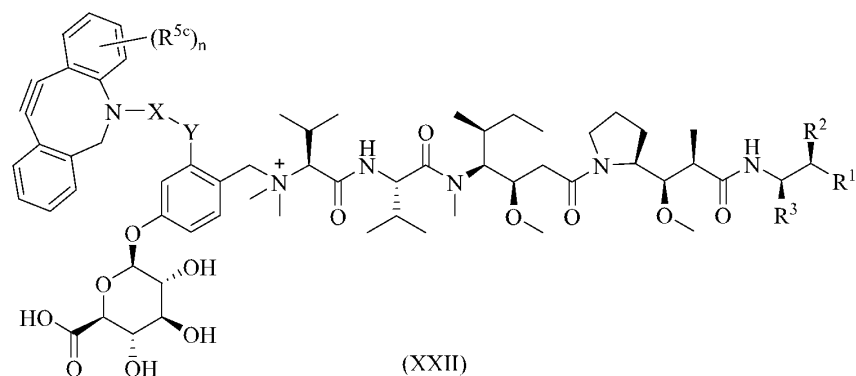
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5c} , X , Y , and n are each as defined herein.

[0096] In yet another embodiment, provided herein is a compound of Formula (XXI):



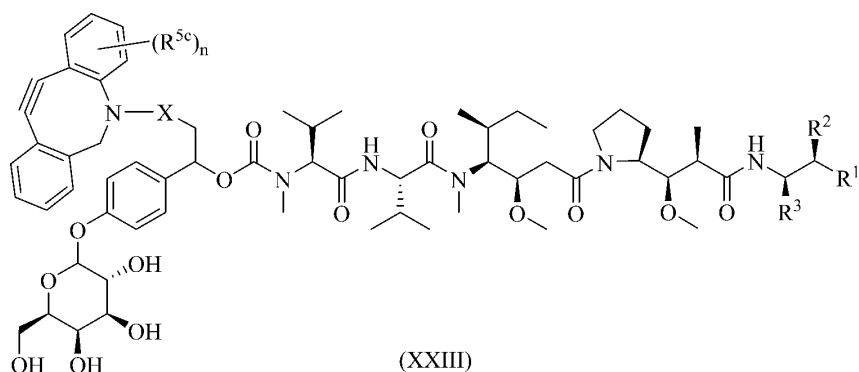
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5c} , X , Y , and n are each as defined herein.

[0097] In yet another embodiment, provided herein is a compound of Formula (XXII):



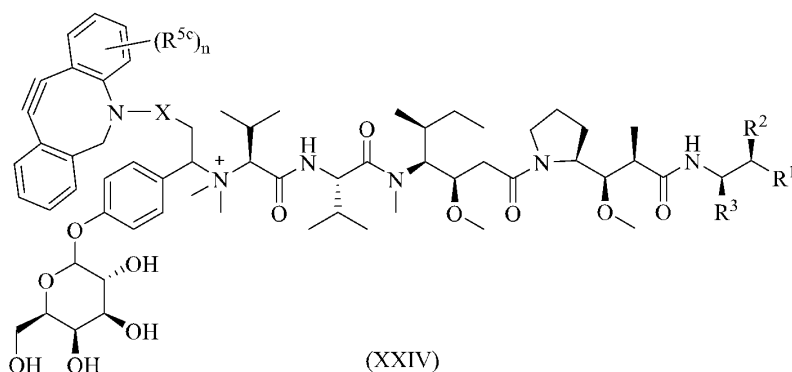
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5c} , X , Y , and n are each as defined herein.

[0098] In yet another embodiment, provided herein is a compound of Formula (XXIII):



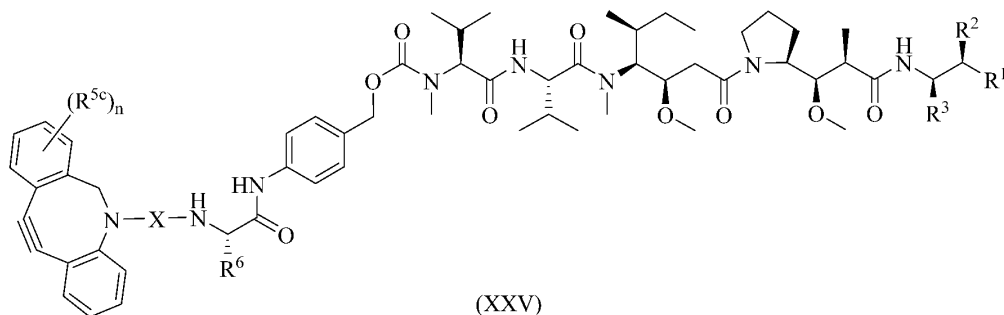
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5c} , X , and n are each as defined herein.

[0099] In yet another embodiment, provided herein is a compound of Formula (XXIV):



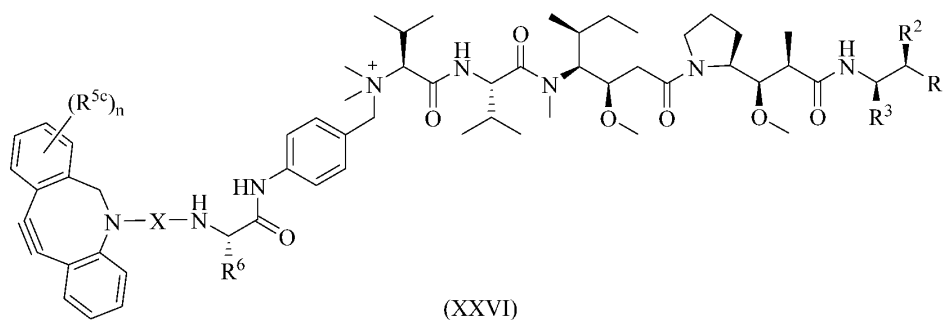
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5c} , X , and n are each as defined herein.

[00100] In yet another embodiment, provided herein is a compound of Formula (XXV):



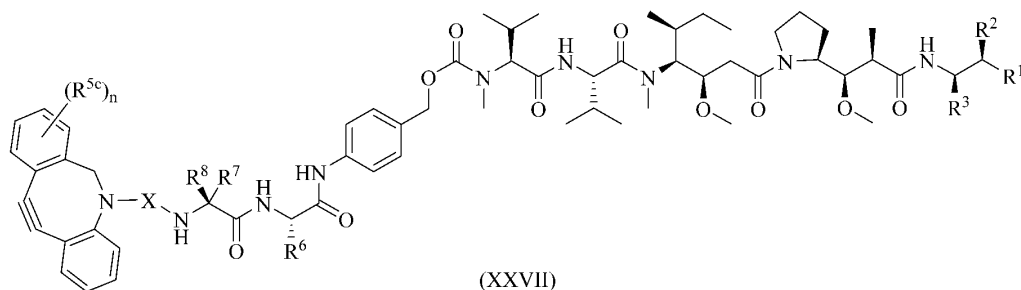
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^6 , R^{5c} , X, and n are each as defined herein.

[00101] In yet another embodiment, provided herein is a compound of Formula (XXVI):



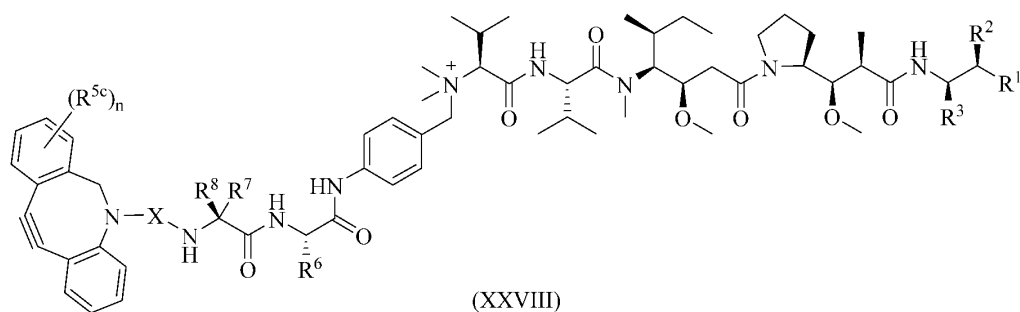
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^6 , R^{5c} , X, and n are each as defined herein.

[00102] In yet another embodiment, provided herein is a compound of Formula (XXVII):



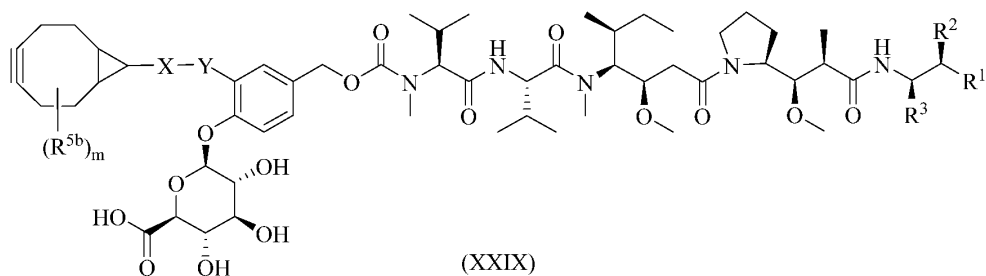
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^6 , R^7 , R^8 , R^{5c} , X, and n are each as defined herein.

[00103] In still another embodiment, provided herein is a compound of Formula (XXVIII):



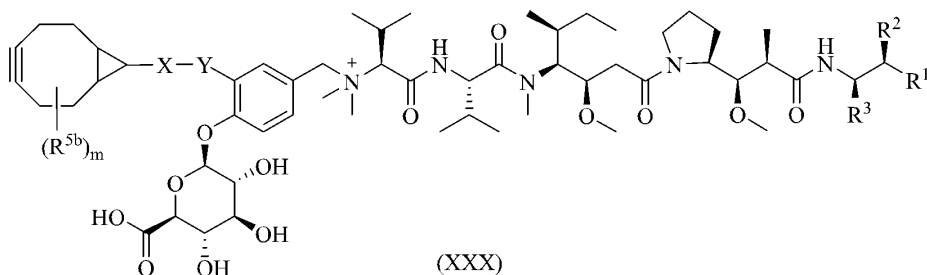
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^6 , R^7 , R^8 , R^{5c} , X, and n are each as defined herein.

[00104] In one embodiment, provided herein is a compound of Formula (XXIX):



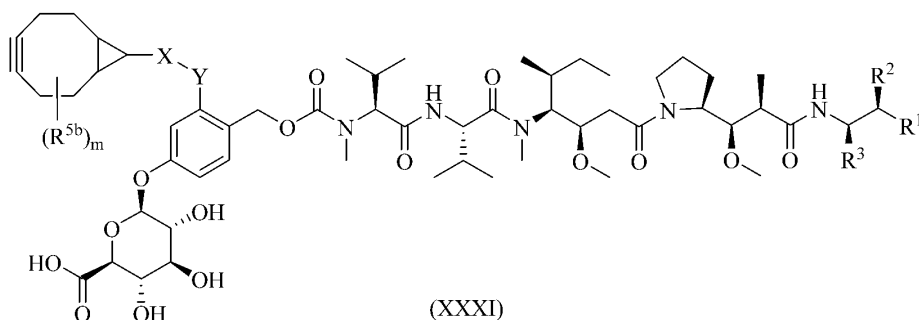
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5b} , X, Y, and m are each as defined herein.

[00105] In another embodiment, provided herein is a compound of Formula (XXX):



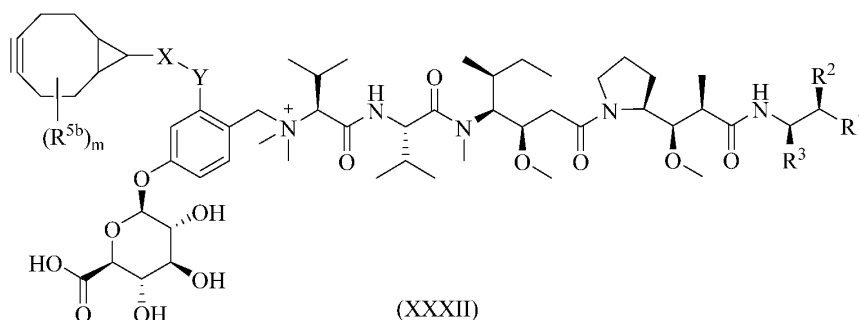
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5b} , X , Y , and m are each as defined herein.

[00106] In yet another embodiment, provided herein is a compound of Formula (XXXI):



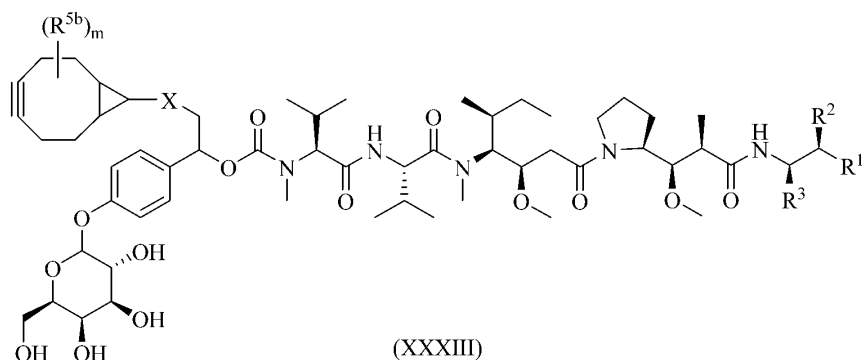
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5b} , X , Y , and m are each as defined herein.

[00107] In yet another embodiment, provided herein is a compound of Formula (XXXII):



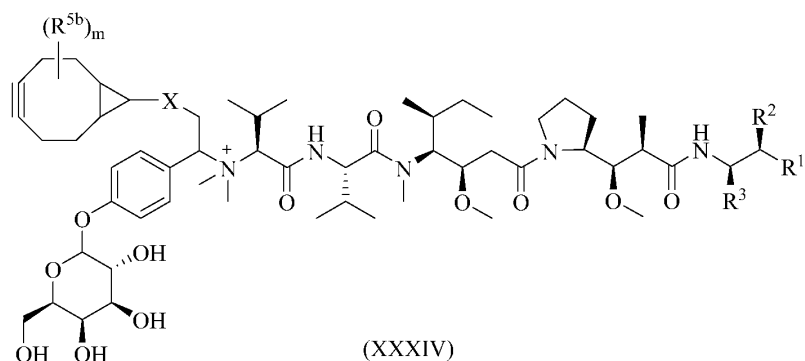
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5b} , X, Y, and m are each as defined herein.

[00108] In yet another embodiment, provided herein is a compound of Formula (XXXIII):



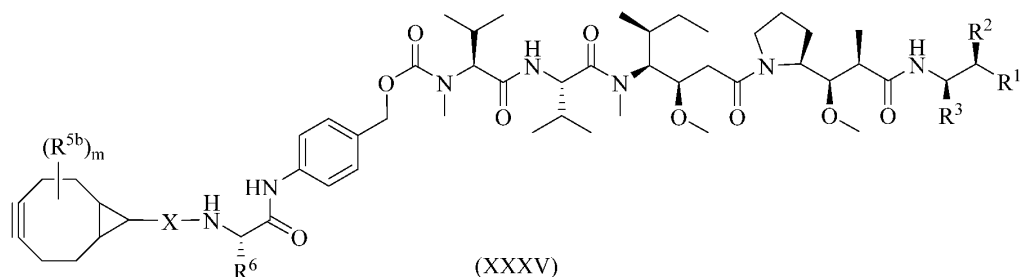
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5b} , X, and m are each as defined herein.

[00109] In yet another embodiment, provided herein is a compound of Formula (XXXIV):



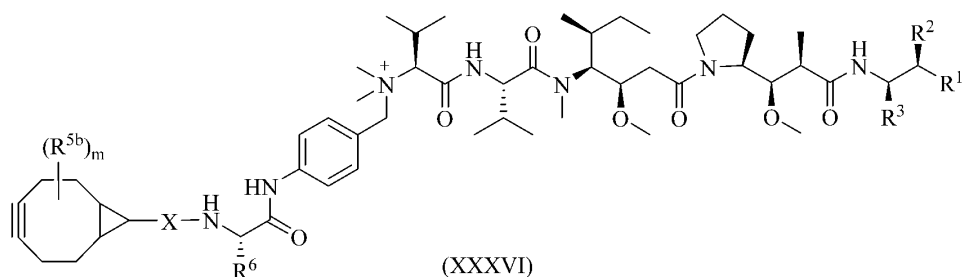
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^{5b} , X, and m are each as defined herein.

[00110] In yet another embodiment, provided herein is a compound of Formula (XXXV):



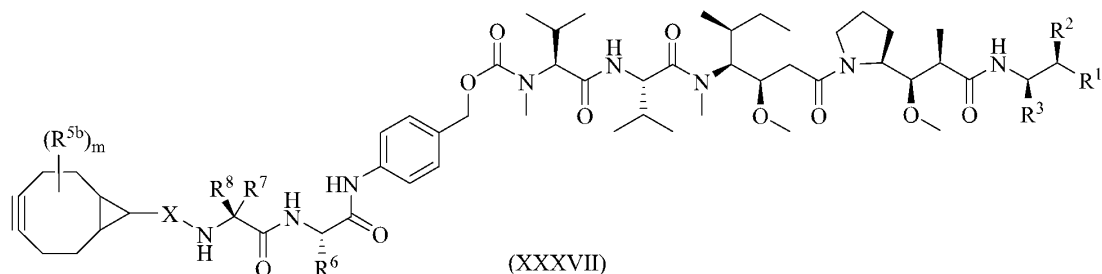
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^6 , R^{5b} , X , and m are each as defined herein.

[00111] In yet another embodiment, provided herein is a compound of Formula (XXXVI):



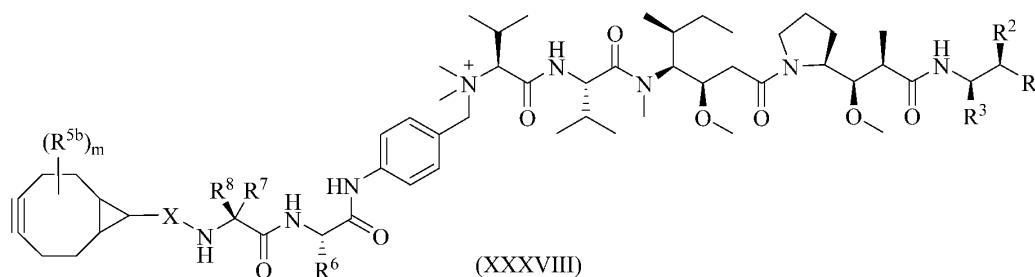
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^6 , R^{5b} , X , and m are each as defined herein.

[00112] In yet another embodiment, provided herein is a compound of Formula (XXXVII):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^6 , R^7 , R^8 , R^{5b} , X, and m are each as defined herein.

[00113] In still another embodiment, provided herein is a compound of Formula (XXXVIII):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^2 , R^3 , R^6 , R^7 , R^8 , R^{5b} , X, and m are each as defined herein.

[00114] In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^1 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^1 is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^1 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^1 is monocyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^1 is 5- or 6-membered heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^1 is 5-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^1 is 6-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^1 is pyridinyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^1 is pyridinyl, optionally substituted with one or more substituents Q.

to (XXXVIII), R^1 is pyridin-2-yl, optionally substituted with one or more substituents Q.

[00115] In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^2 is hydrogen. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^2 is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^2 is hydroxyl.

[00116] In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is hydrogen. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is methyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is monocyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is 5- or 6-membered heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is 5-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is thiazolyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is thiazol-2-yl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is 6-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is carboxy or methoxycarbonyl. In certain embodiments, in any one of Formulae (I) to (XXXVIII), R^3 is carboxy.

[00117] In one embodiment, in any one of Formulae (I) to (XXXVIII), R^1 is phenyl; R^2 is hydroxyl; and R^3 is methyl. In another embodiment, in any one of Formulae (I) to (XXXVIII), R^1 is phenyl; R^2 is hydrogen; and R^3 is carboxy. In yet embodiment, in any one of Formulae (I) to (XXXVIII), R^1 is phenyl; R^2 is hydrogen; and R^3 is thiazol-2-yl.

[00118] In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII),

(XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is (i) hydrogen; or (ii) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, or C₇₋₁₅ aralkyl, each optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is (i) hydrogen; or (ii) C₁₋₆ alkyl or C₇₋₁₅ aralkyl, each optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is (i) hydrogen; or (ii) C₁₋₆ alkyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is hydrogen. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is C₁₋₆ alkyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is C₁₋₆ alkyl, optionally substituted with a substituent selected from the group consisting of (i) C₆₋₁₄ aryl or heteroaryl, each optionally substituted with one or more substituents Q; or (ii) -C(O)OR^{1a}, -C(O)NR^{1b}R^{1c}, -OR^{1a}, -NR^{1b}R^{1c}, -NR^{1a}C(O)NR^{1b}R^{1c}, -NR^{1a}C(NR^{1d})NR^{1b}R^{1c}, or -SR^{1a}; wherein each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is as defined herein. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is C₁₋₆ alkyl, optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, -C(O)OH, -C(O)NH₂, -OH, -NH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -SH, or -SCH₃. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is methyl, ethyl, propyl, or butyl, each optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, -C(O)OH, -C(O)NH₂, -OH, -NH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -SH, or -SCH₃. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is methyl, isopropyl, isobutyl, *sec*-butyl, benzyl, 4-hydroxybenzyl, imidazol-4-ylmethyl, indol-3-ylmethyl, carboxymethyl, 2-carboxyethyl, aminocarbonylmethyl, 2-amino-carbonyl-ethyl, hydroxymethyl, 1-hydroxyethyl, 3-aminopropyl, 4-aminobutyl, 3-ureidopropyl, 3-guanidinyl-propyl, mercaptomethyl, or 2-methylthioethyl. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to

(XXXVIII), R⁶ is 3-aminopropyl, 4-aminobutyl, 3-ureidopropyl, or 3-guanidinyl-propyl. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is 3-aminopropyl. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is 4-aminobutyl. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is 3-ureidopropyl. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is 3-guanidinylpropyl.

[00119] In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is C₇₋₁₅ aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is benzyl, optionally substituted with -OR^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, in any one of Formulae (V), (VI), (XI), (XII), (XVII), (XVIII), (XXV) to (XXVIII), and (XXXV) to (XXXVIII), R⁶ is benzyl or 4-hydroxybenzyl.

[00120] In one embodiment, in any one of Formulae (V), (XI), (XVII), (XXV), and (XXVI), (XXXV), and (XXXVI), R⁶ is 4-aminobutyl.

[00121] In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁷ is (i) hydrogen; or (ii) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, or C₇₋₁₅ aralkyl, each optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁷ is (i) hydrogen; or (ii) C₁₋₆ alkyl or C₇₋₁₅ aralkyl, each optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁷ is (i) hydrogen; or (ii) C₁₋₆ alkyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁷ is hydrogen. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII),

(XXXVII), and (XXXVIII), R^7 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 is C_{1-6} alkyl, optionally substituted with a substituent selected from the group consisting of (i) C_{6-14} aryl or heteroaryl, each optionally substituted with one or more substituents Q; or (ii) $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-OR^{1a}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, or $-SR^{1a}$; wherein each R^{1a} , R^{1b} , R^{1c} , and R^{1d} is as defined herein. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 is C_{1-6} alkyl, optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NH_2$, $-NHC(O)NH_2$, $-NHC(NH)NH_2$, $-SH$, or $-SCH_3$. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 is methyl, ethyl, propyl, or butyl, each optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NH_2$, $-NHC(O)NH_2$, $-NHC(NH)NH_2$, $-SH$, or $-SCH_3$. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 is methyl, isopropyl, isobutyl, *sec*-butyl, benzyl, 4-hydroxybenzyl, imidazol-4-ylmethyl, indol-3-ylmethyl, carboxymethyl, 2-carboxyethyl, aminocarbonylmethyl, 2-amino-carbonylethyl, hydroxymethyl, 1-hydroxyethyl, 3-aminopropyl, 4-aminobutyl, 3-ureidopropyl, 3-guanidinyl-propyl, mercaptomethyl, or 2-methylthioethyl. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 is hydrogen, methyl, isopropyl, or benzyl. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 is methyl. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 is isopropyl. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 is benzyl.

[00122] In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, Formula (V), (XII), or (XIII), R^7 is benzyl, optionally substituted with $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, in

any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁷ is benzyl or 4-hydroxybenzyl.

[00123] In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁸ is (i) hydrogen; or (ii) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, or C₇₋₁₅ aralkyl, each optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁸ is (i) hydrogen; or (ii) C₁₋₆ alkyl or C₇₋₁₅ aralkyl, each optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁸ is (i) hydrogen; or (ii) C₁₋₆ alkyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁸ is hydrogen. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁸ is C₁₋₆ alkyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁸ is C₁₋₆ alkyl, optionally substituted with a substituent selected from the group consisting of (i) C₆₋₁₄ aryl or heteroaryl, each optionally substituted with one or more substituents Q; or (ii) -C(O)OR^{1a}, -C(O)NR^{1b}R^{1c}, -OR^{1a}, -NR^{1b}R^{1c}, -NR^{1a}C(O)NR^{1b}R^{1c}, -NR^{1a}C(NR^{1d})NR^{1b}R^{1c}, or -SR^{1a}; wherein each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is as defined herein. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁸ is C₁₋₆ alkyl, optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, -C(O)OH, -C(O)NH₂, -OH, -NH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -SH, or -SCH₃. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁸ is methyl, ethyl, propyl, or butyl, each optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, -C(O)OH, -C(O)NH₂, -OH, -NH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -SH, or -SCH₃. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁸ is methyl, isopropyl, isobutyl, *sec*-butyl, benzyl, 4-hydroxybenzyl, imidazol-4-ylmethyl, indol-3-yl-methyl, carboxymethyl, 2-carboxyethyl, aminocarbonylmethyl, 2-amino-carbonylethyl, hydroxy-methyl, 1-hydroxyethyl, 3-aminopropyl, 4-aminobutyl, 3-ureidopropyl, 3-guanidinylpropyl, mercaptomethyl, or 2-methylthioethyl. In certain embodiments, in any one

of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^8 is methyl, isopropyl, or benzyl. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^8 is methyl. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^8 is isopropyl. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^8 is benzyl.

[00124] In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^8 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^8 is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, Formula (V), (XII), or (XIII), R^8 is benzyl, optionally substituted with $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^8 is benzyl or 4-hydroxybenzyl.

[00125] In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 and R^8 together with the carbon atom to which they are attached form C_{3-10} cycloalkylene, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 and R^8 together with the carbon atom to which they are attached form monocyclic C_{3-10} cycloalkylene, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 and R^8 together with the carbon atom to which they are attached form cyclopropane-1,1-diyl, cyclobutane-1,1-diyl, cyclopentane-1,1-diyl, or cyclohexane-1,1-diyl, each optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^7 and R^8 together with the carbon atom to which they are attached form cyclobutane-1,1-diyl, optionally substituted with one or more substituents Q.

[00126] In one embodiment, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R^6 is methyl; R^7 is hydrogen; and R^8 is isopropyl. In

another embodiment, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁶ is 3-ureidopropyl; R⁷ is hydrogen; and R⁸ is isopropyl. In yet certain embodiment, in any one of Formulae (VI), (XII), (XVIII), (XXVII), (XXVIII), (XXXVII), and (XXXVIII), R⁶ is 3-ureidopropyl; and R⁷ and R⁸ together with the carbon atom to which they are attached form cyclobutane-1,1-diyl.

[00127] In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5b} is independently halo. In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5b} is independently fluoro, chloro, or bromo. In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5b} is fluoro. In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5b} is chloro. In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5b} is bromo.

[00128] In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5c} is independently halo or nitro. In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5c} is independently halo. In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5c} is independently fluoro, chloro, or bromo. In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5c} is fluoro. In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5c} is chloro. In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5c} is bromo. In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5c} is nitro. In certain embodiments, in any one of Formulae (I) to (XXXVIII), each R^{5c} is independently fluoro, chloro, bromo, or nitro.

[00129] In certain embodiments, in any one of Formulae (I) to (XXXVIII), m is an integer of 0, 1, or 2. In certain embodiments, in any one of Formulae (I) to (XXXVIII), m is an integer of 0. In certain embodiments, in any one of Formulae (I) to (XXXVIII), m is an integer of 1. In certain embodiments, in any one of Formulae (I) to (XXXVIII), m is an integer of 2.

[00130] In certain embodiments, in any one of Formulae (I) to (XXXVIII), n is an integer of 0, 1, or 2. In certain embodiments, in any one of Formulae (I) to (XXXVIII), n is an integer of 0. In certain embodiments, in any one of Formulae (I) to (XXXVIII), n is an integer of 1. In certain embodiments, in any one of Formulae (I) to (XXXVIII), n is an integer of 2.

[00131] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X comprises sulfo ($-\text{SO}_3\text{H}$).

[00132] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is a divalent linker having the structure of $-\text{Z}^n-(\text{R}^n-\text{Z}^n)_z-$, wherein:

each R^n is independently C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene, each of which is optionally substituted with one or more substituents Q;

each Z^n is independently a bond, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{1b}-$, $-\text{C}(\text{O})\text{S}-$, $-\text{C}(\text{NR}^{1a})\text{NR}^{1b}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{S})\text{O}-$, $-\text{C}(\text{S})\text{NR}^{1b}-$, $-\text{O}-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{NR}^{1b}-$, $-\text{OC}(\text{O})\text{S}-$, $-\text{OC}(\text{NR}^{1a})\text{NR}^{1b}-$, $-\text{OC}(\text{S})\text{O}-$, $-\text{OC}(\text{S})\text{NR}^{1b}-$, $-\text{OS}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{OS}(\text{O})\text{NR}^{1b}-$, $-\text{OS}(\text{O})_2\text{NR}^{1b}-$, $-\text{NR}^{1b}-$, $-\text{NR}^{1a}\text{C}(\text{O})\text{NR}^{1b}-$, $-\text{NR}^{1a}\text{C}(\text{O})\text{S}-$, $-\text{NR}^{1a}\text{C}(\text{NR}^{1d})\text{NR}^{1b}-$, $-\text{NR}^{1a}\text{C}(\text{S})\text{NR}^{1b}-$, $-\text{NR}^{1a}\text{S}(\text{O})\text{NR}^{1b}-$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{NR}^{1b}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{1b}-$, or $-\text{S}(\text{O})_2\text{NR}^{1b}-$; wherein each R^{1a} , R^{1b} , and R^{1d} is as defined herein; and

z is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[00133] In certain embodiments, each R^n is independently C_{1-6} alkylene, C_{3-6} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene, each optionally substituted with one or more substituents Q. In certain embodiments, each R^n is independently C_{1-6} alkylene, C_{3-6} cycloalkylene, or heterocyclylene, each optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently C_{1-6} alkylene or heterocyclylene, each optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently C_{1-6} alkylene, optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently methanediyl, ethanediyl, propanediyl, butanediyl, pentanediyl, or hexanediyl, each optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently methanediyl, ethane-1,2-diyl, propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl, or hexane-1,6-diyl, each optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently ethane-1,2-diyl or 1-sulfoethane-1,2-diyl.

[00134] In certain embodiments, R^n is independently heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently monocyclic heterocyclylene, optionally substituted with one or more substituents Q. In certain

embodiments, R^n is independently 3-, 4-, 5-, 6-, or 7-membered heterocyclylene, each optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently 3-membered heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently 4-membered heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently 5-membered heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently 6-membered heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently 7-membered heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently azetidindiyl, piperidindiyl, or piperazindiyl. In certain embodiments, R^n is independently azetidin-1,3-diyl, piperidindiyl, or piperazin-1,4-diyl. In certain embodiments, R^n is independently bicyclic heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently bridged, fused, or spiro heterocyclylene, each optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently bridged heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently fused heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently spiro heterocyclylene, optionally substituted with one or more substituents Q.

[00135] In certain embodiments, R^n is independently methanediyl, ethanediyl, propanediyl, butanediyl, pentanediyl, hexanediyl, ethynediyl, cyclobutanediyl, cyclopentanediyl, cyclohexanediyl, cycloheptanediyl, bicyclo[2.2.2]octanediyl, phenediyl, pyrazoldiyl, imidazoldiyl, tetrazoldiyl, pyrimidindiyl, 5,6,7,8,9,10-hexahydrocyclo-octa[d]pyridazindiyl, azetidindiyl, 1,3-dioxandiyl, pyrrolidindiyl, piperazindiyl, piperidindiyl, or 3,9-diazaspiro[5.5]-undecanediyl, each optionally substituted with one or more substituents Q. In certain embodiments, R^n is independently methanediyl, ethane-1,2-diyl, propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl, hexane-1,6-diyl, ethyne-1,2-diyl, cyclobutane-1,3-diyl, cyclopentane-1,3-diyl, cyclohexane-1,3-diyl, cyclohexane-1,4-diyl, cycloheptane-1,3-diyl, cycloheptane-1,4-diyl, bicyclo[2.2.2]octane-1,4-diyl, phen-1,3-diyl, phen-1,4-diyl, pyrazol-1,3-diyl, pyrazol-1,4-diyl, imidazol-1,4-diyl, 1,2,3-triazol-1,4-diyl, pyrimidin-2,4-diyl, pyrimidin-2,5-diyl, 5,6,7,8,9,10-hexahydrocycloocta[d]-pyridazin-1,7-diyl, pyrazolidin-1,3-diyl, pyrazolidin-1,4-diyl, azetidin-1,3-diyl, 1,3-dioxan-2,5-diyl, pyrrolidin-1,3-diyl, piperazin-1,4-diyl, piperidin-1,3-diyl,

piperidin-1,4-diyl, or 3,9-diazaspiro[5.5]-undecane-3,9-diyl, each optionally substituted with one or more substituents Q.

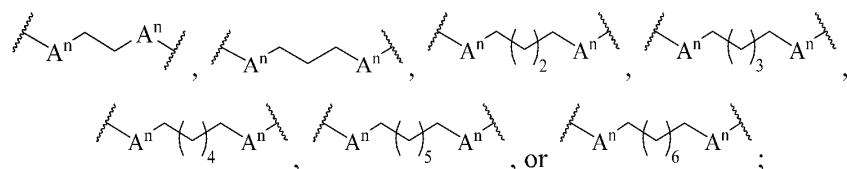
[00136] In certain embodiments, each Z^n is independently a bond, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{1b}-$, $-O-$, $-OC(O)NR^{1b}-$, $-NR^{1b}-$, $-NR^{1a}C(O)NR^{1b}-$, $-NR^{1a}S(O)NR^{1b}-$, $-NR^{1a}S(O)_2NR^{1b}-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{1b}-$, or $-S(O)_2NR^{1b}-$; wherein each R^{1a} and R^{1b} is as defined herein. In certain embodiments, Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NR^{1b}-$, $-OC(O)NR^{1b}-$, or $-O-$; wherein each R^{1b} is as defined herein. In certain embodiments, Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)NH-$, or $-O-$.

[00137] In certain embodiments, z is an integer of 1. In certain embodiments, z is an integer of 2. In certain embodiments, z is an integer of 3. In certain embodiments, z is an integer of 4. In certain embodiments, z is an integer of 5. In certain embodiments, z is an integer of 6. In certain embodiments, z is an integer of 7. In certain embodiments, z is an integer of 8. In certain embodiments, z is an integer of 9. In certain embodiments, z is an integer of 10.

[00138] In certain embodiments, each R^n is independently C_{1-6} alkylene, optionally substituted with one or more substituents Q; each Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NR^{1b}-$, $-OC(O)NR^{1b}-$, or $-O-$, wherein each R^{1b} is as defined herein; and z is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In certain embodiments, each R^n is independently methanediyl, ethanediyl, propanediyl, butanediyl, pentanediyl, or hexanediyl, each optionally substituted with one or more substituents Q; each Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)NH-$, or $-O-$; and z is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In certain embodiments, each R^n is independently methanediyl, ethane-1,2-diyl, propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl, or hexane-1,6-diyl, each optionally substituted with one or more substituents Q; each Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)NH-$, or $-O-$; and z is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In certain embodiments, each R^n is independently methanediyl or ethane-1,2-diyl, each optionally substituted with one or more substituents Q; each Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)NH-$, or $-O-$; and z is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In certain embodiments, each R^n is independently methanediyl, ethane-1,2-diyl, or 1-sulfoethane-1,2-diyl; each Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)NH-$, or $-O-$; and z is an integer of 1, 2, 3, 4, 5, 6, 7, 8,

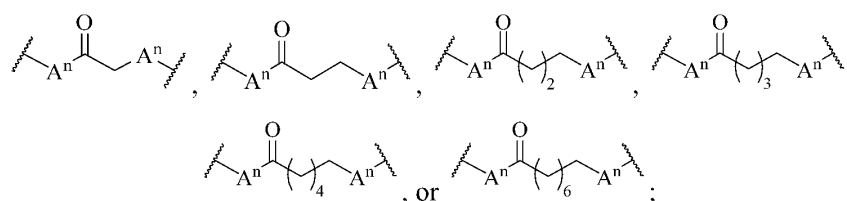
9, or 10.

[00139] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:



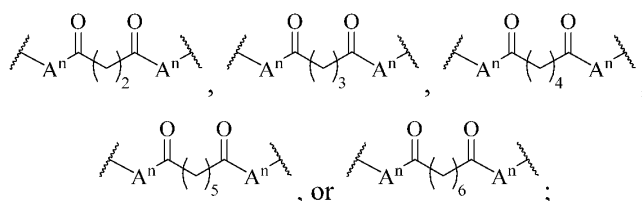
wherein each Aⁿ is independently a bond, -C(O)-, -C(O)O-, or -C(O)NH-; and each methylene (CH₂) group is optionally substituted with sulfo.

[00140] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:



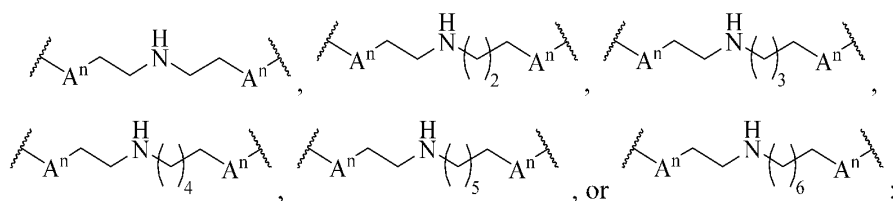
wherein each Aⁿ is independently a bond, -C(O)-, -C(O)O-, or -C(O)NH-; and each methylene (CH₂) group is optionally substituted with sulfo.

[00141] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:



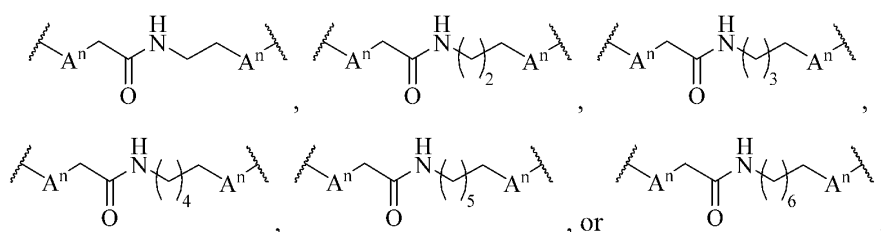
wherein each Aⁿ is independently a bond, -C(O)-, -C(O)O-, or -C(O)NH-; and wherein each methylene (CH₂) group is optionally substituted with sulfo.

[00142] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:



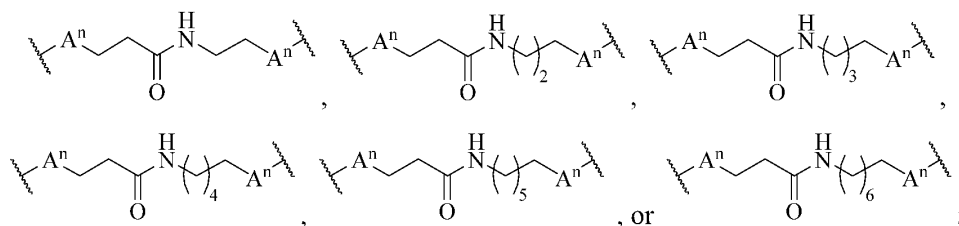
wherein each A^n is independently a bond, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, or $-\text{C}(\text{O})\text{NH}-$; each NH group is optionally substituted with methyl; and each methylene (CH_2) group is optionally substituted with sulfo.

[00143] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:



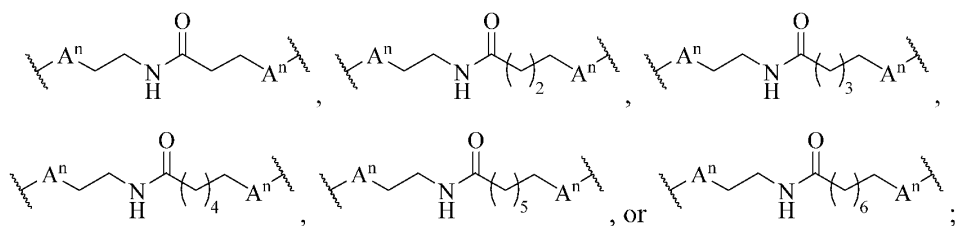
wherein each A^n is independently a bond, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, or $-\text{C}(\text{O})\text{NH}-$; each NH group is optionally substituted with methyl; and each methylene (CH_2) group is optionally substituted with sulfo.

[00144] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:



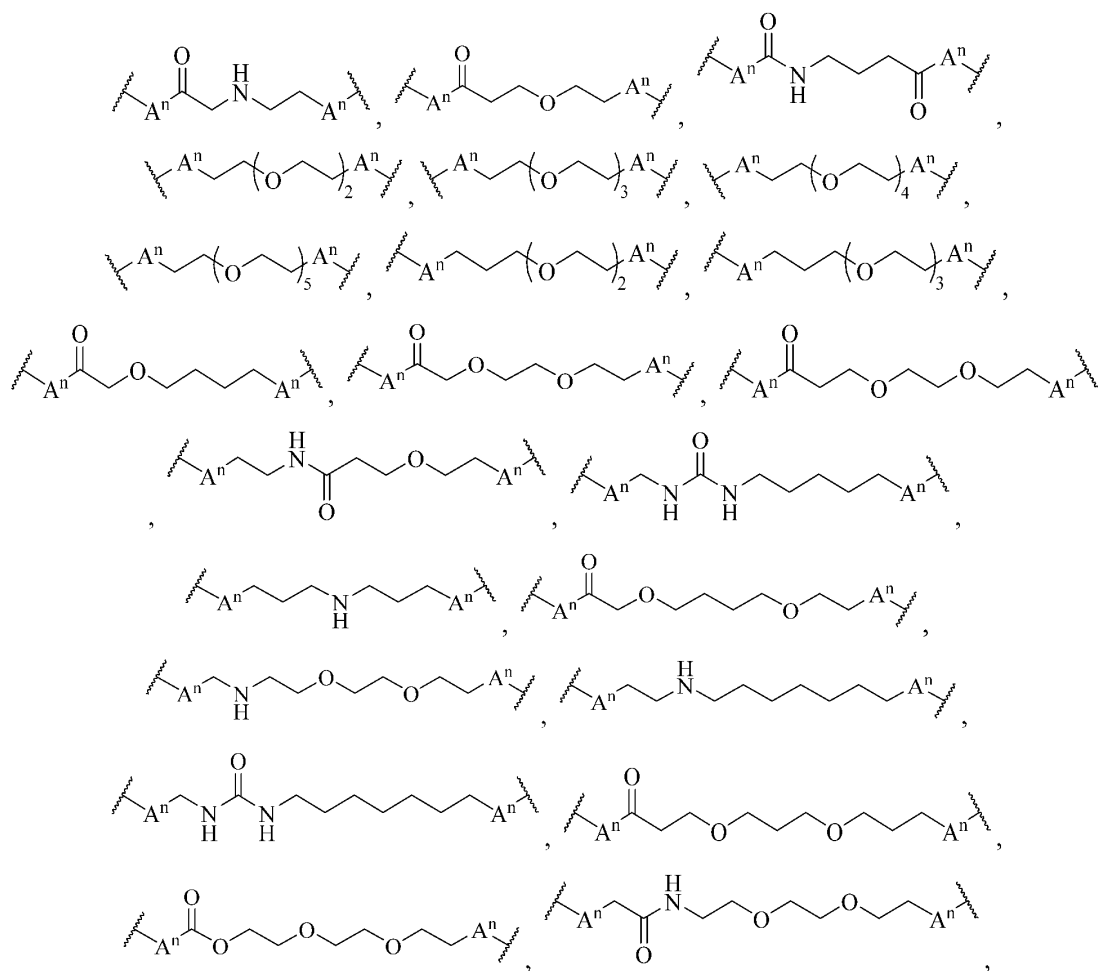
wherein each A^n is independently a bond, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, or $-\text{C}(\text{O})\text{NH}-$; and wherein each NH group is optionally substituted with methyl and each methylene (CH_2) group is optionally substituted with sulfo.

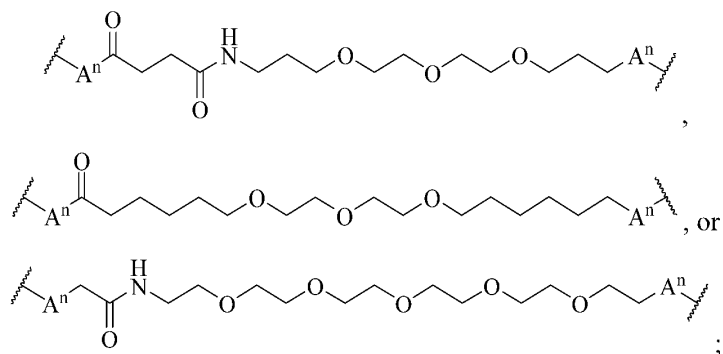
[00145] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:



wherein each A^n is independently a bond, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, or $-\text{C}(\text{O})\text{NH}-$; and wherein each NH group is optionally substituted with methyl and each methylene (CH_2) group is optionally substituted with sulfo.

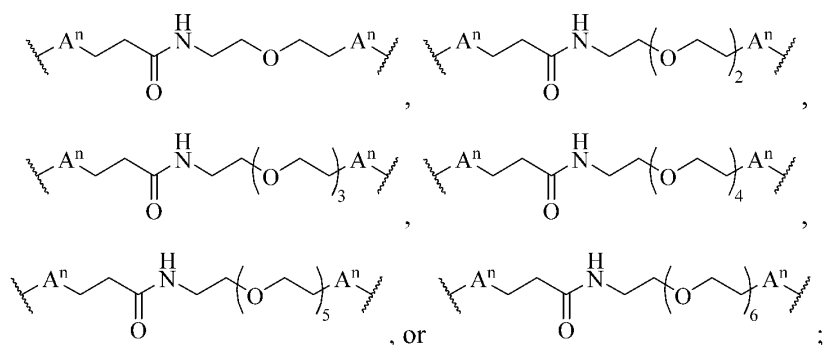
[00146] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:





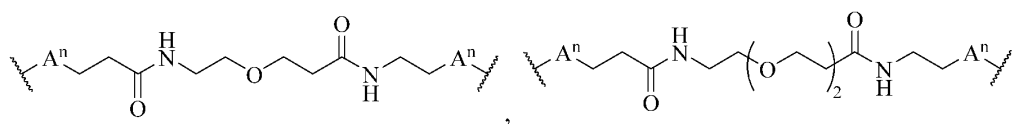
wherein each A^n is independently a bond, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, or $-\text{C}(\text{O})\text{NH}-$; and wherein each NH group is optionally substituted with methyl and each methylene (CH_2) group is optionally substituted with sulfo.

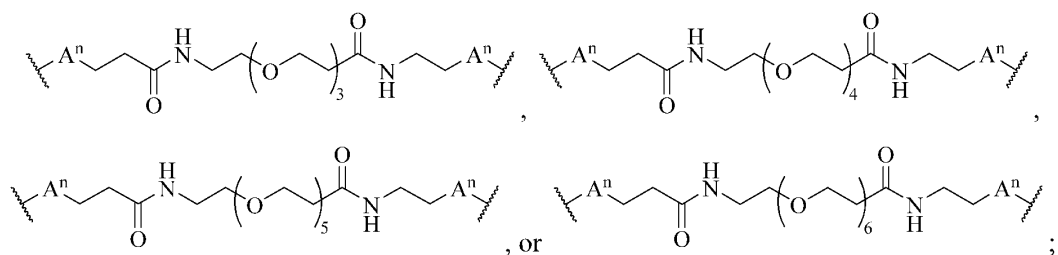
[00147] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:



wherein each A^n is independently a bond, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, or $-\text{C}(\text{O})\text{NH}-$; and wherein each NH group is optionally substituted with methyl and each methylene (CH_2) group is optionally substituted with sulfo.

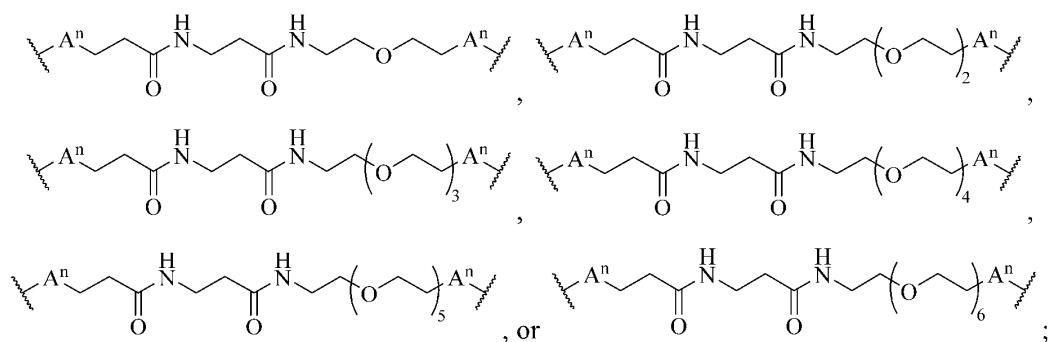
[00148] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:





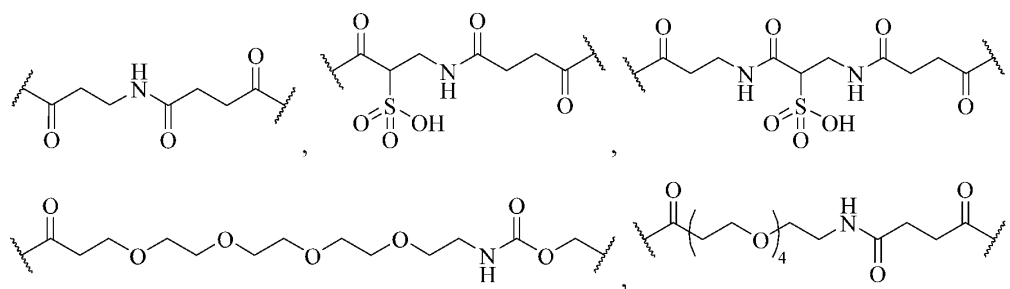
wherein each A^n is independently a bond, $-C(O)-$, $-C(O)O-$, or $-C(O)NH-$; and wherein each NH group is optionally substituted with methyl and each methylene (CH_2) group is optionally substituted with sulfo.

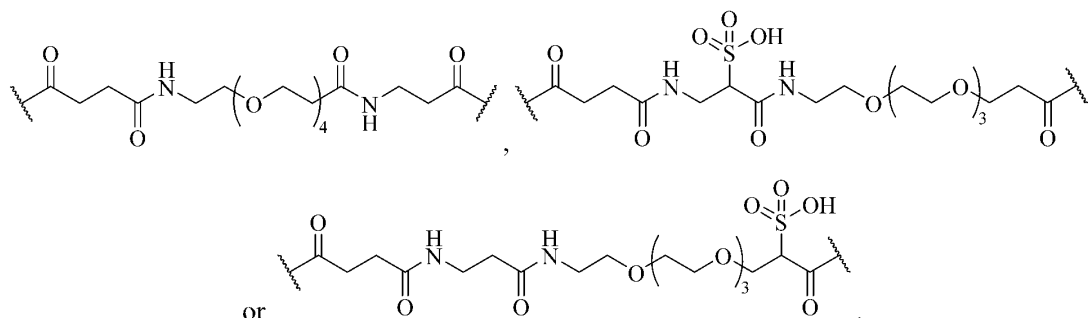
[00149] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:



wherein each A^n is independently a bond, $-C(O)-$, $-C(O)O-$, or $-C(O)NH-$; and wherein each NH group is optionally substituted with methyl and each methylene (CH_2) group is optionally substituted with sulfo.

[00150] In certain embodiments, in any one of Formulae (II) to (VI), (VIII) to (XII), and (XIV) to (XXXVIII), X is:





[00151] In certain embodiments, in any one of Formulae (II), (III), (VIII), (IX), (XIV), (XV), (XIX) to (XXII), and (XXIX) to (XXXII), Y is a bond. In certain embodiments, in any one of Formulae (II), (III), (VIII), (IX), (XIV), (XV), (XIX) to (XXII), and (XXIX) to (XXXII), Y is $-O-$. In certain embodiments, in any one of Formulae (II), (III), (VIII), (IX), (XIV), (XV), (XIX) to (XXII), and (XXIX) to (XXXII), Y is $-N(R^{1b})-$, wherein R^{1b} is as defined herein. In certain embodiments, in any one of Formulae (II), (III), (VIII), (IX), (XIV), (XV), (XIX) to (XXII), and (XXIX) to (XXXII), Y is $-N(H)-$.

[00152] The groups, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{5a} , R^{5b} , R^{5c} , L, X, Y, Z, m, and n, in formulae described herein, including Formulae (I) to (XXXVIII), are further defined in the embodiments described herein. All combinations of the embodiments provided herein for such groups are within the scope of this disclosure.

[00153] In certain embodiments, R^1 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is phenyl or 4-aminophenyl. In certain embodiments, R^1 is bicyclic C_{8-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is monocyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is 5- or 6-membered heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, R^1 is 5-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is imidazolyl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is imidazol-1-yl, imidazol-2-yl, or imidazol-4-yl, each optionally substituted with one or more

substituents Q. In certain embodiments, R¹ is 6-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R¹ is pyridinyl, optionally substituted with one or more substituents Q. In certain embodiments, R¹ is pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each optionally substituted with one or more substituents Q. In certain embodiments, R¹ is bicyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R¹ is 5,5-, 5,6-, or 6,6-fused heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, R¹ is 5,5-fused heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R¹ is 5,6-fused heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R¹ is 6,6-fused heteroaryl, optionally substituted with one or more substituents Q.

[00154] In certain embodiments, R² is hydrogen. In certain embodiments, R² is -OR^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, R² is -OR^{1a}, wherein R^{1a} is hydrogen or C₁₋₆ alkyl optionally substituted with one or more substituents Q. In certain embodiments, R² is hydroxyl. In certain embodiments, R² is C₁₋₆ alkoxy, optionally substituted with one or more substituents Q.

[00155] In certain embodiments, R³ is hydrogen. In certain embodiments, R³ is C₁₋₆ alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R³ is methyl, optionally substituted with one or more substituents Q. In certain embodiments, R³ is C₁₋₆ heteroalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R³ is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R³ is monocyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R³ is 5- or 6-membered heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, R³ is 5-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R³ is thiazolyl, optionally substituted with one or more substituents Q. In certain embodiments, R³ is thiazol-2-yl, thiazol-4-yl, or thiazol-5-yl, each optionally substituted with one or more substituents Q. In certain embodiments, R³ is 6-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R³ is bicyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R³ is 5,5-, 5,6-, or 6,6-fused heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, R³ is 5,5-fused heteroaryl,

optionally substituted with one or more substituents Q. In certain embodiments, R³ is 5,6-fused heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R³ is 6,6-fused heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R³ is -C(O)OR^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, R³ is -C(O)OR^{1a}, wherein R^{1a} is hydrogen or C₁₋₆ alkyl optionally substituted with one or more substituents Q. In certain embodiments, R³ is carboxy. In certain embodiments, R³ is -C(O)OR^{1a}, wherein R^{1a} is C₁₋₆ alkyl optionally substituted with one or more substituents Q. In certain embodiments, R³ is methoxycarbonyl.

[00156] In certain embodiments, R⁴ is absent. In certain embodiments, R⁴ is C₁₋₆ alkyl, optionally substituted with one or more substituents Q; and the N atom to which R⁴ is attached is positively charged. In certain embodiments, R⁴ is methyl, and the N atom to which R⁴ is attached is positively charged. In certain embodiments, R⁴ is C₁₋₆ heteroalkyl, optionally substituted with one or more substituents Q; and the N atom to which R⁴ is attached is positively charged.

[00157] In certain embodiments, R⁵ is as defined herein.

[00158] In certain embodiments, R⁶ is hydrogen. In certain embodiments, R⁶ is deuterium. In certain embodiments, R⁶ is C₁₋₆ alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁶ is C₁₋₆ alkyl, optionally substituted with a substituent selected from the group consisting of (i) C₆₋₁₄ aryl and heteroaryl, each optionally substituted with one or more substituents Q; and (ii) -C(O)OR^{1a}, -C(O)NR^{1b}R^{1c}, -OR^{1a}, -NR^{1b}R^{1c}, -NR^{1a}C(O)NR^{1b}R^{1c}, -NR^{1a}C(NR^{1d})NR^{1b}R^{1c}, and -SR^{1a}; wherein each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is as defined herein. In certain embodiments, R⁶ is C₁₋₆ alkyl, optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, -C(O)OH, -C(O)NH₂, -OH, -NH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -SH, and -SCH₃. In certain embodiments, R⁶ is methyl, ethyl, propyl, or butyl, each optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, -C(O)OH, -C(O)NH₂, -OH, -NH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -SH, and -SCH₃. In certain embodiments, R⁶ is methyl, isopropyl, isobutyl, *sec*-butyl, benzyl, 4-hydroxybenzyl, imidazol-4-ylmethyl, indol-3-ylmethyl, carboxymethyl, 2-carboxyethyl, aminocarbonylmethyl,

2-aminocarbonylethyl, hydroxymethyl, 1-hydroxyethyl, 3-aminopropyl, 4-aminobutyl, 3-ureidopropyl, 3-guanidinylpropyl, mercaptomethyl, or 2-methylthioethyl.

[00159] In certain embodiments, R^6 is C_{1-6} heteroalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is monocyclic C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is bicyclic C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is bridged, fused, or spiro C_{4-10} cycloalkyl, each optionally substituted with one or more substituents Q. In certain embodiments, R^6 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is benzyl, optionally substituted with $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^6 is benzyl or 4-hydroxybenzyl.

[00160] In certain embodiments, R^6 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is monocyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is 5- or 6-membered heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, R^6 is bicyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is 5,5-, 5,6-, or 6,6-fused heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, R^6 is heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is monocyclic heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is 3-, 4-, 5-, 6-, or 7-membered heterocyclyl, each optionally substituted with one or more substituents Q. In certain embodiments, R^6 is bicyclic heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is bridged, fused, or spiro heterocyclyl, each optionally substituted with one or more substituents Q.

[00161] In certain embodiments, R^7 is hydrogen. In certain embodiments, R^7 is deuterium. In certain embodiments, R^7 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is C_{1-6} alkyl, optionally substituted with a substituent selected from the group consisting of (i) C_{6-14} aryl and heteroaryl, each optionally substituted with one or more substituents Q; and (ii) $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-OR^{1a}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, and $-SR^{1a}$; wherein each R^{1a} , R^{1b} , R^{1c} , and R^{1d} is as defined herein. In certain embodiments, R^7 is C_{1-6} alkyl, optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NH_2$, $-NHC(O)NH_2$, $-NHC(NH)NH_2$, $-SH$, and $-SCH_3$. In certain embodiments, R^7 is methyl, ethyl, propyl, or butyl, each optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NH_2$, $-NHC(O)NH_2$, $-NHC(NH)NH_2$, $-SH$, and $-SCH_3$. In certain embodiments, R^7 is methyl, isopropyl, isobutyl, *sec*-butyl, benzyl, 4-hydroxybenzyl, imidazol-4-ylmethyl, indol-3-ylmethyl, carboxymethyl, 2-carboxyethyl, aminocarbonylmethyl, 2-aminocarbonyl ethyl, hydroxymethyl, 1-hydroxyethyl, 3-aminopropyl, 4-aminobutyl, 3-ureido-propyl, 3-guanidinylpropyl, mercaptomethyl, or 2-methylthioethyl.

[00162] In certain embodiments, R^7 is C_{1-6} heteroalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is monocyclic C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is bicyclic C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is bridged, fused, or spiro C_{4-10} cycloalkyl, each optionally substituted with one or more substituents Q. In certain embodiments, R^7 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is benzyl, optionally substituted with $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^7 is benzyl or 4-hydroxybenzyl.

[00163] In certain embodiments, R^7 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is monocyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is 5- or 6-membered heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, R^7 is bicyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is 5,5-, 5,6-, or 6,6-fused heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, R^7 is heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is monocyclic heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is 3-, 4-, 5-, 6-, or 7-membered heterocyclyl, each optionally substituted with one or more substituents Q. In certain embodiments, R^7 is bicyclic heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is bridged, fused, or spiro heterocyclyl, each optionally substituted with one or more substituents Q.

[00164] In certain embodiments, R^8 is hydrogen. In certain embodiments, R^8 is deuterium. In certain embodiments, R^8 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^8 is C_{1-6} alkyl, optionally substituted with a substituent selected from the group consisting of (i) C_{6-14} aryl and heteroaryl, each optionally substituted with one or more substituents Q; and (ii) $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-OR^{1a}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, and $-SR^{1a}$; wherein each R^{1a} , R^{1b} , R^{1c} , and R^{1d} is as defined herein. In certain embodiments, R^8 is C_{1-6} alkyl, optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NH_2$, $-NHC(O)NH_2$, $-NHC(NH)NH_2$, $-SH$, and $-SCH_3$. In certain embodiments, R^8 is methyl, ethyl, propyl, or butyl, each optionally substituted with a substituent selected from the group consisting of phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NH_2$, $-NHC(O)NH_2$, $-NHC(NH)NH_2$, $-SH$, and $-SCH_3$. In certain embodiments, R^8 is methyl, isopropyl, isobutyl, *sec*-butyl, benzyl, 4-hydroxybenzyl, imidazol-4-ylmethyl, indol-3-ylmethyl, carboxymethyl, 2-carboxyethyl, aminocarbonylmethyl, 2-aminocarbonylethyl, hydroxymethyl, 1-hydroxyethyl, 3-aminopropyl, 4-aminobutyl, 3-ureidopropyl, 3-guanidinylpropyl, mercaptomethyl, or 2-methylthioethyl.

[00165] In certain embodiments, R^8 is C_{1-6} heteroalkyl, optionally substituted with one or

more substituents Q. In certain embodiments, R⁸ is C₂₋₆ alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is C₂₋₆ alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is C₃₋₁₀ cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is monocyclic C₃₋₁₀ cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is bicyclic C₃₋₁₀ cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is bridged, fused, or spiro C₄₋₁₀ cycloalkyl, each optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is C₆₋₁₄ aryl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is C₇₋₁₅ aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is benzyl, optionally substituted with -OR^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, R⁸ is benzyl or 4-hydroxybenzyl.

[00166] In certain embodiments, R⁸ is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is monocyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is 5- or 6-membered heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is bicyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is 5,5-, 5,6-, or 6,6-fused heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is monocyclic heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is 3-, 4-, 5-, 6-, or 7-membered heterocyclyl, each optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is bicyclic heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R⁸ is bridged, fused, or spiro heterocyclyl, each optionally substituted with one or more substituents Q.

[00167] In certain embodiments, R⁷ and R⁸ together with the carbon atom to which they are attached form C₃₋₁₀ cycloalkylene or heterocyclylene, each optionally substituted with one or more substituents Q. In certain embodiments, R⁷ and R⁸ together with the carbon atom to which they are attached form C₃₋₁₀ cycloalkylene, optionally substituted with one or more substituents

Q. In certain embodiments, R^7 and R^8 together with the carbon atom to which they are attached form monocyclic C_{3-10} cycloalkylene, optionally substituted with one or more substituents Q. In certain embodiments, R^7 and R^8 together with the carbon atom to which they are attached form cyclopropane-1,1-diyl, cyclobutane-1,1-diyl, cyclopentane-1,1-diyl, or cyclohexane-1,1-diyl, each optionally substituted with one or more substituents Q. In certain embodiments, R^7 and R^8 together with the carbon atom to which they are attached form cyclobutane-1,1-diyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 and R^8 together with the carbon atom to which they are attached form bicyclic C_{3-10} cycloalkylene, optionally substituted with one or more substituents Q. In certain embodiments, R^7 and R^8 together with the carbon atom to which they are attached form bridged, fused, or spiro C_{3-10} cycloalkylene, each optionally substituted with one or more substituents Q. In certain embodiments, R^7 and R^8 together with the carbon atom to which they are attached form heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^7 and R^8 together with the carbon atom to which they are attached form monocyclic heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^7 and R^8 together with the carbon atom to which they are attached form 3-, 4-, 5-, 6-, or 7-membered heterocyclylene, each optionally substituted with one or more substituents Q. In certain embodiments, R^7 and R^8 together with the carbon atom to which they are attached form bicyclic heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, R^7 and R^8 together with the carbon atom to which they are attached form bridged, fused, or spiro heterocyclylene, each optionally substituted with one or more substituents Q.

[00168] In certain embodiments, R^{5a} is hydrogen. In certain embodiments, R^{5a} is deuterium.

[00169] In certain embodiments, each R^{5b} is deuterium. In certain embodiments, each R^{5b} is cyano. In certain embodiments, each R^{5b} is independently halo. In certain embodiments, each R^{5b} is fluoro. In certain embodiments, each R^{5b} is chloro. In certain embodiments, each R^{5b} is bromo. In certain embodiments, each R^{5b} is nitro. In certain embodiments, each R^{5b} is independently C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5b} is methyl. In certain embodiments, each R^{5b} is independently C_{1-6} heteroalkyl, optionally substituted with one or more substituents Q. In certain embodiments,

each R^{5b} is trifluoromethyl. In certain embodiments, each R^{5b} is independently C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5b} is independently C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5b} is independently C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5b} is independently C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5b} is independently C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5b} is independently heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5b} is independently heterocyclyl, optionally substituted with one or more substituents Q.

[00170] In certain embodiments, each R^{5b} is independently $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-C(O)SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a} , R^{1b} , and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-C(S)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-C(S)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-C(S)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-OC(S)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-OC(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a} , R^{1b} , and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-OC(S)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-OC(S)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-OC(S)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain

embodiments, each R^{5b} is independently $-\text{OS}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{OS}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1b}\text{R}^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{C}(\text{O})\text{R}^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{C}(\text{O})\text{OR}^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, wherein R^{1a} , R^{1b} , and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{C}(\text{O})\text{SR}^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{C}(\text{NR}^{1d})\text{NR}^{1b}\text{R}^{1c}$, wherein R^{1a} , R^{1b} , R^{1c} , and R^{1d} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{C}(\text{S})\text{R}^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{C}(\text{S})\text{OR}^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{C}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, wherein R^{1a} , R^{1b} , and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{S}(\text{O})\text{R}^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{S}(\text{O})_2\text{R}^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, wherein R^{1a} , R^{1b} , and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{NR}^{1a}\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, wherein R^{1a} , R^{1b} , and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{SR}^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-\text{S}(\text{O})\text{R}^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-\text{S}(\text{O})_2\text{R}^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-\text{S}(\text{O})_2\text{OR}^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5b} is independently $-\text{S}(\text{O})_2\text{OH}$. In certain embodiments, each R^{5b} is independently $-\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, each R^{5b} is independently $-\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00171] In certain embodiments, each R^{5c} is deuterium. In certain embodiments, each R^{5c} is cyano. In certain embodiments, each R^{5c} is independently halo. In certain embodiments, each R^{5c} is fluoro. In certain embodiments, each R^{5c} is chloro. In certain embodiments, each R^{5c} is bromo. In certain embodiments, each R^{5c} is nitro. In certain embodiments, each R^{5c} is

independently C₁₋₆ alkyl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5c} is methyl. In certain embodiments, each R^{5c} is independently C₁₋₆ heteroalkyl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5c} is trifluoromethyl. In certain embodiments, each R^{5c} is independently C₂₋₆ alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5c} is independently C₂₋₆ alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5c} is independently C₃₋₁₀ cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5c} is independently C₆₋₁₄ aryl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5c} is independently C₇₋₁₅ aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5c} is independently heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, each R^{5c} is independently heterocyclyl, optionally substituted with one or more substituents Q.

[00172] In certain embodiments, each R^{5c} is independently –C(O)R^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5c} is independently –C(O)OR^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5c} is independently –C(O)NR^{1b}R^{1c}, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, each R^{5c} is independently –C(O)SR^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5c} is independently –C(NR^{1a})NR^{1b}R^{1c}, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, each R^{5c} is independently –C(S)R^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5c} is independently –C(S)OR^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5c} is independently –C(S)NR^{1b}R^{1c}, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, each R^{5c} is independently –OR^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5c} is independently –OC(O)R^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5c} is independently –OC(O)OR^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5c} is independently –OC(O)NR^{1b}R^{1c}, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, each R^{5c} is independently –OC(S)R^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5c} is independently –OC(NR^{1a})NR^{1b}R^{1c}, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, each R^{5c} is independently –OC(S)R^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5c} is independently –OC(S)OR^{1a}, wherein R^{1a} is as defined herein. In certain embodiments, each R^{5c}

[illegible]

[00173] In certain embodiments, L is a self-immolative linker as defined herein.

[00174] In certain embodiments, X is a divalent linker as defined herein.

[00175] In certain embodiments, Y is a bond. In certain embodiments, Y is --O-- . In certain embodiments, Y is $\text{--N(R}^{1b}\text{)--}$, wherein R^{1b} is as defined herein. In certain embodiments, Y is --N(H)-- .

[00176] In certain embodiments, Z is a bond. In certain embodiments, Z is --OC(O)-- .

[00177] In certain embodiments, m is an integer of 0. In certain embodiments, m is an integer of 1. In certain embodiments, m is an integer of 2. In certain embodiments, m is an integer of 3. In certain embodiments, m is an integer of 4. In certain embodiments, m is an integer of 5. In certain embodiments, m is an integer of 6. In certain embodiments, m is an integer of 7. In certain embodiments, m is an integer of 8. In certain embodiments, m is an integer of 9. In certain embodiments, m is an integer of 10.

[00178] In certain embodiments, n is an integer of 0. In certain embodiments, n is an integer of 1. In certain embodiments, n is an integer of 2. In certain embodiments, n is an integer of 3. In certain embodiments, n is an integer of 4. In certain embodiments, n is an integer of 5. In certain embodiments, n is an integer of 6. In certain embodiments, n is an integer of 7. In certain embodiments, n is an integer of 8. In certain embodiments, n is an integer of 9. In certain embodiments, n is an integer of 10.

[00179] In one embodiment, provided herein is compound **A1**, **A2**, **A3**, **A4**, **A5**, **A6**, **A7**, **A8**, **A9**, or **A10**; or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00180] In another embodiment, provided herein is compound **B1**, **B2**, **B3**, **B4**, **B5**, or **B6**; or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00181] In yet another embodiment, provided herein is compound **C1**, or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a

mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00182] In certain embodiments, a compound provided herein is isolated or purified. In certain embodiments, a compound provided herein has a purity of at least about 90%, at least about 95%, at least about 98%, at least about 99%, or at least about 99.5% by weight. In certain embodiments, a compound provided herein has a purity of at least about 90% by weight. In certain embodiments, a compound provided herein has a purity of at least about 95% by weight. In certain embodiments, a compound provided herein has a purity of at least about 98% by weight. In certain embodiments, a compound provided herein has a purity of at least about 99% by weight. In certain embodiments, a compound provided herein has a purity of at least about 99.5% by weight.

[00183] The compounds provided herein are intended to encompass all possible stereoisomers unless a particular stereochemistry is specified. Where a compound provided herein contains an alkenyl group, the compound may exist as one or mixture of geometric *cis/trans* (or *Z/E*) isomers. Where structural isomers are interconvertible, the compound may exist as a single tautomer or a mixture of tautomers. This can take the form of proton tautomerism in the compound that contains, for example, an imino, keto, or oxime group; or so-called valence tautomerism in the compound that contains an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

[00184] A compound provided herein can be enantiomerically pure, such as a single enantiomer or a single diastereomer, or be stereoisomeric mixtures, such as a mixture of enantiomers, *e.g.*, a racemic mixture of two enantiomers; or a mixture of two or more diastereomers. As such, one of ordinary skill in the art will recognize that administration of a compound in its (*R*) form is equivalent, for the compound that undergoes epimerization *in vivo*, to administration of the compound in its (*S*) form. Conventional techniques for the preparation/isolation of individual enantiomers include synthesis from a suitable optically pure precursor, asymmetric synthesis from achiral starting materials, or resolution of an enantiomeric mixture, for example, chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

[00185] When a compound provided herein contains an acidic or basic moiety, it can also be provided as a pharmaceutically acceptable salt. See, Berge *et al.*, *J. Pharm. Sci.* **1977**, *66*, 1-19; *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, 2nd ed.; Stahl and Wermuth Eds.; John Wiley & Sons, 2011. In certain embodiments, a pharmaceutically acceptable salt of a compound provided herein is a solvate. In certain embodiments, a pharmaceutically acceptable salt of a compound provided herein is a hydrate.

[00186] Suitable acids for use in the preparation of pharmaceutically acceptable salts of a compound provided herein include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1*S*)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α -oxoglutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-*L*-lactic acid, ($\pm$)-*DL*-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-*L*-malic acid, malonic acid, ($\pm$)-*DL*-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-*L*-tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, undecylenic acid, and valeric acid.

[00187] Suitable bases for use in the preparation of pharmaceutically acceptable salts of a compound provided herein include, but are not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, and sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including, but not limited to, L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethyl-amino)ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, *N*-methyl-glucamine, hydrabamine, 1*H*-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine,

methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, triethanolamine, trimethylamine, triethylamine, *N*-methyl-*D*-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

[00188] A compound provided herein may also be provided as a prodrug, which is a functional derivative of the compound and is readily convertible into the parent compound *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have enhanced solubility in pharmaceutical compositions over the parent compound. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis.

Pharmaceutical Compositions

[00189] In one embodiment, provided herein is a pharmaceutical composition, comprising a compound provided herein, *e.g.*, a compound of Formula (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and a pharmaceutically acceptable excipient.

[00190] The pharmaceutical composition provided herein can be formulated in various dosage forms, including, but not limited to, dosage forms for oral, parenteral, and topical administration. The pharmaceutical composition can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art. *See, e.g., Remington: The Science and Practice of Pharmacy, supra; Modified-Release Drug Delivery Technology*, 2nd ed.; Rathbone *et al.*, Eds.; Drugs and the Pharmaceutical Sciences 184; CRC Press: Boca Raton, FL, 2008.

[00191] In one embodiment, the pharmaceutical composition provided herein is formulated in a dosage form for oral administration. In another embodiment, the pharmaceutical composition provided herein is formulated in a dosage form for parenteral administration. In yet

another embodiment, the pharmaceutical composition provided herein is formulated in a dosage form for intravenous administration. In yet another embodiment, the pharmaceutical composition provided herein is formulated in a dosage form for intramuscular administration. In yet another embodiment, the pharmaceutical composition provided herein is formulated in a dosage form for subcutaneous administration. In still another embodiment, the pharmaceutical composition provided herein is formulated in a dosage form for topical administration.

[00192] The pharmaceutical composition provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) (*e.g.*, a compound provided herein) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical excipient(s). Examples of a unit-dosage form include, but are not limited to, an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in a segregated unit-dosage form. Examples of a multiple-dosage form include, are not limited to, a vial, bottle of tablets or capsules, or bottle of pints or gallons.

[00193] The pharmaceutical composition provided herein can be administered at once or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the subject being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the subject's need and the professional judgment of the person administering or supervising the administration of the pharmaceutical composition.

A. Oral Administration

[00194] The pharmaceutical composition provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage

forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical composition can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

[00195] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (*e.g.*, STARCH 1500®); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, Panwar gum, Ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), VEEGUM®, larch arabinogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); and microcrystalline celluloses, such as AVICEL® PH-101, AVICEL® PH-103, AVICEL® PH-105, and AVICEL® RC-581. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, and pre-gelatinized starch. The amount of a binder or filler in the pharmaceutical composition provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical composition provided herein.

[00196] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets

that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical composition provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[00197] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and VEEGUM® HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrillin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; and algin. The amount of a disintegrant in the pharmaceutical composition provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical composition provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[00198] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, such as peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; and silica or silica gels, such as AEROSIL® 200 and CAB-O-SIL®. The amount of a lubricant in the pharmaceutical composition provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[00199] Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL®, and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes. A color lake is a combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as

peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN[®] 20), polyoxyethylene sorbitan monooleate 80 (TWEEN[®] 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, VEEGUM[®], acacia, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic acid, and sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

[00200] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[00201] The pharmaceutical composition provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredient(s) from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film

coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00202] The tablet dosage forms can be prepared from an active ingredient(s) in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00203] The pharmaceutical composition provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient(s). The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient(s).

[00204] The pharmaceutical composition provided herein for oral administration can be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquid or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically

acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, *e.g.*, acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[00205] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing an active ingredient(s), and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These dosage forms can further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00206] The pharmaceutical composition provided herein for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00207] The pharmaceutical composition provided herein for oral administration can be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00208] Coloring and flavoring agents can be used in all of the dosage forms described herein.

[00209] The pharmaceutical composition provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

[00210] The pharmaceutical composition provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, includes intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[00211] The pharmaceutical composition provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including, but not limited to, solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science. *See, e.g., Remington: The Science and Practice of Pharmacy, supra.*

[00212] The pharmaceutical composition provided herein for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[00213] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringer's injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringer's injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil,

sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (*e.g.*, polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[00214] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl *p*-hydroxybenzoates, thimerosal, benzalkonium chloride (*e.g.*, benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants include those described herein, such as bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents include those described herein, such as sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents include those described herein, such as polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to, EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α -cyclodextrin, β -cyclodextrin, hydroxypropyl- β -cyclodextrin, sulfobutylether- β -cyclodextrin, and sulfobutylether 7- β -cyclodextrin (CAPTISOL[®]).

[00215] When the pharmaceutical composition provided herein is formulated for multiple dosage administration, multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00216] In one embodiment, the pharmaceutical composition for parenteral administration is provided as a ready-to-use sterile solution. In another embodiment, the pharmaceutical composition is provided as a sterile dry soluble product, including a lyophilized powder and hypodermic tablet, to be reconstituted with a vehicle prior to use. In yet another embodiment,

the pharmaceutical composition is provided as a ready-to-use sterile suspension. In yet another embodiment, the pharmaceutical composition is provided as a sterile dry insoluble product to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical composition is provided as a ready-to-use sterile emulsion.

[00217] The pharmaceutical composition provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00218] The pharmaceutical composition provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical composition provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient(s) in the pharmaceutical composition to diffuse through.

[00219] Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers (such as hydrogels of esters of acrylic and methacrylic acid), collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[00220] Suitable outer polymeric membranes include, but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

C. Topical Administration

[00221] The pharmaceutical composition provided herein can be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, includes (intra)dermal, conjunctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, urethral, respiratory, and rectal administration.

[00222] The pharmaceutical composition provided herein can be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including, but not limited to, emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, and dermal patches. The topical formulations of the pharmaceutical composition provided herein can also comprise liposomes, micelles, microspheres, and nanosystems.

[00223] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryoprotectants, lyoprotectants, thickening agents, and inert gases.

[00224] The pharmaceutical composition can also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis, or microneedle or needle-free injection, such as POWDERJECT™ and BIOJECT™.

[00225] The pharmaceutical composition provided herein can be provided in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon vehicles, including lard, benzoinated lard, olive oil, cottonseed oil, and other oils, white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, including polyethylene glycols of varying molecular weight; emulsion vehicles, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid. *See, e.g., Remington: The Science and*

Practice of Pharmacy, supra. These vehicles are emollient but generally require addition of antioxidants and preservatives.

[00226] Suitable cream base can be oil-in-water or water-in-oil. Suitable cream vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the “internal” phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation may be a nonionic, anionic, cationic, or amphoteric surfactant.

[00227] Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include, but are not limited to, crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, and CARBOPOL[®]; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

[00228] The pharmaceutical composition provided herein can be administered rectally, urethrally, vaginally, or perivaginally in the forms of suppositories, pessaries, bougies, poultices or cataplasm, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes as described in *Remington: The Science and Practice of Pharmacy, supra.*

[00229] Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with an active

ingredient(s); and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, and appropriate mixtures of mono-, di- and triglycerides of fatty acids, and hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, and polyacrylic acid. Combinations of the various vehicles can also be used. Rectal and vaginal suppositories may be prepared by compressing or molding. The typical weight of a rectal and vaginal suppository is about 2 to about 3 g.

[00230] The pharmaceutical composition provided herein can be administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

[00231] The pharmaceutical composition provided herein can be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical composition can be provided in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. The pharmaceutical composition can also be provided as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder can comprise a bioadhesive agent, including chitosan or cyclodextrin.

[00232] Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer can be formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of an active ingredient(s); a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00233] The pharmaceutical composition provided herein can be micronized to a size suitable for delivery by inhalation, such as about 50 micrometers or less, or about 10 micrometers or less. Particles of such sizes can be prepared using a comminuting method known to those skilled in the art, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00234] Capsules, blisters, and cartridges for use in an inhaler or insufflator can be formulated to contain a powder mix of the pharmaceutical composition provided herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as *L*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate. Other suitable excipients or carriers include, but are not limited to, dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical composition provided herein for inhaled/intranasal administration can further comprise a suitable flavor, such as menthol and levomenthol; and/or sweeteners, such as saccharin and saccharin sodium.

[00235] The pharmaceutical composition provided herein for topical administration can be formulated to be immediate release or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted, and programmed release.

D. Modified Release

[00236] The pharmaceutical composition provided herein can be formulated as a modified release dosage form. As used herein, the term “modified release” refers to a dosage form in which the rate or place of release of an active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include, but are not limited to, delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical composition in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix-controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphism of the active ingredient(s).

1. Matrix Controlled Release Devices

[00237] The pharmaceutical composition provided herein in a modified release dosage form can be fabricated using a matrix-controlled release device known to those skilled in the art. See, e.g., Takada *et al.* in *Encyclopedia of Controlled Drug Delivery*, Mathiowitz Ed.; Wiley, 1999; Vol. 2.

[00238] In certain embodiments, the pharmaceutical composition provided herein in a modified release dosage form is formulated using an erodible matrix device, which is water-swallowable, erodible, or soluble polymers, including, but not limited to, synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00239] Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum Ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; cellulose, such as ethyl cellulose (EC), methylcellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethyl hydroxyethyl cellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; and other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methyl methacrylate, ethyl methacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chloride.

[00240] In certain embodiments, the pharmaceutical composition provided herein is formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once

administered. Materials suitable for use as a non-erodible matrix device include, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinyl acetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubbers, epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, ethylene/vinyloxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, and silicone carbonate copolymers; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00241] In a matrix-controlled release system, the desired release kinetics can be controlled, for example, *via* the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus the polymer, and other excipients or carriers in the compositions.

[00242] The pharmaceutical composition provided herein in a modified release dosage form can be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, and melt-granulation followed by compression.

2. Osmotic Controlled Release Devices

[00243] The pharmaceutical composition provided herein in a modified release dosage form can be fabricated using an osmotic controlled release device, including, but not limited to, one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) a core which contains an active ingredient; and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00244] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents is water-swellaable hydrophilic polymers, which are also referred to as “osmopolymers” and “hydrogels.” Suitable water-swellaable hydrophilic polymers as osmotic agents include, but are not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarboxiphil, gelatin, xanthan gum, and sodium starch glycolate.

[00245] The other class of osmotic agents is osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00246] Osmotic agents of different dissolution rates can be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as MANNOGEM™ EZ can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

[00247] The core can also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00248] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxylated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00249] Semipermeable membrane can also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00250] The delivery port(s) on the semipermeable membrane can be formed post-coating by mechanical or laser drilling. Delivery port(s) can also be formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation

in the core. In addition, delivery ports can be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00251] The total amount of the active ingredient(s) released and the release rate can substantially be modulated *via* the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00252] The pharmaceutical composition in an osmotic controlled-release dosage form can further comprise additional conventional excipients or carriers as described herein to promote performance or processing of the formulation.

[00253] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art. *See, e.g., Remington: The Science and Practice of Pharmacy, supra*; Santus and Baker, *J. Controlled Release*, **1995**, 35, 1-21; Verma *et al.*, *Drug Dev. Ind. Pharm.*, **2000**, 26, 695-708; Verma *et al.*, *J. Controlled Release*, **2002**, 79, 7-27.

[00254] In certain embodiments, the pharmaceutical composition provided herein is formulated as an AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients or carriers. *See, e.g., U.S. Pat. No. 5,612,059 and WO 2002/17918*. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00255] In certain embodiments, the pharmaceutical composition provided herein is formulated as an ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxyethyl cellulose, and other pharmaceutically acceptable excipients or carriers.

3. Multiparticulate Controlled Release Devices

[00256] The pharmaceutical composition provided herein in a modified release dosage form can be fabricated as a multiparticulate controlled release device, which comprises a

multiplicity of particles, granules, or pellets, ranging from about 10 μm to about 3 mm, about 50 μm to about 2.5 mm, or from about 100 μm to about 1 mm in diameter. Such multiparticulates can be made by the processes known to those skilled in the art, including wet-and dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, and by spray-coating seed cores. See, e.g., *Multiparticulate Oral Drug Delivery*; Ghebre-Sellassie Eds.; Drugs and the Pharmaceutical Sciences 65; CRC Press: 1994; and *Pharmaceutical Palletization Technology*; Ghebre-Sellassie Eds.; Drugs and the Pharmaceutical Sciences 37; CRC Press: 1989.

[00257] Other excipients or carriers as described herein can be blended with the pharmaceutical composition to aid in processing and forming the multiparticulates. The resulting particles can themselves constitute the multiparticulate device or can be coated by various film-forming materials, such as enteric polymers, water-swellaable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

4. Targeted Delivery

[00258] The pharmaceutical composition provided herein can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, those disclosed in U.S. Pat. Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874.

Methods of Use

[00259] In one embodiment, provided herein is a method of treating, treating, preventing, or ameliorating one or more symptoms of a proliferative disease in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound provided herein, e.g., a compound of Formula (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

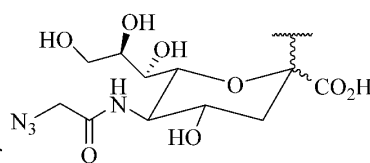
[00260] In certain embodiments, the proliferative disease is cancer. In certain

embodiments, the cancer is refractory and/or relapsed. In certain embodiments, the cancer is refractory. In certain embodiments, the cancer is relapsed. In certain embodiments, the cancer is metastatic. In certain embodiments, the cancer is unresectable. In certain embodiments, the cancer is metastatic.

[00261] In certain embodiments, the cancer is azido-labelled.

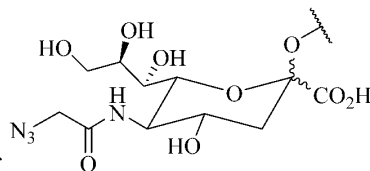
[00262] Thus, in another embodiment, provided herein is a method of treating, treating, preventing, or ameliorating one or more symptoms of azido-labelled cancer in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound provided herein, *e.g.*, a compound of Formula (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00263] In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yl,



which has the structure of . In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yl on a glycoprotein. In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yl on a cell surface glycoprotein.

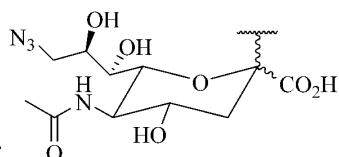
[00264] In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-



yl, which has the structure of . In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-

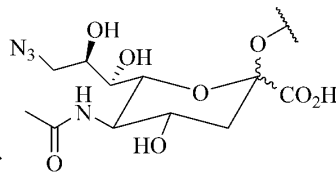
1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy on a glycoprotein. In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy on a cell surface glycoprotein.

[00265] In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-



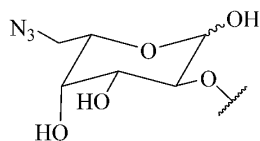
pyran-2-yl, which has the structure of . In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yl on a glycoprotein. In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yl on a cell surface glycoprotein.

[00266] In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-



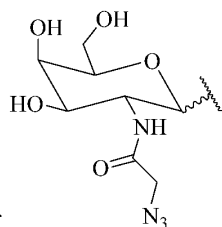
pyran-2-yloxy, which has the structure of . In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy on a glycoprotein. In certain embodiments, the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy on a cell surface glycoprotein.

[00267] In certain embodiments, the cancer is azido-labelled with ((3*S*,4*R*,5*S*,6*S*)-6-(azido-methyl)-2,4,5-trihydroxytetrahydro-2*H*-pyran-3-yl)oxy, which has the structure of



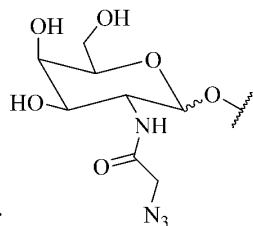
. In certain embodiments, the cancer is azido-labelled with ((3*S*,4*R*,5*S*,6*S*)-6-(azidomethyl)-2,4,5-trihydroxytetrahydro-2*H*-pyran-3-yl)oxy on a glycoprotein. In certain embodiments, the cancer is azido-labelled with ((3*S*,4*R*,5*S*,6*S*)-6-(azidomethyl)-2,4,5-trihydroxytetrahydro-2*H*-pyran-3-yl)oxy on a cell surface glycoprotein.

[00268] In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl, which has the



structure of . In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl on a glycoprotein. In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl on a cell surface glycoprotein.

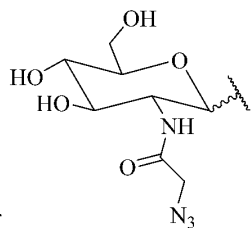
[00269] In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy, which has the

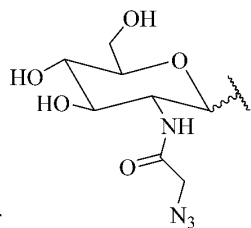


structure of . In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy on a glycoprotein. In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy on a cell surface glycoprotein.

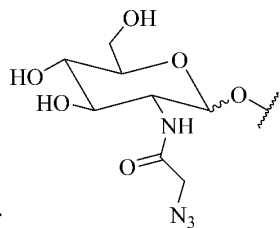
[00270] In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-

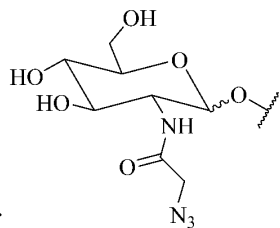
azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl, which has the



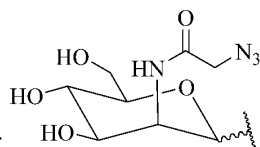
structure of . In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl on a glycoprotein. In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl on a cell surface glycoprotein.

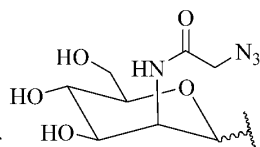
[00271] In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy, which has the



structure of . In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy on a glycoprotein. In certain embodiments, the cancer is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy on a cell surface glycoprotein.

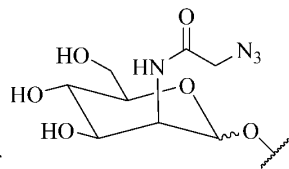
[00272] In certain embodiments, the cancer is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl, which has the



structure of . In certain embodiments, the cancer is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl on a glycoprotein. In certain embodiments, the cancer is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl on a cell surface

glycoprotein.

[00273] In certain embodiments, the cancer is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy, which has the



structure of . In certain embodiments, the cancer is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy on a glycoprotein. In certain embodiments, the cancer is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy on a cell surface glycoprotein.

[00274] In certain embodiments, the cancer is azido-labelled by administering an effective amount of an azido compound to the subject in need thereof; wherein the azido compound is *N*-azidoacetylmannosamine, *N*-azidoacetyl neuraminic acid, *N*-acetyl-9-azido-9-deoxy neuraminic acid, *N*-azidoacetylgalactosamine, *N*-azido-acetylglucosamine, or 6-azidofucose, or a derivative thereof. *See, e.g.*, Laughlin and Bertozzi, *Nat. Protoc.* **2007**, 2, 2930-44; Wang *et al.*, *Nat. Chem. Biol.* **2017**, 13, 415-424; Wang and Mooney, *Nat. Chem.* **2020**, 12, 1102-14; and US 11,014,953; the disclosure of each of which is incorporated herein by reference in its entirety. In certain embodiments, the azido compound is tetraacetyl-*N*-azido-acetylmannosamine, tetraacetyl-*N*-azidoacetyl neuraminic acid, 2,4,7,8-tetra-*O*-acetyl-*N*-acetyl-9-azido-9-deoxy neuraminic acid, tetraacetyl-*N*-azidoacetyl-galactosamine, tetraacetyl-*N*-azidoacetyl-glucosamine, or tetraacetyl-6-azidofucose.

[00275] In certain embodiments, the cancer is azido-labelled by administering an effective amount of tetraacetyl-*N*-azidoacetylmannosamine to the subject in need thereof. In certain embodiments, the cancer is azido-labelled by administering an effective amount of tetraacetyl-*N*-azidoacetyl neuraminic acid to the subject in need thereof. In certain embodiments, the cancer is azido-labelled by administering an effective amount of 2,4,7,8-tetra-*O*-acetyl-*N*-acetyl-9-azido-9-deoxy neuraminic acid to the subject in need thereof. In certain embodiments, the cancer is azido-labelled by administering an effective amount of tetraacetyl-*N*-azidoacetylgalactosamine to

the subject in need thereof. In certain embodiments, the cancer is azido-labelled by administering an effective amount of tetraacetyl-*N*-azidoacetylglucosamine to the subject in need thereof. In certain embodiments, the cancer is azido-labelled by administering an effective amount of tetraacetyl-6-azidofucose to the subject in need thereof.

[00276] In certain embodiments, the cancer is azido-labelled by administering intratumorally an effective amount of an azido compound described herein to the subject in need thereof. In certain embodiments, the cancer is azido-labelled by administering intratumorally an effective amount of tetraacetyl-*N*-azidoacetylmannosamine to the subject in need thereof. In certain embodiments, the cancer is azido-labelled by administering intratumorally an effective amount of tetraacetyl-*N*-azidoacetyl neuraminic acid to the subject in need thereof. In certain embodiments, the cancer is azido-labelled by administering intratumorally an effective amount of 2,4,7,8-tetra-*O*-acetyl-*N*-acetyl-9-azido-9-deoxy neuraminic acid to the subject in need thereof. In certain embodiments, the cancer is azido-labelled by administering intratumorally an effective amount of tetraacetyl-*N*-azidoacetyl galactosamine to the subject in need thereof. In certain embodiments, the cancer is azido-labelled by administering intratumorally an effective amount of tetraacetyl-*N*-azidoacetylglucosamine to the subject in need thereof. In certain embodiments, the cancer is azido-labelled by administering intratumorally an effective amount of tetraacetyl-6-azidofucose to the subject in need thereof.

[00277] In certain embodiments, the cancer is azido-labelled selectively by administering an effective amount of an azido compound described herein. *See, e.g., Wang et al., Nat. Chem. Biol.* **2017**, *13*, 415-424; Wang *et al., Chem. Commun. (Camb).* **2018**, *54*, 4878-81; Bo *et al., Biomaterials*, **2020**, *238*, 119843; and US 11,014,953; the disclosure of each of which is incorporated herein by reference in its entirety.

[00278] In certain embodiments, the cancer is drug-resistant. In certain embodiment, the cancer is multidrug-resistant. In certain embodiments, the cancer is resistant to a chemotherapy. In certain embodiments, the cancer is resistant to an immunotherapy. In certain embodiments, the cancer is resistant to a standard therapy for the cancer.

[00279] In certain embodiments, the proliferative disease is breast cancer, melanoma, or ovarian cancer. In certain embodiments, the proliferative disease is breast cancer. In certain

embodiments, the proliferative disease is triple-negative breast cancer. In certain embodiments, the proliferative disease is melanoma. In certain embodiments, the proliferative disease is ovarian cancer. In certain embodiments, the proliferative disease is drug-resistant ovarian cancer.

[00280] In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a human.

[00281] In certain embodiments, the therapeutically effective amount of a compound provided herein is ranging from about 0.1 to about 500 mg/kg/day, from about 0.1 to about 200 mg/kg/day, from about 0.1 to about 100 mg/kg/day, from about 0.1 to about 50 mg/kg/day, from about 0.1 to about 25 mg/kg/day, from about 0.1 to about 20 mg/kg/day, from about 0.1 to about 15 mg/kg/day, from about 0.1 to about 10 mg/kg/day, or from about 0.1 to about 5 mg/kg/day. In one embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 0.1 to about 500 mg/kg/day. In another embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 0.1 to about 200 mg/kg/day. In yet another embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 0.1 to about 100 mg/kg/day. In yet another embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 0.1 to about 50 mg/kg/day. In yet another embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 0.1 to about 25 mg/kg/day. In yet another embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 0.1 to about 20 mg/kg/day. In yet another embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 0.1 to about 15 mg/kg/day. In yet another embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 0.1 to about 10 mg/kg/day. In still another embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 0.1 to about 5 mg/kg/day.

[00282] It is understood that the administered dose can also be expressed in units other than mg/kg/day. For example, doses for parenteral administration can be expressed as mg/m²/day. One of ordinary skill in the art would readily know how to convert doses from mg/kg/day to mg/m²/day to given either the height or weight of a subject or both. For example, a

dose of 1 mg/m²/day for a 65 kg human is approximately equal to 58 mg/kg/day.

[00283] In certain embodiments, the therapeutically effective amount of a compound provided herein is ranging from about 1 to about 1,000 mg per day, from about 1 to about 500 mg per day, from about 1 to about 200 mg per day, or from about 1 to about 100 mg per day. In one embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 1 to about 1,000 mg per day. In another embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 1 to about 500 mg per day. In yet another embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 1 to about 200 mg per day. In still another embodiment, the therapeutically effective amount of a compound provided herein is ranging from about 1 to about 100 mg per day.

[00284] Depending on the disorder, disease, or condition to be treated and the subject's condition, a compound provided herein may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, CIV, intracisternal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (*e.g.*, transdermal or local) routes of administration. A compound provided herein may be formulated in suitable dosage unit with a pharmaceutically acceptable excipient, carrier, adjuvant, or vehicle, appropriate for each route of administration.

[00285] In one embodiment, a compound provided herein is administered orally. In another embodiment, a compound provided herein is administered parenterally. In yet another embodiment, a compound provided herein is administered intravenously. In yet another embodiment, a compound provided herein is administered intramuscularly. In yet another embodiment, a compound provided herein is administered subcutaneously. In still another embodiment, a compound provided herein is administered topically.

[00286] A compound provided herein can be delivered as a single dose such as, *e.g.*, a single bolus injection, or oral tablets or pills; or over time such as, *e.g.*, continuous infusion over time or divided bolus doses over time. A compound provided herein can be administered repetitively, if necessary, for example, until the subject experiences stable disease or regression, or until the subject experiences disease progression or unacceptable toxicity.

[00287] A compound provided herein can be administered once daily (QD) or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). In addition, the administration can be continuous, *i.e.*, every day, or intermittently. The term “intermittent” or “intermittently” as used herein is intended to mean stopping and starting at either regular or irregular intervals. For example, intermittent administration of a compound provided herein is administration for one to six days per week, administration in cycles (*e.g.*, daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week), or administration on alternate days.

[00288] In certain embodiments, a compound provided herein is cyclically administered to a subject. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

[00289] A compound provided herein can also be combined or used in combination with other therapeutic agents useful in the treatment and/or prevention of a condition, disorder, or disease described herein.

[00290] As used herein, the term “in combination” includes the use of more than one therapy (*e.g.*, one or more prophylactic and/or therapeutic agents). However, the use of the term “in combination” does not restrict the order in which therapies (*e.g.*, prophylactic and/or therapeutic agents) are administered to a subject with a disease or disorder. A first therapy (*e.g.*, a prophylactic or therapeutic agent such as a compound provided herein) can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 50 minutes, 65 minutes, 1 hour, 2 hours, 6 hours, 6 hours, 12 hours, 26 hours, 68 hours, 72 hours, 96 hours, 1 week, 2 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 50 minutes, 65 minutes, 1 hour, 2 hours, 6 hours, 12 hours, 26 hours, 68 hours, 72 hours, 96 hours, 1 week, 2 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (*e.g.*, a prophylactic or therapeutic agent) to the subject. Triple therapy is also contemplated herein.

[00291] The route of administration of a compound provided herein is independent of the

route of administration of a second therapy. In one embodiment, a compound provided herein is administered orally. In another embodiment, a compound provided herein is administered intravenously. Thus, in accordance with these embodiments, a compound provided herein is administered orally or intravenously, and the second therapy can be administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, *via* inhalation, vaginally, intraocularly, *via* local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form. In one embodiment, a compound provided herein and a second therapy are administered by the same mode of administration, orally or by IV. In another embodiment, a compound provided herein is administered by one mode of administration, *e.g.*, by IV, whereas the second agent (an anticancer agent) is administered by another mode of administration, *e.g.*, orally.

[00292] In one embodiment, provided herein is a method of inhibiting the growth of a cell, comprising contacting the cell with an effective amount of a compound provided herein, *e.g.*, a compound of Formula (I), or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00293] In certain embodiments, the cell is azido-labelled. In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yl. In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yl on a glycoprotein. In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yl on a cell surface glycoprotein.

[00294] In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy. In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy on a glycoprotein. In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azido-

acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy on a cell surface glycoprotein.

[00295] In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yl. In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yl on a glycoprotein. In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yl on a cell surface glycoprotein.

[00296] In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy. In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy on a glycoprotein. In certain embodiments, the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy on a cell surface glycoprotein.

[00297] In certain embodiments, the cell is azido-labelled with ((3*S*,4*R*,5*S*,6*S*)-6-(azidomethyl)-2,4,5-trihydroxytetrahydro-2*H*-pyran-3-yl)oxy. In certain embodiments, the cell is azido-labelled with ((3*S*,4*R*,5*S*,6*S*)-6-(azidomethyl)-2,4,5-trihydroxytetrahydro-2*H*-pyran-3-yl)oxy on a glycoprotein. In certain embodiments, the cell is azido-labelled with ((3*S*,4*R*,5*S*,6*S*)-6-(azidomethyl)-2,4,5-trihydroxytetrahydro-2*H*-pyran-3-yl)oxy on a cell surface glycoprotein.

[00298] In certain embodiments, the cell is azido-labelled. In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl. In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl on a glycoprotein. In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl on a cell surface glycoprotein.

[00299] In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy. In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy on a glycoprotein. In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy on a cell surface glycoprotein.

[00300] In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl. In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl on a glycoprotein. In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl on a cell surface glycoprotein.

[00301] In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy. In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy on a glycoprotein. In certain embodiments, the cell is azido-labelled with (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy on a cell surface glycoprotein.

[00302] In certain embodiments, the cell is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl. In certain embodiments, the cell is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl on a glycoprotein. In certain embodiments, the cell is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl on a cell surface glycoprotein.

[00303] In certain embodiments, the cell is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy. In certain embodiments, the cell is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy on a glycoprotein. In certain embodiments, the cell is azido-labelled with (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxy-

methyl)tetrahydro-2H-pyran-2-yloxy on a cell surface glycoprotein.

[00304] In certain embodiments, the cell is azido-labelled by contacting the cell with an effective amount of an azido compound, wherein the azido compound is *N*-azidoacetylmannosamine, *N*-azidoacetyl neuraminic acid, *N*-acetyl-9-azido-9-deoxy neuraminic acid, *N*-azidoacetylgalactosamine, *N*-azido-acetylglucosamine, or 6-azidofucose, or a derivative thereof. . See, e.g., Laughlin and Bertozzi, *Nat. Protoc.* **2007**, 2, 2930-44; Wang *et al.*, *Nat. Chem. Biol.* **2017**, 13, 415-424; Wang and Mooney, *Nat. Chem.* **2020**, 12, 1102-14; and US 11,014,953; the disclosure of each of which is incorporated herein by reference in its entirety. In certain embodiments, the azido compound is tetraacetyl-*N*-azido-acetylmannosamine, tetraacetyl-*N*-azidoacetyl neuraminic acid, 2,4,7,8-tetra-*O*-acetyl-*N*-acetyl-9-azido-9-deoxy neuraminic acid, tetraacetyl-*N*-azidoacetyl-galactosamine, tetraacetyl-*N*-azidoacetyl-glucosamine, or tetraacetyl-6-azidofucose.

[00305] In certain embodiments, the cell is azido-labelled by administering an effective amount of tetraacetyl-*N*-azidoacetylmannosamine to the subject in need thereof. In certain embodiments, the cell is azido-labelled by administering an effective amount of tetraacetyl-*N*-azidoacetyl neuraminic acid to the subject in need thereof. In certain embodiments, the cell is azido-labelled by administering an effective amount of 2,4,7,8-tetra-*O*-acetyl-*N*-acetyl-9-azido-9-deoxy neuraminic acid to the subject in need thereof. In certain embodiments, the cell is azido-labelled by administering an effective amount of tetraacetyl-*N*-azidoacetylgalactosamine to the subject in need thereof. In certain embodiments, the cell is azido-labelled by administering an effective amount of tetraacetyl-*N*-azidoacetylglucosamine to the subject in need thereof. In certain embodiments, the cell is azido-labelled by administering an effective amount of tetraacetyl-6-azidofucose to the subject in need thereof.

[00306] In certain embodiments, the cell is selectively azido-labelled by contacting the cell with an effective amount of an azido compound. See, e.g., Wang *et al.*, *Nat. Chem. Biol.* **2017**, 13, 415-424; the disclosure of which is incorporated herein by reference in its entirety.

[00307] In certain embodiments, the cell is a cancerous cell. In certain embodiments, the cell is a human cell. In certain embodiments, the cell is a human cancerous cell.

[00308] In certain embodiments, the cell is a drug-resistant cancerous cell. In certain embodiments, the cell is a multidrug-resistant cancerous cell. In certain embodiments, the cell is a cancerous cell resistant to a chemotherapy. In certain embodiments, the cell is cancerous cell resistant to an immunotherapy. In certain embodiments, the cell is cancerous cell resistant to a standard therapy for the cancer.

[00309] In certain embodiments, the cell is a breast cancer, melanoma, or ovarian cancer cell. In certain embodiments, the cell is a breast cancer cell. In certain embodiments, the cell is a triple-negative breast cancer cell. In certain embodiments, the cell disease is a melanoma cell. In certain embodiments, the cell is an ovarian cancer cell. In certain embodiments, the cell is a drug-resistant ovarian cancer cell.

[00310] A compound provided herein can also be provided as an article of manufacture using packaging materials well known to those of skill in the art. *See, e.g.*, U.S. Pat. Nos. 5,525,907; 5,052,558; and 5,055,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[00311] In certain embodiments, provided herein is a kit which, when used by a medical practitioner, can simplify the administration of an appropriate amount of a compound provided herein as an active ingredient to a subject. In certain embodiments, the kit provided herein includes a container and a dosage form of a compound provided herein.

[00312] Kits provided herein can further include devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, needle-less injectors drip bags, patches, and inhalers. The kits provided herein can also include condoms for administration of the active ingredients.

[00313] Kits provided herein can further include pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved

to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: aqueous vehicles, including, but not limited to, water for injection USP, sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, and lactated Ringer's injection; water-miscible vehicles, including, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles, including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[00314] The disclosure will be further understood by the following non-limiting examples.

EXAMPLES

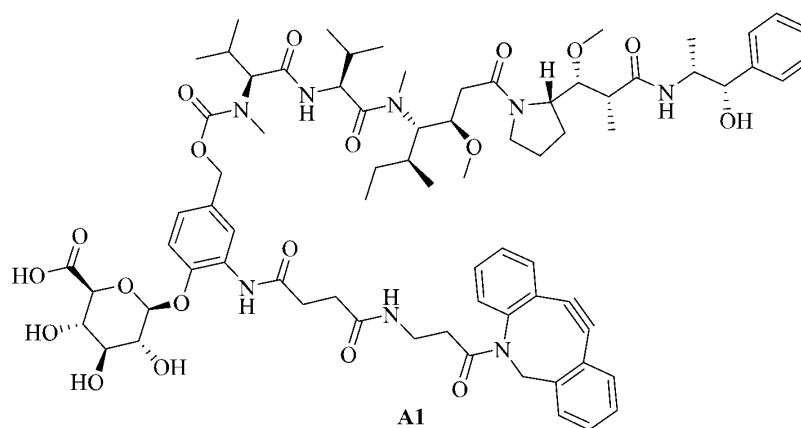
[00315] As used herein, the symbols and conventions used in these processes, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society, the Journal of Medicinal Chemistry, or the Journal of Biological Chemistry. Specifically, but without limitation, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); mL (milliliters); μ L (microliters); mM (millimolar); μ M (micromolar); mmol (millimoles); min (minute or minutes); h (hour or hours); Ac (acetyl); ACN (acetonitrile); *t*-Bu (*tert*-butyl); DCM (dichloromethane); DEA (diethylamine); DIEA (*N,N*-diisopropylethylamine); DMAP (4-dimethylaminopyridine); DMF (dimethylformamide); DMSO (dimethylsulfoxide); DMTMM (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholin-4-ium chloride); EtOAc (ethyl acetate); EDCI (1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide); FA (formic acid); Fmoc (fluorenylmethyloxycarbonyl); HATU (2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate); HOBT (1-hydroxybenzotriazole); HSTU (*O*-(*N*-succinimidyl)-1,1,3,3-tetramethyluronium hexafluorophosphate); Me (methyl); MeOH (methanol); MMAE ((*S*)-*N*-((3*R*,4*S*,5*S*)-1-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-3-methoxy-5-methyl-1-oxoheptan-4-yl)-*N*,3-dimethyl-2-((*S*)-3-methyl-2-(methylamino)-butanamido)butanamide); NHS (*N*-hydroxysuccinimide); NMM (*N*-methylmorpholine); PE (petroleum ether); PPh₃ (triphenylphosphine); PyBop (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate); T₃P (propylphosphonic anhydride); TEA (triethylamine);

THF (tetrahydrofuran); MS (mass spectrometry); NMR (nuclear magnetic resonance); prep-HPLC (preparative high performance liquid chromatography); and prep TLC (preparative thin-layer chromatography).

[00316] For all of the following examples, standard work-up and purification methods known to those skilled in the art can be utilized. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted at room temperature unless otherwise specified. Synthetic methodologies illustrated herein are intended to exemplify the applicable chemistry through the use of specific examples and are not indicative of the scope of the disclosure.

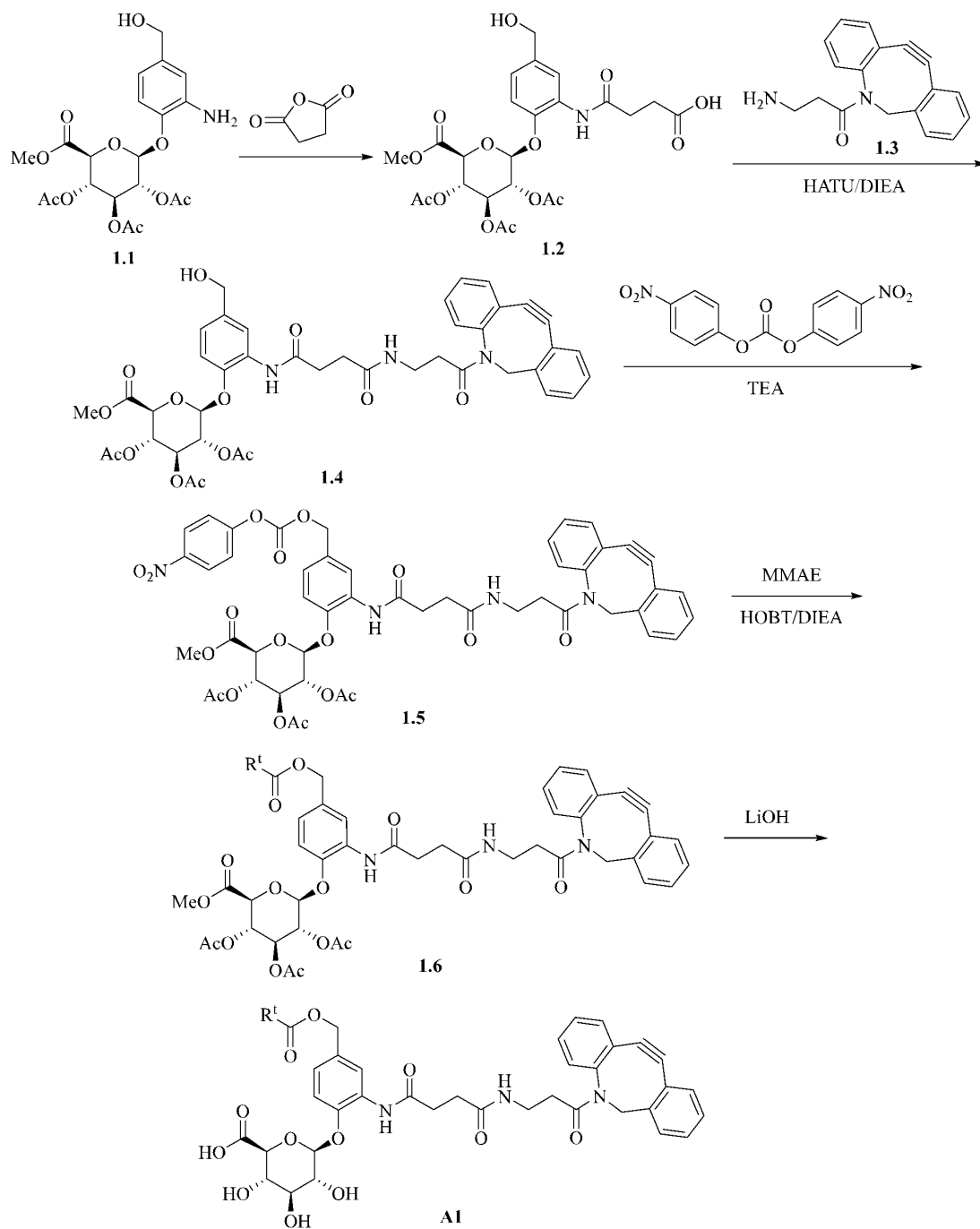
Example 1

Preparation of compound A1



[00317] Compound **A1** was prepared as shown in Scheme 1, wherein R¹ is ((*S*)-1-(((*S*)-1-(((3*R*,4*S*,5*S*)-1-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-3-methoxy-5-methyl-1-oxoheptan-4-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)amino.

Scheme 1



[00318] Preparation of 4-((5-(hydroxymethyl)-2-(((2*S*,3*R*,4*S*,5*S*,6*S*)-3,4,5-triacetoxy-6-

(methoxycarbonyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)amino)-4-oxobutanoic acid **1.2**. To a solution of (2*S*,3*R*,4*S*,5*S*,6*S*)-2-(2-amino-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **1.1** (9.3 g, 20.4 mmol) in THF (93 mL) was added succinic anhydride (2.6 g, 26.5 mmol). After stirring for 16 h under N₂, the reaction mixture was concentrated and purified by column chromatography (SiO₂, MeOH/DCM) to afford compound **1.2** (11.2 g) in 84% yield. MS (ESI) *m/z*: 578.3 [M+Na]⁺.

[00319] Preparation of compound **1.4**. To a solution of compound **1.2** (1.06 g, 1.91 mmol) in DMF (21 mL) were added HATU (870 mg, 2.29 mmol), DIEA (738 mg, 5.72 mmol), and DBCO-NH₂ **1.3** (527 mg 1.91 mmol). After stirring overnight, the reaction mixture was diluted with DCM (25 mL) and distilled water (50 mL), and extracted with DCM (25 mL x 3). The combined organic layers were washed with brine (25 mL x 3), dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **1.4** (1.2 g) in 77% yield. MS (ESI) *m/z*: 814.9 [M+H]⁺.

[00320] Preparation of compound **1.5**. To a solution of compound **1.4** (500 mg, 0.61 mmol) in DCM (20 mL) were added TEA (143 mg, 1.4 mmol) and bis(4-nitrophenyl) carbonate (374 mg, 1.23 mmol). After stirring for 2 h under N₂, the reaction mixture was concentrated and purified by column chromatography (SiO₂, EtOAc/DCM) to afford compound **1.5** (400 mg) in 67% yield. MS (ESI) *m/z*: 979.4 [M+H]⁺.

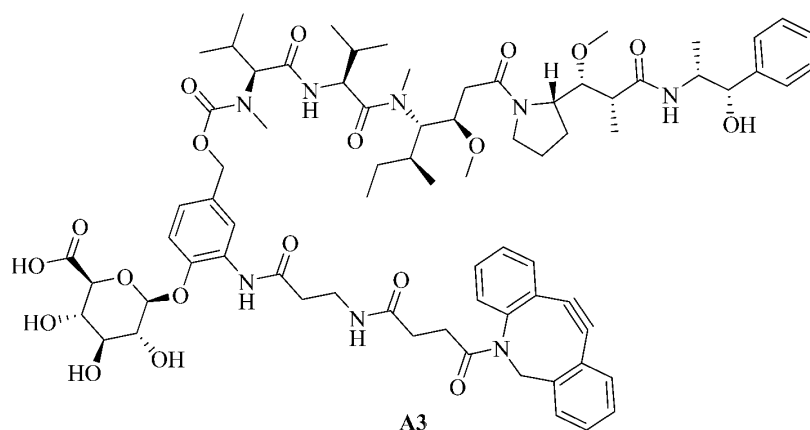
[00321] Preparation of compound **1.6**. To a solution of compound **1.5** (200 mg, 0.204 mmol) in DMF (2 mL) were added MMAE (146 mg, 0.204 mmol), HOBT (42.0 mg, 0.306 mmol), pyridine (80 mg, 1.02 mmol), and DIEA (132 mg, 1.02 mmol). After stirring for 15 h under N₂, the reaction mixture was purified by column chromatography (C18, ACN/H₂O) to afford compound **1.6** (144 mg) in 45% yield. MS (ESI) *m/z*: 1557.8 [M+H]⁺.

[00322] Preparation of compound **A1**. To a solution of compound **1.6** (1.7 g, 1.09 mmol) in MeOH (17 mL) was added a solution of LiOH (78.6 mg, 3.27 mmol) in H₂O (10 mL). After stirring for 2 h, the reaction mixture was purified by column chromatography (C18, ACN/H₂O) to afford compound **A1** (1.28 g) in 83% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.20 (s, 1H), 8.30 (br, 1H), 8.13 (s, 1H), 7.89 (br, 1H), 7.69-6.57 (m, 16H), 5.67 (d, *J* = 7.6 Hz, 1H), 5.43-5.36 (m, 2H), 5.05 (s, 2H), 5.01 (d, *J* = 14.0 Hz, 1H), 4.86-4.83 (m, 2H), 4.73 (d, *J* = 7.6 Hz, 1H),

4.58-4.25 (m, 3H), 4.04-3.88 (m, 2H), 3.78 (d, $J = 7.6$ Hz, 1H), 3.62 (d, $J = 14.0$ Hz, 1H), 3.58-3.32 (m, 4H), 3.25-3.11 (m, 12H), 3.06-2.84 (m, 3H), 2.64-2.58 (m, 1H), 2.43-2.28 (m, 5H), 2.12-1.88 (m, 3H), 1.80-1.59 (m, 4H), 1.53-1.28 (m, 4H), 1.05-0.99 (m, 6H), 0.86-0.75 (m, 18H); MS (ESI) m/z : 1440.7 $[M+Na]^+$.

Example 2

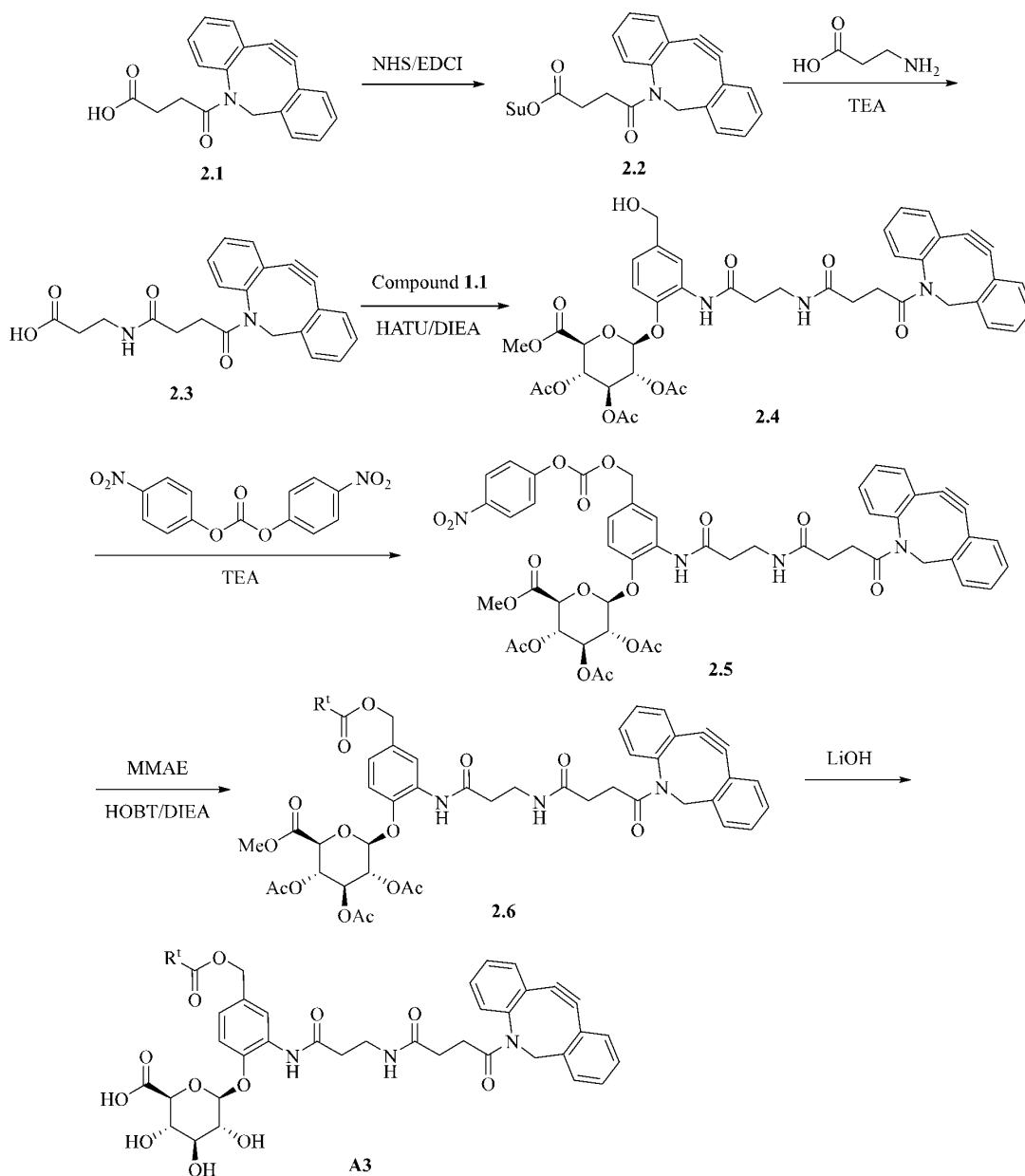
Preparation of compound A3



[00323] Compound **A3** was prepared as shown in Scheme 2, wherein R¹ is ((*S*)-1-(((*S*)-1-(((3*R*,4*S*,5*S*)-1-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-3-methoxy-5-methyl-1-oxoheptan-4-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)amino.

[00324] Preparation of compound **2.2**. To a solution of compound DBCO-acid **2.1** (23.8 g, 78.2 mmol) in DCM (250 mL) were added EDCI (18 g, 93.8 mmol) and NHS (10.8 g, 93.8 mmol). After stirring overnight, the reaction mixture was diluted with DCM (250 mL) and distilled water (500 mL), and extracted with DCM (250 mL x 3). The combined organic layers were washed with brine (250 mL x 3), dried over anhydrous Na₂SO₄, and concentrated to afford compound **2.2** (28 g), which was used directly in the next step without further purification.

Scheme 2



[00325] Preparation of compound **2.3**. To a solution of compound **2.2** (1.3 g, 3.23 mmol) in DCM (20 mL) were added TEA (1 g, 9.9 mmol) and 3-aminopropanoic acid (239 mg, 3.88 mmol). After stirring overnight, the reaction mixture was purified by column chromatography (C18, ACN/H₂O) to afford compound **2.3** (927 mg) in 76% yield. MS (ESI) m/z : 377.1 $[\text{M}+\text{H}]^+$.

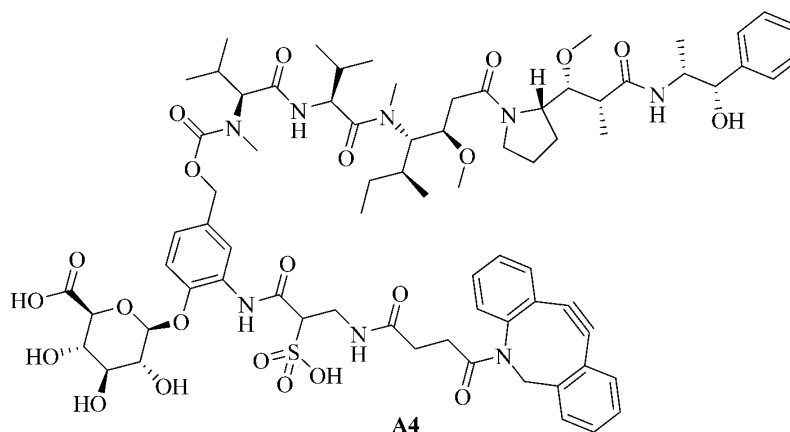
[00326] Preparation of compound **2.4**. To a solution of (2*S*,3*R*,4*S*,5*S*,6*S*)-2-(2-amino-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **1.1** (2.73 g, 6 mmol) in DMF (30 mL) were added DIEA (2.32 g, 18 mmol), HATU (3.42 g, 9 mmol), and compound **2.3** (2.26 g, 6 mmol). After stirring overnight, the reaction mixture was purified by column chromatography (C18, ACN/H₂O) to afford compound **2.4** (1.24 g) in 25% yield. MS (ESI) *m/z*: 836.4 [M+Na]⁺.

[00327] Preparation of compound **2.5**. Compound **2.5** was prepared from compound **2.4** according to the procedures as described in Example 1 for compound **1.5**.

[00328] Preparation of compound **2.6**. Compound **2.6** was prepared from compound **2.5** according to the procedures as described in Example 1 for compound **1.6**.

[00329] Preparation of compound **A3**. Compound **A3** was prepared from compound **2.6** (65.9 mg) in 47% yield, according to the procedures as described in Example 1 for compound **A1**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.25 (s, 1H), 8.33 (br, 1H), 8.12 (s, 1H), 7.85 (br, 1H), 7.74-6.92 (m, 16H), 5.70 (d, *J* = 7.6 Hz, 1H), 5.46-5.40 (m, 2H), 5.05 (s, 2H), 5.01 (d, *J* = 14.0 Hz, 1H), 4.88-4.83 (m, 2H), 4.74 (d, *J* = 7.6 Hz, 1H), 4.57-4.25 (m, 3H), 4.04-3.91 (m, 2H), 3.79 (d, *J* = 7.6 Hz, 1H), 3.61 (d, *J* = 14.0 Hz, 1H), 3.58-3.32 (m, 4H), 3.26-3.11 (m, 12H), 2.97-2.85 (m, 3H), 2.66-2.58 (m, 1H), 2.45-2.30 (m, 5H), 2.09-1.60 (m, 7H), 1.53-1.30 (m, 4H), 1.05-0.97 (m, 6H), 0.89-0.78 (m, 18H); MS (ESI) *m/z*: 709.6 [1/2M+H]⁺.

Example 3

Preparation of compound **A4**

[00330] Compound **A4** was prepared as shown in Scheme 3, wherein R¹ is ((*S*)-1-(((*S*)-1-(((3*R*,4*S*,5*S*)-1-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-3-methoxy-5-methyl-1-oxoheptan-4-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)amino.

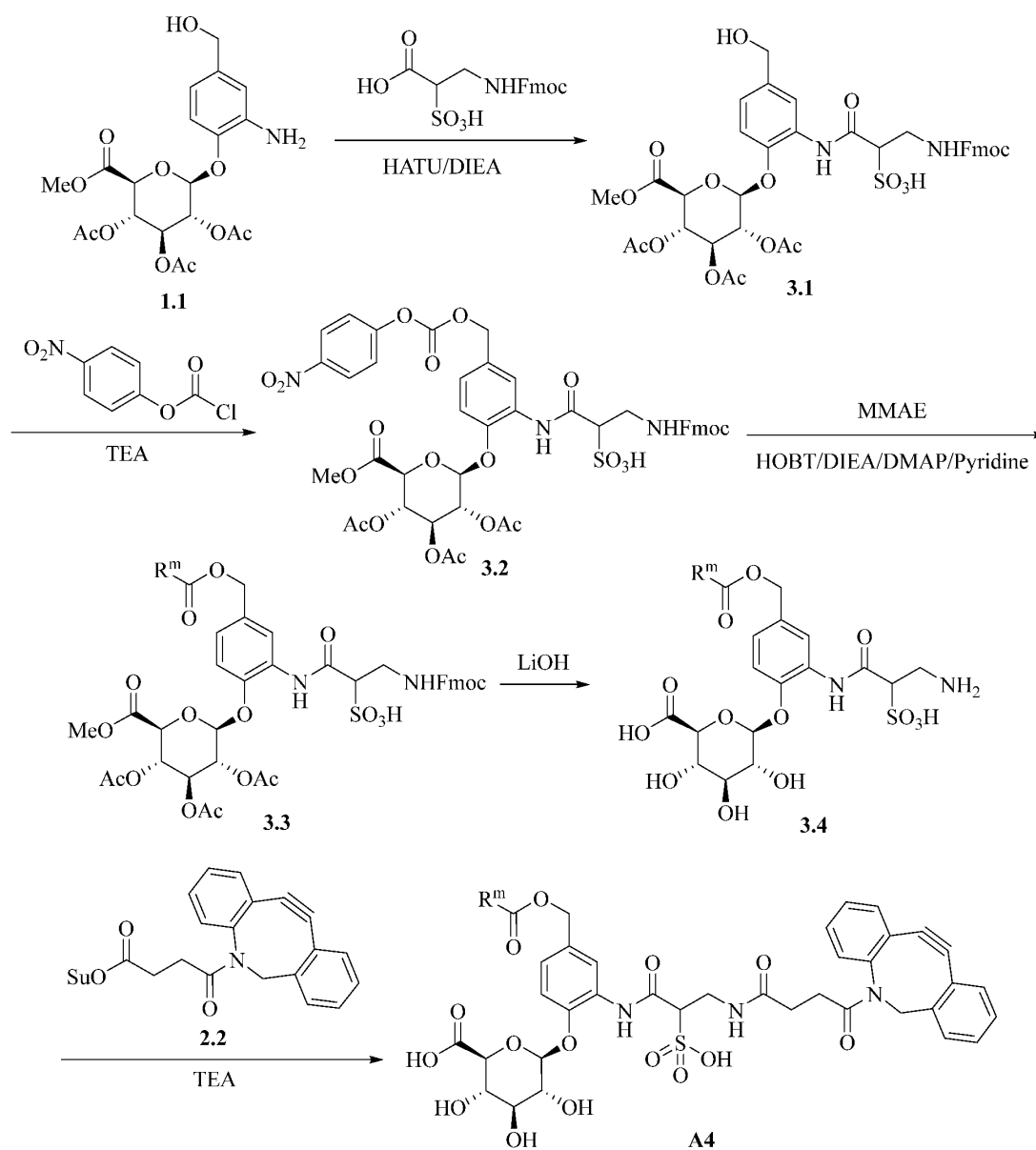
[00331] Preparation of compound **3.1**. To a solution of 3-(((9*H*-fluoren-9-yl)methoxy)-carbonyl)amino)-2-sulfopropanoic acid (640 mg, 1.63 mmol) in DMF (6 mL) were added (2*S*,3*R*,4*S*,5*S*,6*S*)-2-(2-amino-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **1.1** (620 mg, 1.36 mmol), HATU (622 mg, 1.63 mmol), and DIEA (422 mg, 3.27 mmol). After stirring under N₂ overnight, the reaction mixture was concentrated and purified by column chromatography (C18, ACN/H₂O) to afford compound **3.1** (800 mg) in 59% yield. MS (ESI) *m/z*: 827.3 [M-H]⁻.

[00332] Preparation of compound **3.2**. To a solution of compound **3.1** (600 mg, 0.724 mmol) in DCM (6 mL) were added 4-nitrophenyl chloroformate (437 mg, 2.17 mmol) and TEA (292 mg, 2.89 mmol) at 0 °C. After stirring under N₂ for 2 h, the reaction mixture was concentrated and purified by column chromatography (SiO₂, MeOH/DCM) to afford compound **3.2** (550 mg) in 77% yield. MS (ESI) *m/z*: 992.4 [M-H]⁻.

[00333] Preparation of compound **3.3**. To a solution of MMAE (265 mg, 0.369 mmol) in

DMF (6 mL) were added HOBT (74 mg, 0.554 mmol), pyridine (87 mg, 1.1 mmol), DIEA (142 mg, 1.1 mmol), DMAP (2 mg, 18.4 μ mol), and compound **3.2** (550 mg, 0.554 mmol). After stirring under N₂ for 2 h, the reaction mixture was concentrated and purified by column chromatography (C18, ACN/H₂O) to afford compound **3.3** (300 mg) in 52% yield. MS (ESI) m/z : 1573.9 [M+H]⁺.

Scheme 3

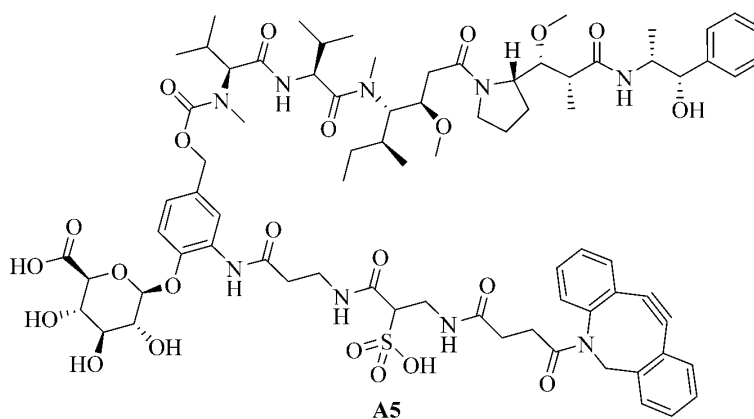


[00334] Preparation of compound **3.4**. To a solution of compound **3.3** (300 mg, 0.191 mmol) in MeOH (2 mL) and THF (2 mL) was added LiOH (27 mg, 1.14 mmol) at 0 °C. After stirring under N₂ for 2 h, the reaction mixture was concentrated to afford compound **3.4** (230 mg), which was used directly in the next step without further purification. MS (ESI) m/z : 1210.7 [M+H]⁺.

[00335] Preparation of compound **A4**. To a solution of compound **3.4** (230 mg, 0.191 mmol) in DMF (3 mL) were added compound **2.2** (76 mg, 0.191 mmol) and TEA (58 mg, 0.573 mmol). After stirring under N₂ for 2 h, the reaction mixture was purified by reverse phase prep-HPLC (ACN/H₂O) to afford compound **A4** (37.8 mg) in 13% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.86 (s, 1H), 8.33 (br, 1H), 8.19 (s, 1H), 7.90 (br, 1H), 7.79-6.94 (m, 16H), 6.62-6.58 (m, 1H), 5.65 (d, J = 7.6 Hz, 1H), 5.46-5.37 (m, 2H), 5.05 (s, 2H), 5.01 (d, J = 14.0 Hz, 1H), 4.92-4.85 (m, 2H), 4.76 (d, J = 7.6 Hz, 1H), 4.58-4.27 (m, 3H), 4.04-3.88 (m, 2H), 3.77 (d, J = 7.6 Hz, 1H), 3.61 (d, J = 14.0 Hz, 1H), 3.56-3.39 (m, 4H), 3.25-3.13 (m, 12H), 2.98-2.84 (m, 3H), 2.64-2.58 (m, 1H), 2.43-2.28 (m, 3H), 2.09-1.87 (m, 3H), 1.76-1.29 (m, 8H), 1.08-0.98 (m, 6H), 0.89-0.77 (m, 18H); MS (ESI) m/z : 1496.7 [M-H]⁻.

Example 4

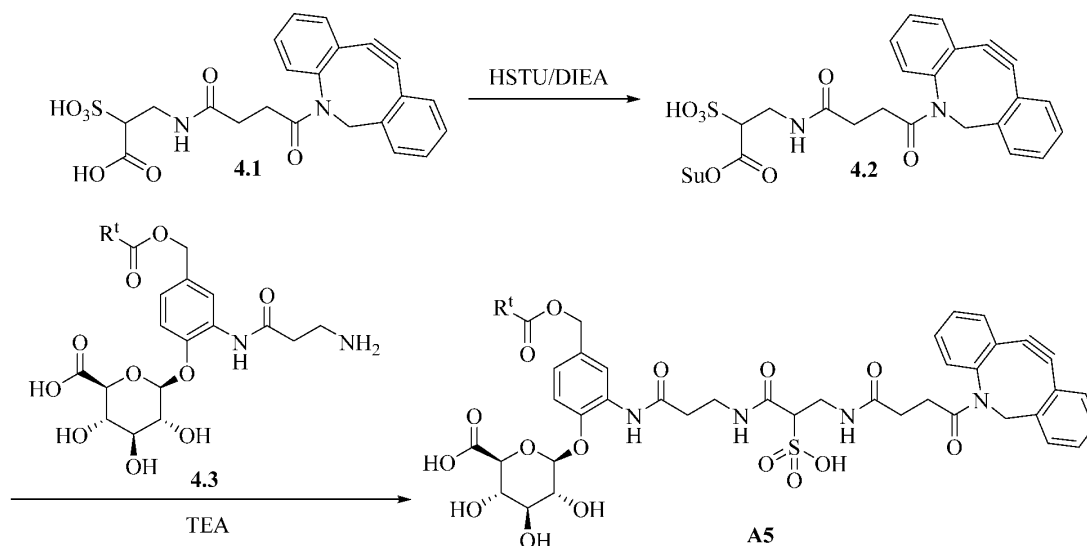
Preparation of compound **A5**



[00336] Compound **A5** was prepared as shown in Scheme 4, wherein R¹ is ((*S*)-1-(((*S*)-1-(((3*R*,4*S*,5*S*)-1-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-3-methoxy-5-methyl-1-oxoheptan-4-yl)(methyl)amino)-

3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)amino.

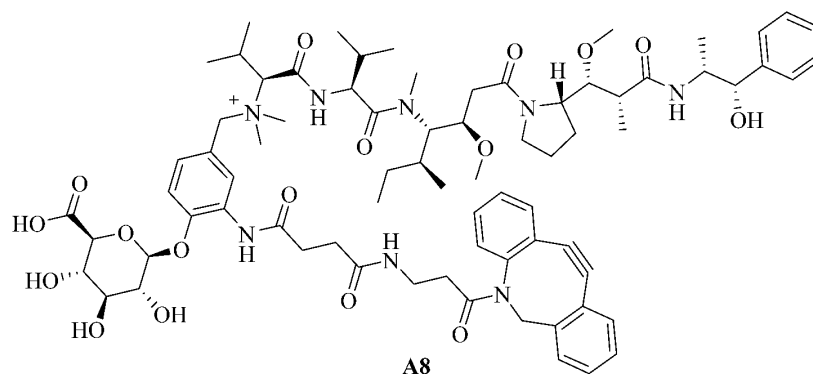
Scheme 4



[00337] Preparation of compound **4.2**. To a solution of compound **4.1** (142 mg, 0.311 mmol) in DMF (3mL) were added DIEA (120 mg, 0.933 mmol) and HSTU (113 mg, 0.374 mmol) at 0 °C. The reaction mixture was stirred overnight to afford compound **4.2**, which was used directly in the next step without further purification. MS (ESI) m/z : 554.2 $[M+H]^+$.

[00338] Preparation of compound **A5**. Compound **A5** was prepared from compounds **4.2** and **4.3** according to the procedures as described in Example 3 for compound **A4**, where compound **4.3** was prepared as described in WO 2016/046574. ^1H NMR (400 MHz, DMSO- d_6) δ 9.31 (s, 1H), 8.15 (s, 1H), 8.03 (br, 1H), 7.95 (s, 1H), 7.88 (br, 1H), 7.76-6.88 (m, 16H), 5.87-5.75 (m, 1H), 5.67 (d, $J = 7.6$ Hz, 1H), 5.42-5.35 (m, 2H), 5.05 (s, 2H), 5.02 (d, $J = 14.0$ Hz, 1H), 4.86-4.80 (m, 2H), 4.73 (d, $J = 7.6$ Hz, 1H), 4.46-4.26 (m, 3H), 4.06-3.97 (m, 2H), 3.78 (d, $J = 7.6$ Hz, 1H), 3.62 (d, $J = 14.0$ Hz, 1H), 3.51-3.43 (m, 6H), 3.27-3.12 (m, 12H), 2.97-2.84 (m, 3H), 2.64-2.52 (m, 1H), 2.48-2.24 (m, 5H), 2.13-1.59 (m, 7H), 1.53-1.28 (m, 4H), 1.05-0.97 (m, 6H), 0.89-0.78 (m, 18H); MS (ESI) m/z : 785.1 $[1/2M+H]^+$.

Example 5

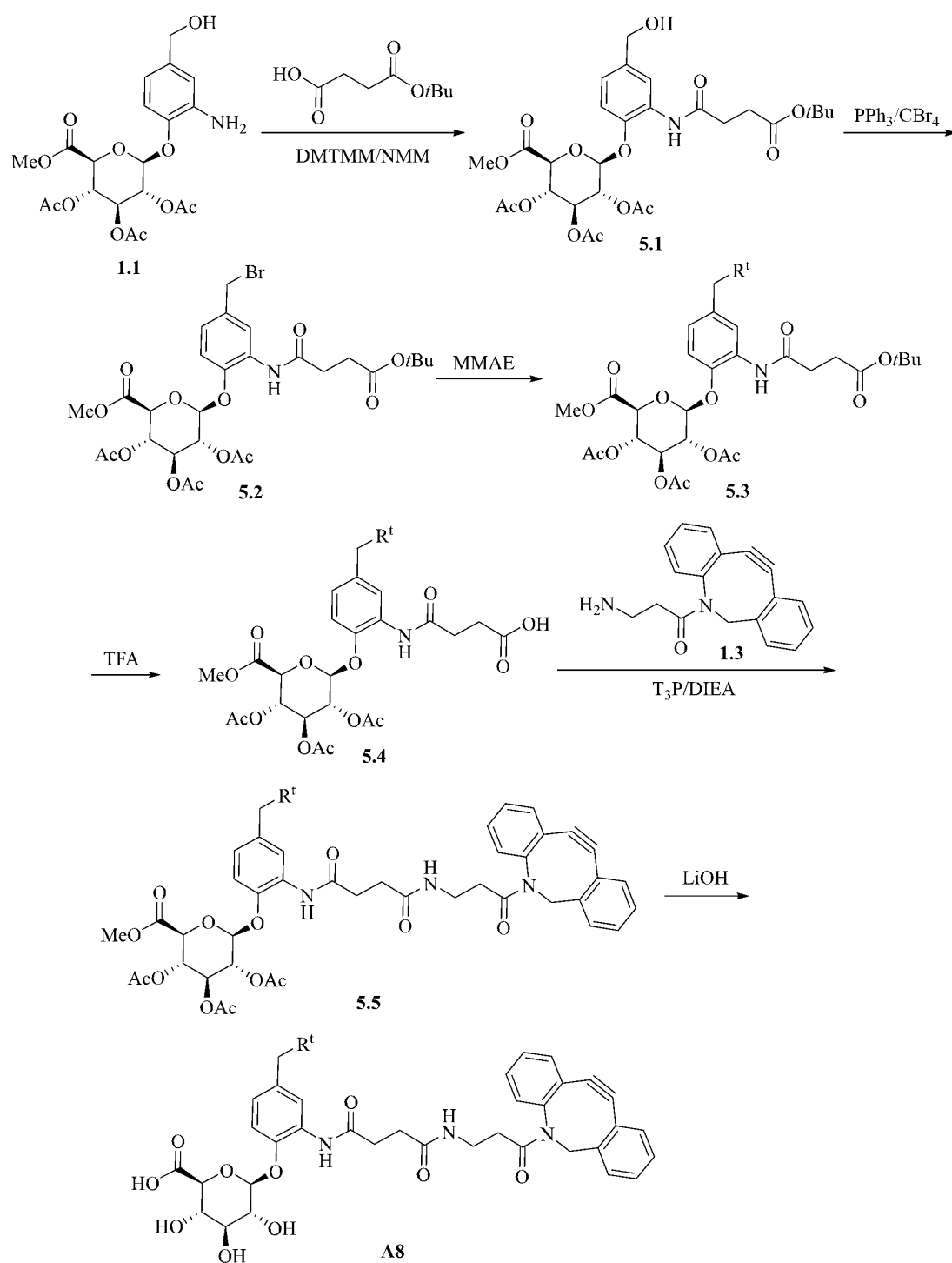
Preparation of compound **A8**

[00339] Compound **A8** was prepared as shown in Scheme 5, wherein R^t is ((*S*)-1-(((*S*)-1-(((3*R*,4*S*,5*S*)-1-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-3-methoxy-5-methyl-1-oxoheptan-4-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(dimethyl)amino).

[00340] Preparation of compound **5.1**. To a solution of (2*S*,3*R*,4*S*,5*S*,6*S*)-2-(2-amino-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **1.1** (2 g, 4.40 mmol) and 4-(*tert*-butoxy)-4-oxobutanoic acid (1.15 g, 6.6 mmol) in MeOH (15 mL) were added DMTMM (3.64 g, 13.2 mmol) and NMM (0.533 g, 5.28 mmol). After stirring under N₂ for 16 h, the reaction mixture was concentrated and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **5.1** (1.8 g) in 67% yield. MS (ESI) *m/z*: 634.3 [M+Na]⁺.

[00341] Preparation of compound **5.2**. To a solution of compound **5.1** (1.8 g, 2.94 mmol) in DCM (15 mL) were added PPh₃ (0.72 g, 4.41 mmol) and CBr₄ (1.46 g, 4.41 mmol). After stirring for 16 h, the reaction mixture was concentrated and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **5.2** (1.2 g) in 68% yield. MS (ESI) *m/z*: 676.1 [M+H]⁺.

Scheme 5



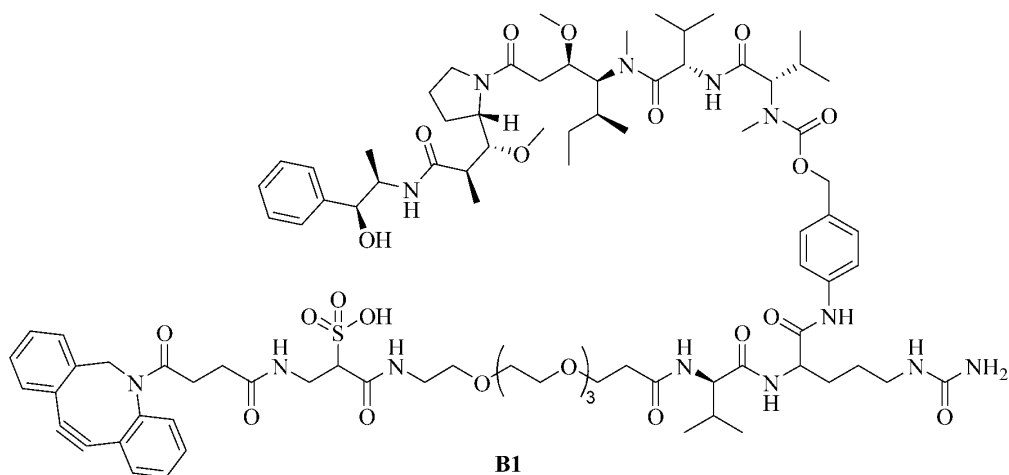
[00342] Preparation of compound **5.3**. To a solution of compound **5.2** (470 mg, 0.697 mmol) in 2-butanone (5 mL) was added MMAE (510 mg, 0.697 mmol). After stirring at 80 °C for three days, the reaction mixture was concentrated and purified by column chromatography (C18, ACN/H₂O (0.1% FA)) to afford compound **5.3** (500 mg) in 51% yield. MS (ESI) *m/z*: 1326.0 [M]⁺.

[00343] Preparation of compound **5.4**. A solution of compound **5.3** (500 mg, 0.377 mmol) in DCM (10 mL) and FA (1 mL) was stirred for 2 h. The reaction mixture was then concentrated and purified by (C18, ACN/H₂O (0.1% FA)) to afford compound **5.4** (260 mg) in 54% yield. MS (ESI) *m/z*: 1270.3 [M]⁺.

[00344] Preparation of compound **5.5**. To a solution of compound **5.4** (100 mg, 78.7 μmol) and DBCO-NH₂ **1.3** (400 mg, 0.145 mmol) in dioxane (1.6 mL) were added DIEA (10 mg, 77.5 μmol) and T₃P (25 mg, 78.6 μmol) under N₂. After stirring at 40 °C for 2 h, the reaction mixture was concentrated and purified by prep-TLC (DCM/MeOH) to afford compound **5.5** (700 mg) in 57% yield. MS (ESI) *m/z*: 1528.2 [M]⁺.

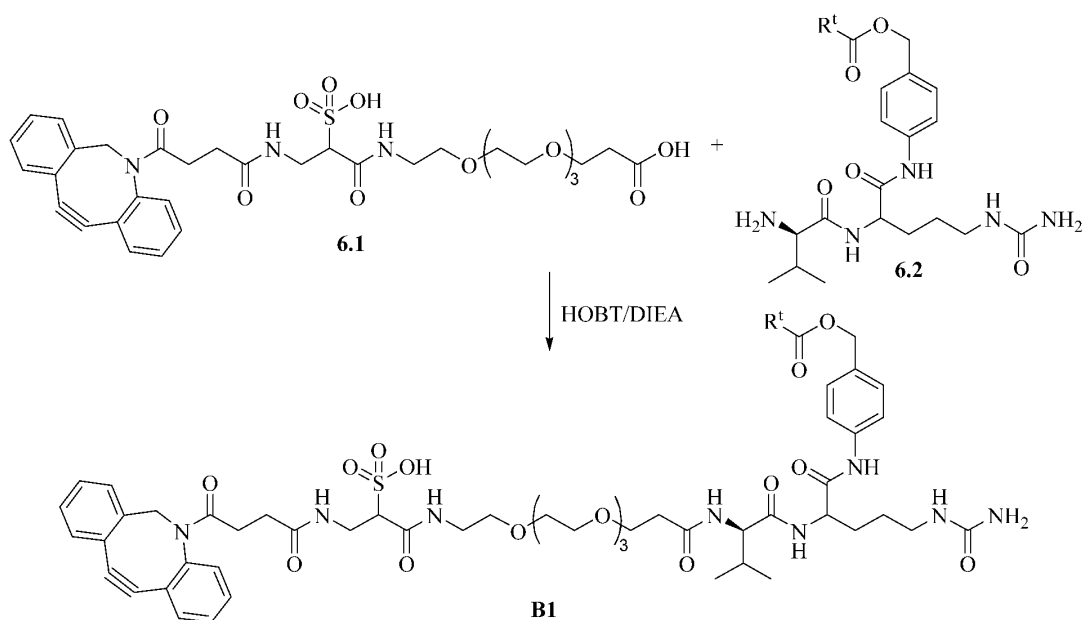
[00345] Preparation of compound **A8**. To a solution of compound **5.5** (600 mg, 0.393 mmol) in MeOH (2 mL) and THF (2 mL) was added a solution of LiOH (19.2 mg, 0.8 mmol) in H₂O (0.5 mL) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was neutralized with FA, concentrated, and purified by reverse phase prep-HPLC (ACN/H₂O) to afford compound **A8** (31.4 mg) in 42% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.25 (s, 1H), 8.96 (s, 1H), 8.34 (br, 1H), 7.83 (br, 1H), 7.66-7.08 (m, 16H), 5.63 (d, *J* = 7.6 Hz, 1H), 5.42-5.36 (m, 2H), 5.06 (s, 1H), 5.02 (d, *J* = 14.0 Hz, 1H), 4.86-4.81 (m, 2H), 4.74 (d, *J* = 7.6 Hz, 1H), 4.69-4.57 (m, 1H), 4.50-4.37 (m, 3H), 4.05-3.88 (m, 2H), 3.77 (d, *J* = 7.6 Hz, 1H), 3.61 (d, *J* = 14.0 Hz, 1H), 3.58-3.32 (m, 4H), 3.20-2.97 (m, 15H), 2.86-2.81 (m, 3H), 2.60-2.57 (m, 1H), 2.46-2.28 (m, 5H), 2.15-1.93 (m, 3H), 1.81-1.57 (m, 4H), 1.51-1.26 (m, 4H), 1.09-0.97 (m, 6H), 0.92-0.69 (m, 18H); MS (ESI) *m/z*: 1388.2 [M]⁺.

Example 6

Preparation of compound **B1**

[00346] Compound **B1** was prepared as shown in Scheme 6, wherein R^t is ((*S*)-1-(((*S*)-1-(((3*R*,4*S*,5*S*)-1-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-3-methoxy-5-methyl-1-oxoheptan-4-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)amino.

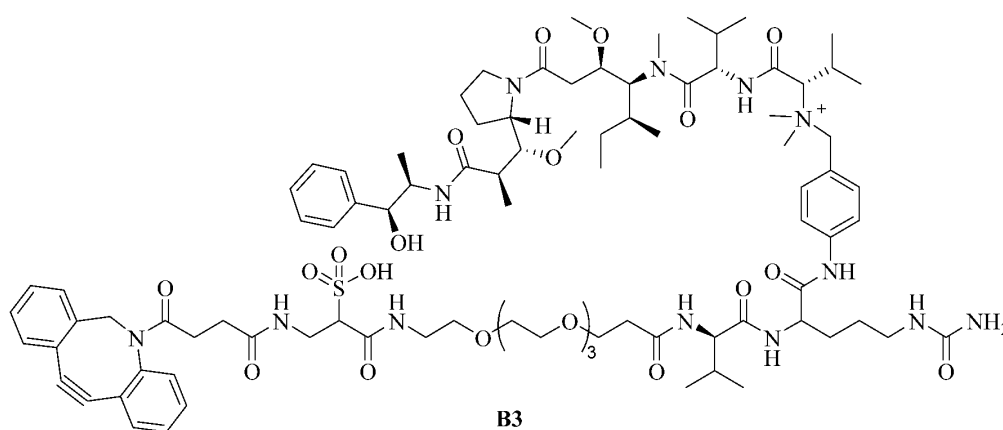
Scheme 6



[00347] Compound **B1**. To a solution of compound **6.1** (63 mg, 89 μ mol) in DMF (4 mL) were added HOBT (75 mg, 0.356 mmol), DIEA (115 mg, 0.89 mmol), and Val-Cit-PAB-MMAE **6.2** (100 mg, 89 μ mol). After stirring under N₂ overnight, the reaction mixture was concentrated and purified by reverse phase prep-HPLC (ACN/H₂O (0.05 % NH₃·H₂O)) to afford compound **B1** (45.8 mg) in 28% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.97 (s, 1H), 8.38 (s, 1H), 8.19 (br, 1H), 8.12 (br, 1H), 8.01 (s, 1H), 7.88 (br, 1H), 7.73 (br, 1H), 7.73-7.01 (m, 17H), 6.02 (t, *J* = 5.6 Hz, 1H), 5.41 (br, 2H), 5.32 (d, *J* = 4.8 Hz, 1H), 5.07-5.04 (m, 2H), 5.01 (d, *J* = 14.0 Hz, 1H), 4.79-4.40 (m, 2H), 4.32-4.28 (m, 2H), 3.98-3.90 (m, 3H), 3.81-3.71 (m, 3H), 3.60 (d, *J* = 14.0 Hz, 1H), 3.56-3.53 (m, 3H), 3.50-3.45 (m, 18H), 3.38-3.05 (m, 12H), 2.97-2.84 (m, 3H), 2.59-2.51 (m, 3H), 2.46-2.07 (m, 7H), 1.96-1.86 (m, 8H), 1.59-1.28 (m, 6H), 1.11-0.97 (m, 6H), 0.86-0.78 (m, 24H); MS (ESI) *m/z*: 1809.1 [M+H]⁺.

Example 7

Preparation of compound **B3**

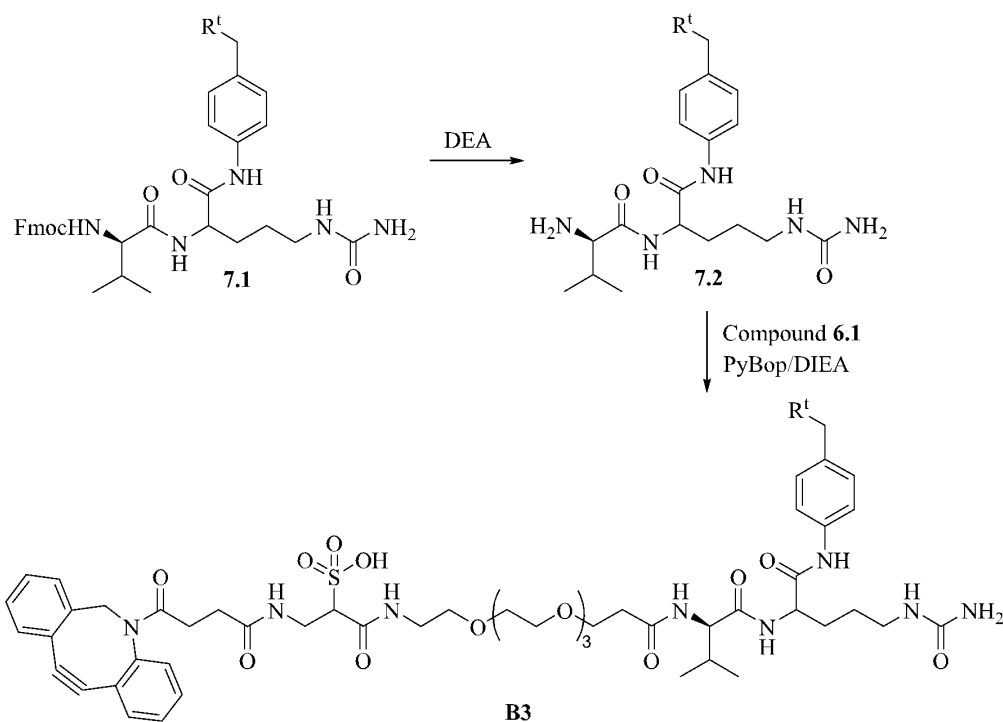


[00348] Compound **B7** was prepared as shown in Scheme 7, wherein R¹ is ((*S*)-1-(((*S*)-1-(((3*R*,4*S*,5*S*)-1-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-3-methoxy-5-methyl-1-oxoheptan-4-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(dimethyl)amino.

[00349] Preparation of compound **7.2**. To a solution of compound **7.1** (350 mg, 0.265 mmol,) in DMF (5 mL) was added DEA (350 mg, 0.265 mmol). After stirring for 2 h, the

reaction mixture was purified by reverse phase prep-HPLC (ACN/H₂O (0.5 % HCl)) to afford compound **7.2** (180 mg) in 62% yield. MS (ESI) m/z : 1093.9 [M]⁺.

Scheme 7

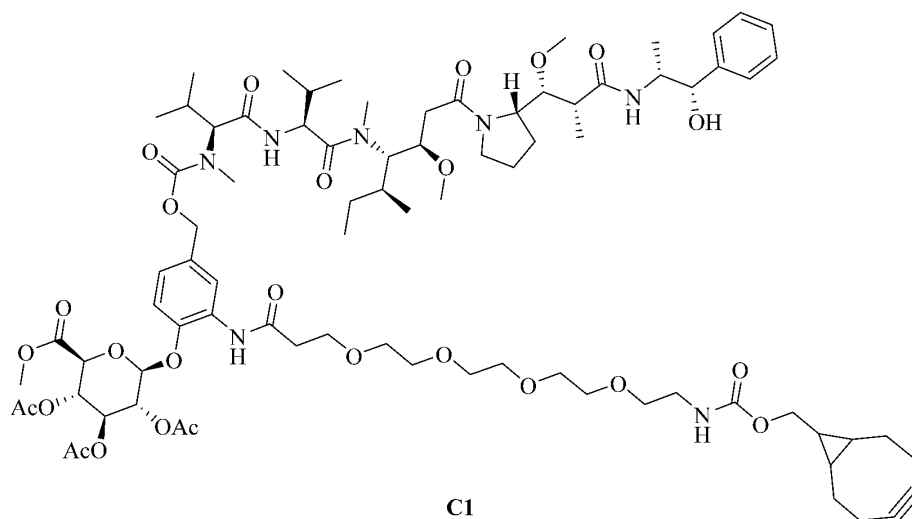


[00350] Preparation of compound **B3**. To a solution of compound **7.2** (180 mg, 0.164 mmol) in DMF (5 mL) was added compound **6.2** (173 mg, 0.246 mmol), PyBop (102 mg, 0.197 mmol), and DIEA (63.5 mg, 0.492 mmol). After stirring for 30 min, the reaction mixture was purified by reverse phase prep-HPLC (ACN/H₂O(10 mmol/L NH₄HCO₃)) to afford compound **B3** (30 mg) in 12% yield. ¹H NMR (400 MHz, CD₃OD) δ 7.82-7.23 (m, 17H), 5.12 (d, J = 14.0 Hz, 1H), 4.87-4.83 (m, 3H) 4.76-4.44 (m, 1H), 4.32-4.26 (m, 2H), 4.11-3.86 (m, 3H), 3.76-3.70 (m, 3H), 3.62 (d, J = 14.0 Hz, 1H), 3.59-3.40 (m, 21H), 3.33-3.10 (m, 15H), 2.86-2.65 (m, 3H), 2.60-2.56 (m, 3H), 2.44-2.02 (m, 7H), 1.95-1.78 (m, 8H), 1.58-1.25 (m, 6H), 1.18-1.08 (m, 6H), 1.03-0.87 (m, 24H); MS (ESI) m/z : 1780.3 [M]⁺.

Example 8

Preparation of (2*S*,3*S*,4*S*,5*R*,6*S*)-6-(2-(1-(bicyclo[6.1.0]non-4-yn-9-yl)-3-oxo-2,7,10,13,16-

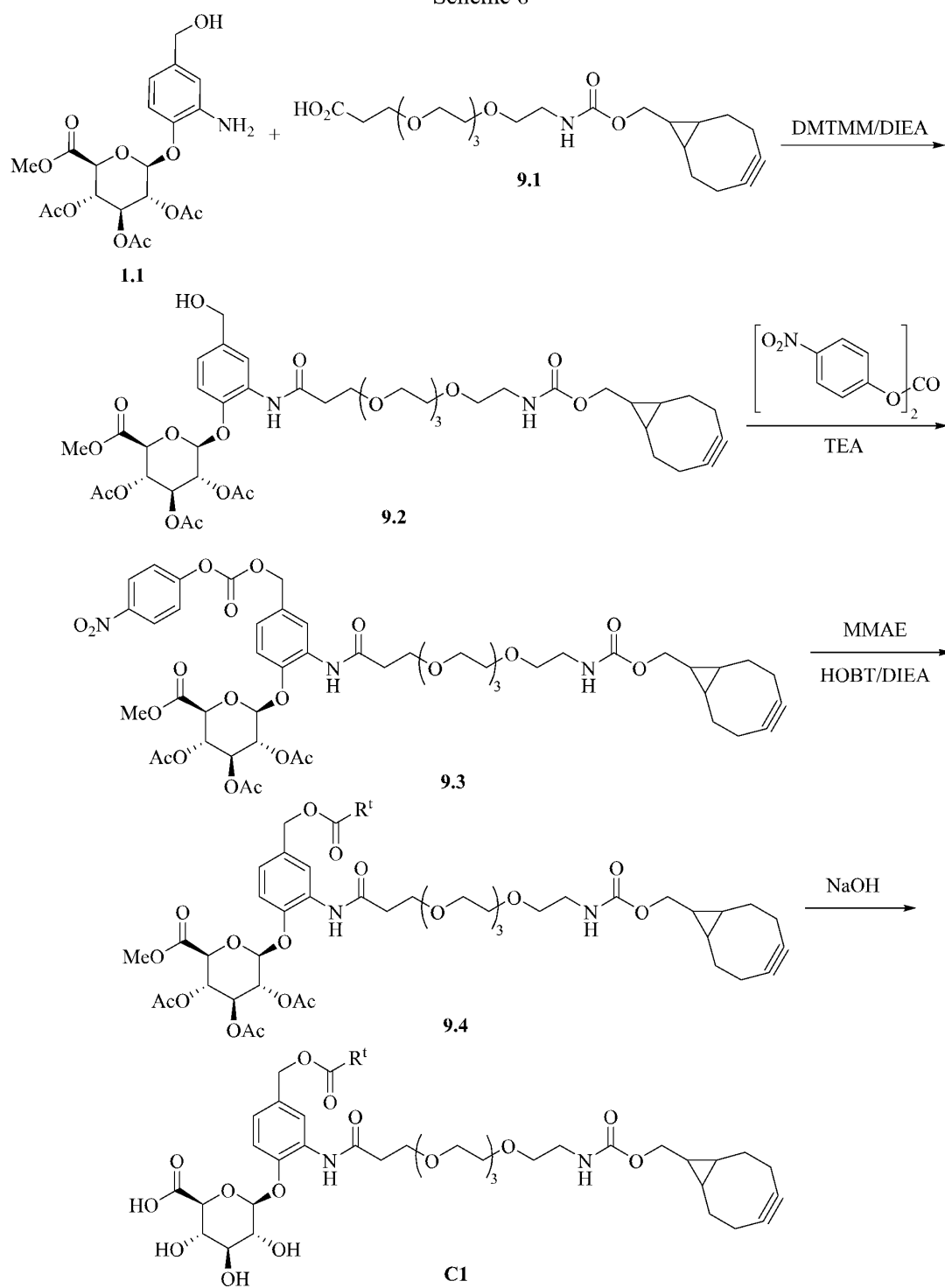
pentaoxa-4-azanonadecan-19-amido)-4-((5*S*,8*S*,11*S*,12*R*)-11-((*S*)-*sec*-butyl)-12-(2-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-2-oxoethyl)-5,8-diisopropyl-4,10-dimethyl-3,6,9-trioxo-2,13-dioxo-4,7,10-triazatetradecyl)phenoxy)-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid **C1**



[00351] Compound **C1** was prepared as shown in Scheme 8, wherein R¹ is ((*S*)-1-(((*S*)-1-(((3*R*,4*S*,5*S*)-1-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-3-methoxy-5-methyl-1-oxoheptan-4-yl)-(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)amino.

[00352] Preparation of (2*S*,3*R*,4*S*,5*S*,6*S*)-2-(2-(1-(bicyclo[6.1.0]non-4-yn-9-yl)-3-oxo-2,7,10,13,16-pentaoxa-4-azanonadecan-19-amido)-4-(hydroxymethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **9.2**. To a solution of methyl (2*S*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tris(acetyloxy)-6-[2-amino-4-(hydroxymethyl)phenoxy]oxane-2-carboxylate **1.1** (386 mg, 0.847 mmol) and 1-(bicyclo[6.1.0]non-4-yn-9-yl)-3-oxo-2,7,10,13,16-pentaoxa-4-azanonadecan-19-oic acid **9.1** (670 mg, 0.986 mmol, 65%) in dry DMF (10 mL) were added DIEA (410 mg, 3.18 mmol) and DMTMM (417 mg, 1.27 mmol). After stirring at 45 °C for 1 h, the reaction mixture was concentrated and purified by column chromatography (SiO₂, MeOH/DCM) to afford compound **9.2** (400 mg) in 46% yield. MS (ESI) *m/z*: 901.5 [M+Na]⁺.

Scheme 8



[00353] Preparation of (2*S*,3*R*,4*S*,5*S*,6*S*)-2-(2-(1-(bicyclo[6.1.0]non-4-yn-9-yl)-3-oxo-2,7,10,13,16-pentaoxa-4-azanonadecan-19-amido)-4-(((4-nitrophenoxy)carbonyloxy)methyl)-phenoxy)-6-(methoxycarbonyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **9.3**. To a mixture of compound **9.2** (300 mg, 0.341 mmol) in DCM (10 mL) were added TEA (83.3 mg, 0.823 mmol) and bis(4-nitrophenyl) carbonate (231 mg, 0.76 mmol). After stirring for 12 h under N₂, the reaction mixture was concentrated and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **9.3** (200 mg) in 56% yield. MS (ESI) *m/z*: 1044.4 [M+H]⁺.

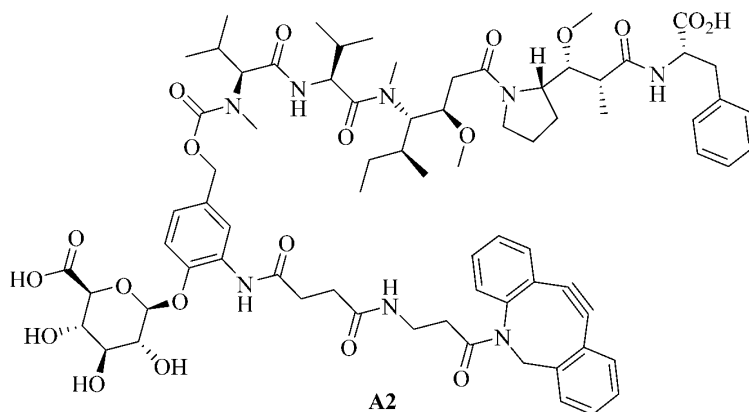
[00354] Preparation of (2*S*,3*R*,4*S*,5*S*,6*S*)-2-(2-(1-(bicyclo[6.1.0]non-4-yn-9-yl)-3-oxo-2,7,10,13,16-pentaoxa-4-azanonadecan-19-amido)-4-((5*S*,8*S*,11*S*,12*R*)-11-((*S*)-*sec*-butyl)-12-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-2-oxoethyl)-5,8-diisopropyl-4,10-dimethyl-3,6,9-trioxo-2,13-dioxo-4,7,10-triazatetradecyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **9.4**. To a solution of compound **9.3** (200 mg, 0.192 mmol) in DMF (3.0 mL) were added MMAE (138 mg, 0.192 mmol), HOBt (38.8 mg, 0.287 mmol), pyridine (75.8 mg, 0.958 mmol) and DIEA (124 mg, 0.958 mmol). After stirring for 15 h under N₂, the reaction mixture was purified by column chromatography (C18, ACN/H₂O) to afford compound **9.4** (140 mg) in 40% yield. MS (ESI) *m/z*: 1623.7 [M+H]⁺.

[00355] Preparation of (2*S*,3*S*,4*S*,5*R*,6*S*)-6-(2-(1-(bicyclo[6.1.0]non-4-yn-9-yl)-3-oxo-2,7,10,13,16-pentaoxa-4-azanonadecan-19-amido)-4-((5*S*,8*S*,11*S*,12*R*)-11-((*S*)-*sec*-butyl)-12-((*S*)-2-((1*R*,2*R*)-3-(((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino)-1-methoxy-2-methyl-3-oxopropyl)pyrrolidin-1-yl)-2-oxoethyl)-5,8-diisopropyl-4,10-dimethyl-3,6,9-trioxo-2,13-dioxo-4,7,10-triazatetradecyl)phenoxy)-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid **C1**. To a solution of compound **9.4** (140 mg, 86.3 μmol) in MeOH (1.5 mL) was added a solution of NaOH (34.5 mg, 0.863 mmol) in H₂O (1.5 mL). After stirring for 2 h, the reaction mixture was purified by reverse phase prep-HPLC to afford compound **C1** (36 mg) in 27% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.80 (s, 1H), 9.10 (s, 1H), 8.38-8.02 (m, 2H), 7.93-7.58 (m, 1H), 7.34-7.22 (m, 4H), 7.21-6.94 (m, 4H), 6.04-5.74 (m, 2H), 5.70-5.48 (m, 2H), 5.42-5.28 (m, 2H), 5.16-4.88 (m, 3H), 4.87-4.54 (m, 3H), 4.51-4.34 (m, 3H), 4.26 (t, *J* = 11.2 Hz, 2H), 4.08-3.56 (m, 36H), 3.56-3.42 (m, 17H), 3.40-3.28 (m, 6H), 3.27-3.5 (m, 8H), 3.14-3.07 (d, *J* = 6.1 Hz, 4H), 3.07-2.94 (m, 2H), 2.86 (t, *J* = 13.4 Hz, 3H), 2.74-2.56 (m, 3H), 2.41 (d, *J* = 15.8 Hz, 3H), 2.30-

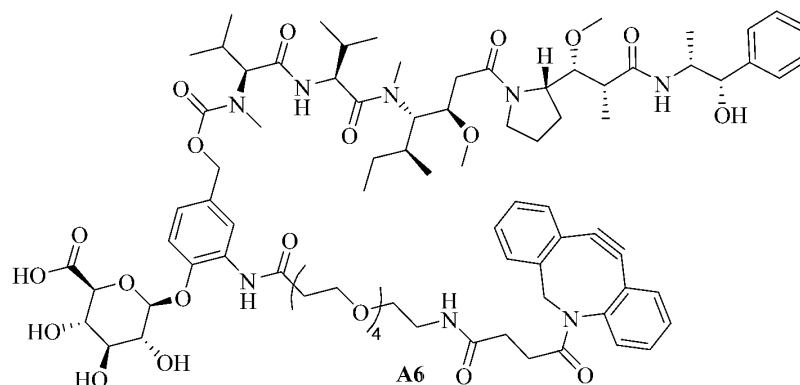
2.18 (m, 2H), 2.19-2.02 (m, 3H), 2.02-1.66 (m, 6H), 1.63-1.26 (m, 6H), 1.07-0.57 (m, 30H); MS (ESI) m/z : 1482.7 $[M+H]^+$.

[00356] The following compounds were prepared similarly according to the synthetic procedures or methodologies exemplified herein.

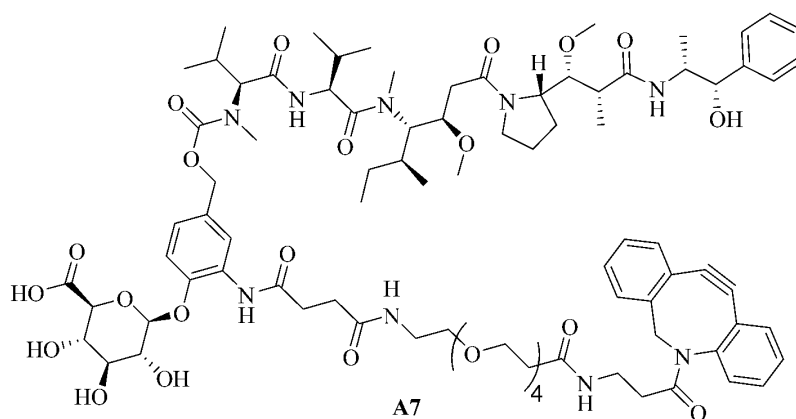
[00357] Compound **A2**. ^1H NMR (400 MHz, CD_3OD) δ 7.48-7.13 (m, 16H), 5.65 (d, J = 7.6 Hz, 1H), 5.42-5.33 (m, 1H), 5.25 (s, 2H), 5.12 (d, J = 14.0 Hz, 1H), 4.92-4.85 (m, 2H), 4.76 (d, J = 7.6 Hz, 1H), 4.65-4.44 (m, 3H), 3.91-3.86 (m, 1H), 3.70 (d, J = 7.6 Hz, 1H), 3.56 (d, J = 14.0 Hz, 1H), 3.43-3.31 (m, 4H), 3.25-3.12 (m, 13H), 2.97-2.93 (m, 4H), 2.64-2.58 (m, 1H), 2.43-2.29 (m, 5H), 2.21-1.78 (m, 3H), 1.72-1.30 (m, 8H), 1.22-1.09 (m, 3H), 1.09-0.87 (m, 18H); MS (ESI) m/z : 1432.5 $[M+H]^+$.



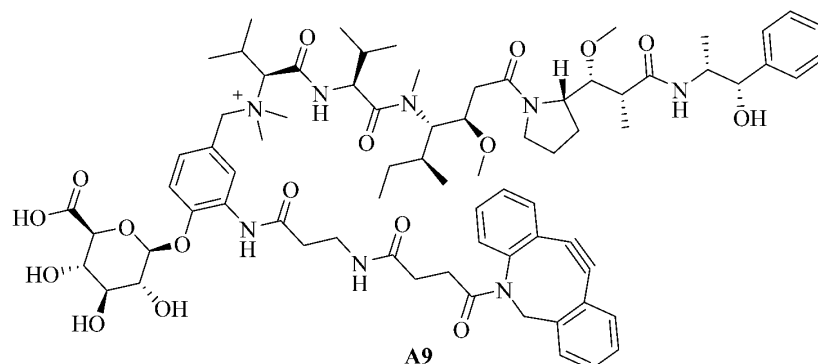
[00358] Compound **A6**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.12 (s, 1H), 8.34 (br, 1H), 8.05 (s, 1H), 7.87 (br, 1H), 7.77-6.95 (m, 16H), 5.77 (d, J = 7.6 Hz, 1H), 5.42-5.39 (m, 2H), 5.05 (s, 2H), 5.01 (d, J = 14.0 Hz, 1H), 4.86-4.83 (m, 2H), 4.72 (d, J = 7.6 Hz, 1H), 4.50-4.13 (m, 3H), 4.05-3.97 (m, 2H), 3.79 (d, J = 7.6 Hz, 1H), 3.71-3.68 (m, 4H), 3.62 (d, J = 14.0 Hz, 1H), 3.59-3.32 (m, 16H), 3.29-3.12 (m, 12H), 3.09-2.83 (m, 3H), 2.62-2.51 (m, 1H), 2.43-2.22 (m, 5H), 2.12-1.88 (m, 3H), 1.80-1.58 (m, 4H), 1.53-1.22 (m, 4H), 1.06-0.96 (m, 6H), 0.86-0.75 (m, 18H); MS (ESI) m/z : 1592.6 $[M+H]^+$.



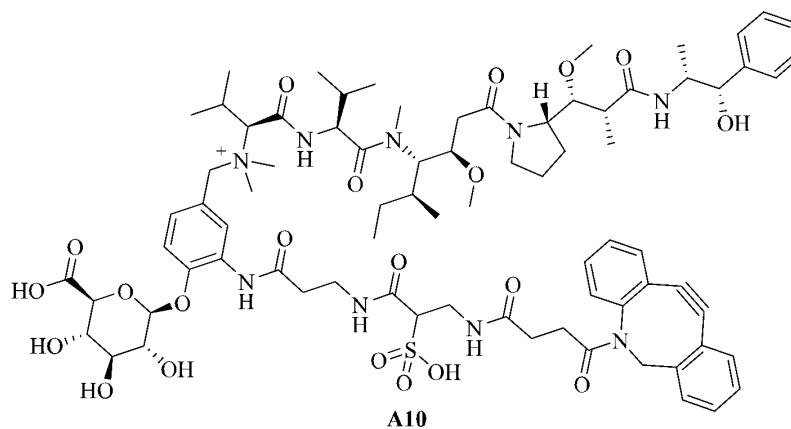
[00359] Compound **A7**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.27 (s, 1H), 8.89 (s, 1H), 8.30 (br, 1H), 8.02 (s, 1H), 7.91 (br, 1H), 7.69-7.00 (m, 16H), 5.72 (d, $J = 7.6$ Hz, 1H), 5.47-5.40 (m, 2H), 5.07 (s, 2H), 5.02 (d, $J = 14.0$ Hz, 1H), 4.92-4.83 (m, 2H), 4.71 (d, $J = 7.6$ Hz, 1H), 4.59-4.18 (m, 3H), 4.01-3.89 (m, 2H), 3.79 (d, $J = 7.6$ Hz, 1H), 3.71-3.68 (m, 4H), 3.65 (d, $J = 14.0$ Hz, 1H), 3.59-3.28 (m, 20H), 3.21-2.84 (m, 15H), 2.64-2.52 (m, 1H), 2.41-2.11 (m, 8H), 2.01-1.62 (m, 4H), 1.51-1.26 (m, 4H), 1.05-0.97 (m, 6H), 0.84-0.78 (m, 18H); MS (ESI) m/z : 1663.6 $[\text{M}-\text{H}]^-$.



[00360] Compound **A9**. ^1H NMR (400 MHz, CD_3OD) δ 7.62-7.22 (m, 16H), 5.63 (d, $J = 7.6$ Hz, 1H), 5.49-5.38 (m, 2H), 5.07 (s, 2H), 5.01 (d, $J = 14.0$ Hz, 1H), 4.88-4.83 (m, 2H), 4.75 (d, $J = 7.6$ Hz, 1H), 4.62-4.17 (m, 2H), 4.07-3.86 (m, 2H), 3.71 (d, $J = 7.6$ Hz, 1H), 3.66 (d, $J = 14.0$ Hz, 1H), 3.59-3.35 (m, 10H), 3.31-3.11 (m, 9H), 2.80-2.70 (m, 2H), 2.66-2.56 (m, 2H), 2.48-2.33 (m, 5H), 2.17-1.88 (m, 3H), 1.33-1.13 (m, 8H), 1.02-0.95 (m, 6H), 0.92-0.67 (m, 18H); MS (ESI) m/z : 1387.6 $[\text{M}]^+$.

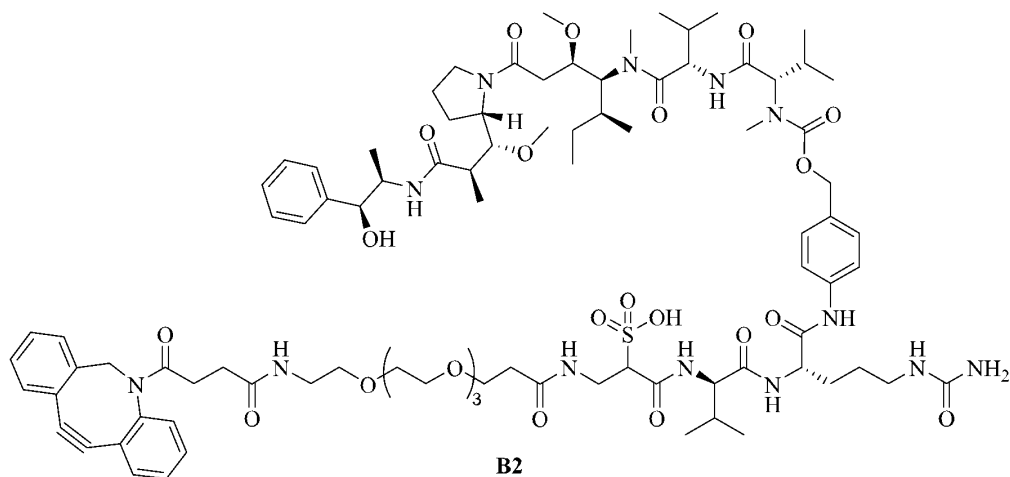


[00361] Compound **A10**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.30 (s, 1H), 8.93 (s, 1H), 8.34 (br, 1H), 8.11 (s, 1H), 7.91 (br, 1H), 7.78-7.12 (m, 16H), 6.66-6.53 (m, 1H), 5.63 (d, $J = 7.6$ Hz, 1H) 5.43-5.32 (m, 2H), 5.04 (s, 2H), 5.02 (d, $J = 14.0$ Hz, 1H), 4.91-4.80 (m, 2H), 4.75 (d, $J = 7.6$ Hz, 1H), 4.64-4.43 (m, 3H), 4.03-3.92 (m, 2H), 3.78 (d, $J = 7.6$ Hz, 1H), 3.61 (d, $J = 14.0$ Hz, 1H), 3.58-3.41 (m, 6H), 3.25-3.12 (m, 15H), 3.02-2.82 (m, 3H), 2.65-2.59 (m, 1H), 2.43-2.21 (m, 5H), 2.12-1.55 (m, 7H), 1.45-1.24 (m, 4H), 1.11-0.94 (m, 6H), 0.87-0.78 (m, 18H); MS (ESI) m/z : 1537.3 $[\text{M-H}]^-$.

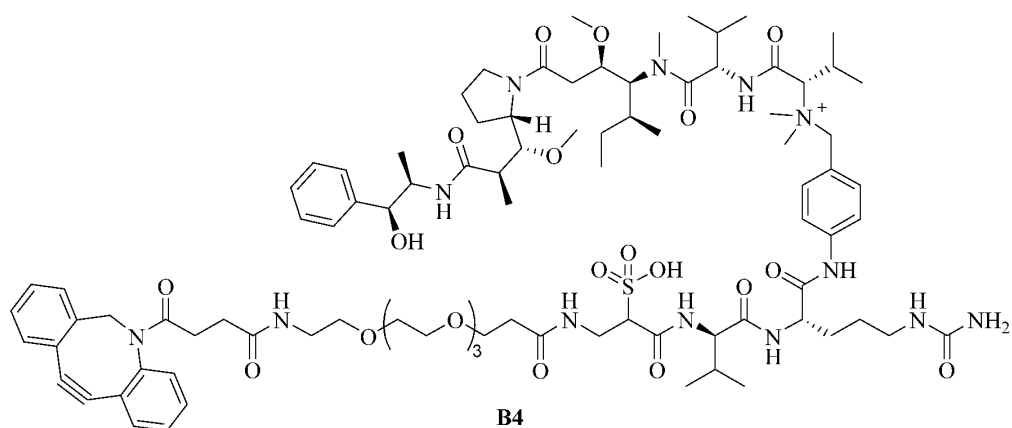


[00362] Compound **B2**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.62 (s, 1H), 8.90 (br, 1H), 8.48 (br, 1H), 8.39 (s, 1H), 8.17 (br, 1H), 8.05 (s, 1H), 7.82 (br, 1H), 7.76-7.08 (m, 17H), 6.03 (t, $J = 5.6$ Hz, 1H), 5.40 (br, 2H), 5.33 (d, $J = 4.8$ Hz, 1H), 5.08-5.03 (m, 2H), 5.02 (d, $J = 14.0$ Hz, 1H), 4.75-4.40 (m, 2H), 4.29-4.27 (m, 2H), 4.04-3.96 (m, 3H), 3.74-3.69 (m, 3H), 3.62 (d, $J = 14.0$ Hz, 1H), 3.59-3.53 (m, 3H), 3.50-3.45 (m, 18H), 3.29-3.05 (m, 12H), 2.97-2.84 (m, 3H),

2.59-2.50 (m, 3H), 2.39-1.98 (m, 7H), 1.91-1.86 (m, 8H), 1.57-1.28 (m, 6H), 1.13-0.98 (m, 6H), 0.86-0.77 (m, 24H); MS (ESI) m/z : 904.9 $[1/2M+H]^+$.

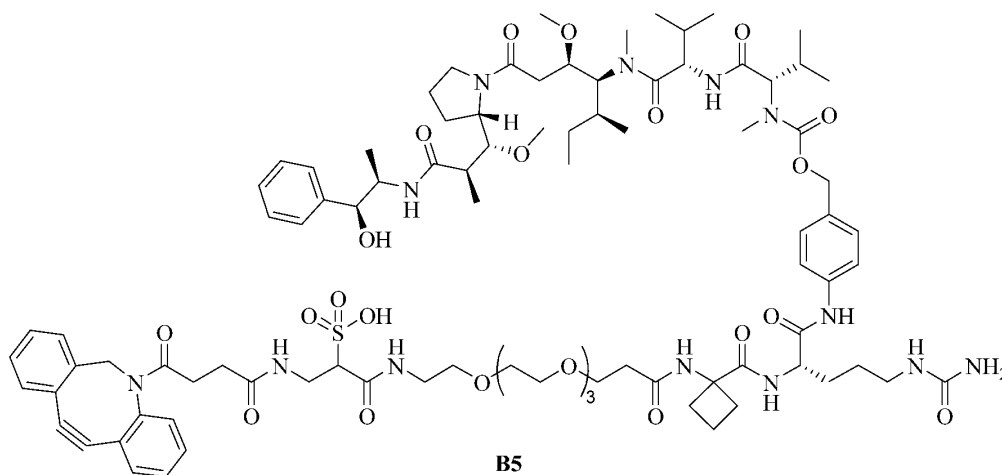


[00363] Compound **B4**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.72 (s, 1H), 9.13 (s, 1H), 8.87 (br, 1H), 8.55 (br, 1H), 8.20 (s, 1H), 7.92 (br, 1H), 7.89 (br, 1H), 7.85-7.17 (m, 17H), 6.05 (t, J = 5.6 Hz, 1H), 5.46 (br, 2H), 5.30 (d, J = 4.8 Hz, 1H), 5.09-5.05 (m, 2H), 5.01 (d, J = 14.0 Hz, 1H), 4.70-4.39 (m, 2H), 4.31-4.26 (m, 2H), 4.04-3.87 (m, 3H), 3.81-3.69 (m, 3H), 3.64 (d, J = 14.0 Hz, 1H), 3.56-3.51 (m, 3H), 3.50-3.43 (m, 18H), 3.30-3.08 (m, 15H), 2.99-2.76 (m, 3H), 2.60-2.53 (m, 3H), 2.47-1.95 (m, 7H), 1.91-1.86 (m, 8H), 1.57-1.28 (m, 6H), 1.09-1.01 (m, 6H), 0.96-0.79 (m, 24H); MS (ESI) m/z : 1780.4 $[M]^+$.

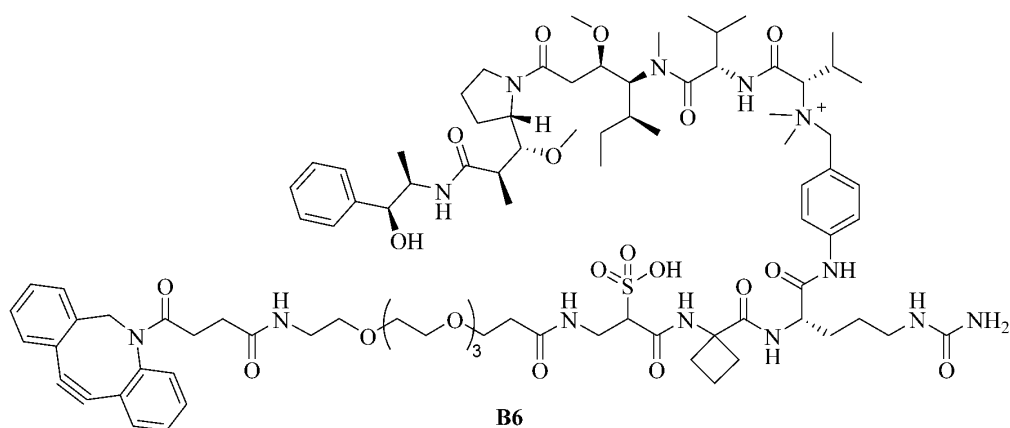


[00364] Compound **B5**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.68 (s, 1H), 8.89 (br, 1H), 8.78 (s, 1H), 7.88 (s, 1H), 7.86 (br, 1H), 7.75 (br, 1H), 7.69 (br, 1H), 7.67-7.26 (m, 17H), 6.01 (t,

$J = 5.6$ Hz, 1H), 5.48 (br, 2H), 5.31 (d, $J = 4.8$ Hz, 1H), 5.07-5.04 (m, 2H), 5.02 (d, $J = 14.0$ Hz, 1H), 4.79-4.37 (m, 2H), 4.29-4.27 (m, 1H), 4.01-3.96 (m, 3H), 3.80-3.69 (m, 3H), 3.62 (d, $J = 14.0$ Hz, 1H), 3.58-3.53 (m, 3H), 3.50-3.43 (m, 18H), 3.26-3.07 (m, 15H), 2.95-2.76 (m, 3H), 2.55-2.48 (m, 3H), 2.39-1.95 (m, 10H), 1.91-1.66 (m, 10H), 1.57-1.28 (m, 6H), 1.08-0.97 (m, 6H), 0.93-0.78 (m, 18H); MS (ESI) m/z : 1780.3 $[M+H]^+$.



[00365] Compound **B6**. ^1H NMR (400 MHz, DMSO- d_6) δ 9.52 (s, 1H), 8.98 (br, 1H), 8.79 (s, 1H), 8.39 (br, 1H), 8.11 (br, 1H), 7.92 (br, 1H), 7.88 (br, 1H), 7.81-7.26 (m, 17H), 6.02 (t, $J = 5.6$ Hz, 1H), 5.49 (br, 2H), 5.30 (d, $J = 4.8$ Hz, 1H), 5.09-5.04 (m, 2H), 5.02 (d, $J = 14.0$ Hz, 1H), 4.69-4.39 (m, 2H), 4.33-4.28 (m, 1H), 4.03-3.97 (m, 3H), 3.80-3.68 (m, 3H), 3.63 (d, $J = 14.0$ Hz, 1H), 3.58-3.45 (m, 21H), 3.32-3.01 (m, 15H), 2.97-2.74 (m, 3H), 2.53-2.49 (m, 3H), 2.32-1.98 (m, 10H), 1.93-1.64 (m, 10H), 1.59-1.38 (m, 6H), 1.19-0.98 (m, 6H), 0.96-0.78 (m, 18H); MS (ESI) m/z : 1778.3 $[M]^+$.



Example B1

In Vitro Cytotoxicity Determination

[00366] The cytotoxicity of a functionalized auristatin provided herein was evaluated using an MTT assay. A375, MDA-MB-231, OVCAR3, SKOV3, and SKOV3R (platinum-resistant SKOV3) cells were seeded in a 96-well plate at 1,000-5,000 cells/well in an FBS-containing DMEM medium (100 μ L). After the cells were incubated overnight at 37 °C under 5% CO₂, the functionalized auristatin (10 μ L) at predetermined concentrations in DMSO was added in the absence or presence of β -glucuronidase (Glu) (25 U). PBS was used as a negative control. After the cells were incubated at 37 °C under 5% CO₂ for 48 h, an MTT solution (20 μ L) at 5 mg/mL was added to each well and the plate was incubated at 37 °C for 3 h. The medium in each well was removed and DMSO (100 μ L) was added to each well. The absorption was measured at 570 nm using a microplate reader. The IC₅₀ values determined are summarized in Tables 1 and 2.

TABLE 1. Cytotoxicity (IC₅₀) of Functionalized Auristatin A1

Cells	Compound A1		MMAE
	-Glu	+Glu	
MDA-MB-231 (Breast cancer)	1.6 nM	0.45 nM	0.0086 nM
A375 (Melanoma)	29 nM	0.49 nM	0.018 nM
SKOV3 (Ovarian cancer)	11 nM	0.24 nM	0.010 nM
SKOV3R (Platinum-resistant ovarian cancer)	5.8 nM	3.5 nM	0.19 nM
OVCAR3 (Ovarian cancer)	1272 nM	0.78 nM	0.028 nM

TABLE 2. Cytotoxicity (IC₅₀) of Functionalized Auristatin A9

Cells	Compound A9		MMAE
	-Glu	+Glu	
OVCAR3 (Ovarian cancer)	75 nM	2.9 nM	0.74 nM

Example B2

Click Reaction Kinetic Study

[00367] A functionalized auristatin provided herein was evaluated using *N*-(azidoacetyl)- α -neuraminic acid (N₃-SA) for its click reaction kinetics. A mixture of a PBS solution of N₃-SA (1 mM, 100 μ L), a PBS solution of a functionalized auristatin provided herein (10 μ L) at 1 mM, and PBS (890 μ L) was incubated at 37 °C. The functionalized auristatin at different time points was quantified by HPLC using UV absorption at 254 nm. A reaction kinetic constant for the functionalized auristatin was calculated by fitting to a pseudo first order kinetic equation. The reaction kinetic constants determined are summarized in Table 3.

TABLE 3. Click Reaction Kinetic Constants of Functionalized Auristatins

Compound	A1	A2	A4	A5	A6	A7	A8	A9	A10	B1	B2	B3	B4	B5	B6
<i>k</i> (M ⁻¹ s ⁻¹)	1.05	0.93	0.98	1.03	1.02	1.06	1.42	1.23	1.35	1.05	1.02	1.43	1.38	1.23	1.18

Example B3

Plasma Stability Determination

[00368] A functionalized auristatin provided herein was dissolved in DMSO as a stock solution (1 mg/mL). An ACN solution of the functionalized auristatin was prepared by a 10-fold dilution of the stock solution with ACN. The ACN solution (10 μ L) at 100 μ g/mL was added to mouse or human plasma (90 μ L). The final concentration of the functionalized auristatin is 10 μ g/mL. The plasma mixture was incubated at 37 °C. After 0, 0.5, 1, and 4 h, an aliquot was removed and mixed with 9 volumes of ACN. The resulting suspension was centrifuged at 15,000 rpm for 5 min and the supernatant was mixed with one volume of 0.1% FA water and quantified by LC-MS/MS. The results are summarized in Table 4.

TABLE 4. Stability of Functionalized Auristatins in Mouse or Human Plasma

Compound	Remaining (%)			
	Mouse		Human	
	1 h	4 h	1 h	4 h
A1	90	84	99	96
A2	92	87	101	93
A3	100	90	99	91
A4	106	86	100	91
A5	92	89	95	90
A6	97	88	96	92
A7	98	91	102	92
A8	94	76	91	87
A9	96	81	101	93
A10	93	70	99	93
B1	97	86	99	88
B2	94	81	94	85
B3	93	82	98	92
B4	96	84	104	100
B5	92	83	93	91
B6	98	85	98	93

Example B4
Pharmacokinetic Study

[00369] The pharmacokinetic parameters of a functionalized auristatin provided herein were determined in pCD-1 mice. The mice were injected with the functionalized auristatin *via* tail vein at a specified dose. Blood samples were collected in EDTA precoated tubes from the facial vein at 0, 5, 15, 30 min, and 1, 2, 4, 8, and 24 h post-dose. Plasma from each blood sample was separated by centrifugation at 1,500 g for 10 min at 4 °C within 1 h of sample collection. The plasma was diluted with 9 volumes of ACN. A supernatant was collected by centrifugation, diluted with one volume of 0.1% FA water, and quantified by LC-MS/MS for the functionalized auristatin and its corresponding free toxin. The PK parameters were calculated using a two-compartment model. The results are summarized in Tables 5 and 6.

TABLE 5. Pharmacokinetic of Functionalized Auristatins Parameters in Mice

Compound	A1	A3	A6	A7	A8
Dose (mg/kg)	10	10	10	10	10
C _{max} ng/mL	24,549	25,381	2,869	80,906	38,929
k/h ⁻¹	1.7	1.8	9.2	5.7	0.2
t _{1/2} /h	0.40	0.38	0.08	0.12	2.9
CL/L*kg ⁻¹ *h ⁻¹	629	705	11,123	336	91
Vd/L*kg ⁻¹	365	324	1,215	37	378
AUC ng/mL*h	61,989 ± 2,242	14,190 ± 375	899 ± 45	29,763 ± 1,143	110,446 ± 10,982
AUC ng/mL*h (free toxin)	367 ± 200	2,075 ± 417	2,259 ± 122	338 ± 44	361 ± 29

TABLE 6. Pharmacokinetic Parameters of Functionalized Auristatins in Mice

Compound	A9	A10	B1	B2	B3	B4
Dose (mg/kg)	10	10	2	2	2	2
C _{max} ng/mL	57,512	33,512	2,446	10,516	10,703	4,815
k/h ⁻¹	0.2	0.2	5.6	1.2	0.3	0.3
t _{1/2} /h	3.4	3.1	0.12	0.58	2.6	2.6
CL/L*kg ⁻¹ *h ⁻¹	46	121	981	87	88	190
Vd/L*kg ⁻¹	221	531	176	72	327	720
AUC ng/mL*h	35,3978 ± 62,117	82,922 ± 14,991	1,605 ± 1,068	23,116 ± 3,927	22,699 ± 2,068	10,530 ± 1,310
AUC ng/mL*h (free toxin)	2,604 ± 1,983	514 ± 92	1,958 ± 237	144 ± 29	448 ± 42	187 ± 23

Example B5

MTD Determination

[00370] The acute toxicity of a functionalized auristatin provided herein was evaluated in CD-1 mice by monitoring body weight loss and clinical observations over 14 days following a single dose i.v. injection *via* tail vein. Maximum tolerated dose (MTD) is defined as the highest dose at which no animals died or were required to be sacrificed due to >20% body weight loss or signs of distress or morbidity (*e.g.*, hunching, lack of movement, inability to eat or drink, or signs of pain/distress). The results are summarized in Table 7.

TABLE 7. Maximum Tolerable Doses (MTD) of Functionalized Auristatins

Compound	A1	A2	A3	A5	A6	A7	A8	A9	A10	B1	B2	B3	B4
MTD (mg/kg)	20	25	15	15	>20	20	>20	10	>20	1.5	5	15	20

Example B6

Anticancer Effect of Functionalized Auristatins in Xenograft Mouse Models

[00371] Tumors were established in 6-8 week-old female BALB/c nude mice by

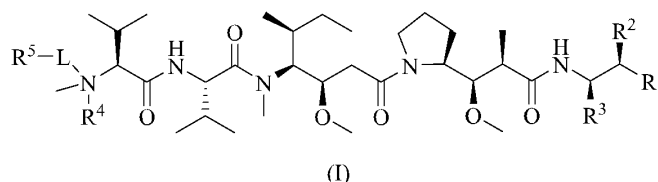
subcutaneous injection of OVCR3, SKOV3, or A2780 cells ($1-10 \times 10^6$ cells) into a flank. When the tumors reached $\sim 100-400 \text{ mm}^3$, the mice were randomly grouped in 6 or 8 mice per group and treated with a functionalized auristatin provided herein. The tumor volumes and body weights of mice were measured and the tumor volumes were calculated using the formula $(\text{length}) \times (\text{width})^2 / 2$, where the long axis diameter was regarded as the length and the short axis diameter was regarded as the width. The statistical analysis was performed by paired student t test. The results were deemed significant at $0.01 < *P \leq 0.05$, highly significant at $0.001 < **P \leq 0.01$, and extremely significant at $***P \leq 0.001$. The results are shown in FIGS. 1 to 8.

* * * * *

[00372] The examples set forth above are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed embodiments and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference.

What is claimed is:

1. A compound of Formula (I):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

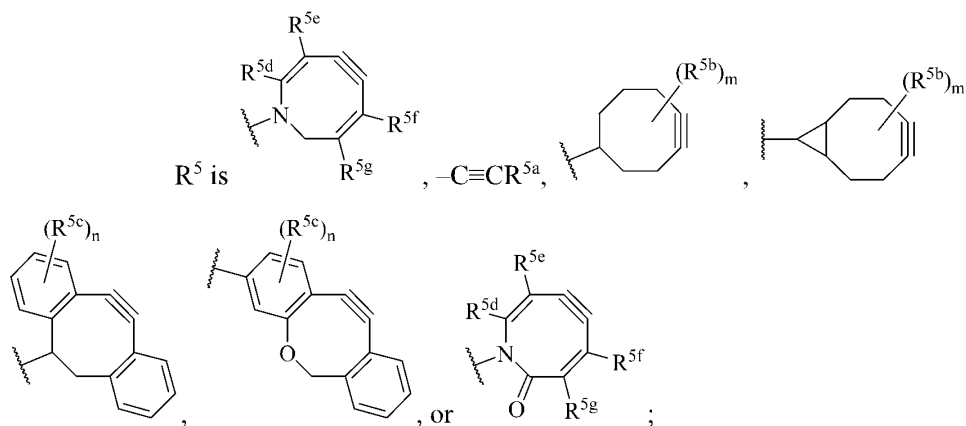
L is a self-immolative linker;

R¹ is C₆₋₁₄ aryl or heteroaryl;

R² is -OR^{1a} or hydrogen;

R³ is (i) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, or heteroaryl; (ii) hydrogen; or (iii) -C(O)OR^{1a};

R⁴ is (i) absent; or (ii) C₁₋₆ alkyl or C₁₋₆ heteroalkyl, and the N atom to which R⁴ is attached is positively charged;



R^{5a} is hydrogen or deuterium;

each R^{5b} and R^{5c} is independently (i) deuterium, cyano, halo, or nitro; (ii) C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (iii) -C(O)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1b}R^{1c}, -C(O)SR^{1a}, -C(NR^{1a})NR^{1b}R^{1c}, -C(S)R^{1a}, -C(S)OR^{1a}, -C(S)NR^{1b}R^{1c}, -OR^{1a}, -OC(O)R^{1a}, -OC(O)OR^{1a},

$-\text{OC}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OC}(\text{O})\text{SR}^{1a}$, $-\text{OC}(\text{NR}^{1a})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OC}(\text{S})\text{R}^{1a}$, $-\text{OC}(\text{S})\text{OR}^{1a}$, $-\text{OC}(\text{S})\text{NR}^{1b}\text{R}^{1c}$,
 $-\text{OS}(\text{O})\text{R}^{1a}$, $-\text{OS}(\text{O})_2\text{R}^{1a}$, $-\text{OS}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{R}^{1d}$,
 $-\text{NR}^{1a}\text{C}(\text{O})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{SR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{NR}^{1d})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{R}^{1d}$,
 $-\text{NR}^{1a}\text{C}(\text{S})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$,
 $-\text{NR}^{1a}\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{SR}^{1a}$, $-\text{S}(\text{O})\text{R}^{1a}$, $-\text{S}(\text{O})_2\text{R}^{1a}$, $-\text{S}(\text{O})_2\text{OR}^{1a}$, $-\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, or
 $-\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$;

each pair of R^{5d} and R^{5e} together with the carbon atoms to which they are attached independently forms C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene;

each pair of R^{5f} and R^{5g} together with the carbon atoms to which they are attached independently forms C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene;

each R^{1a} , R^{1b} , R^{1c} , and R^{1d} is independently hydrogen, deuterium, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and

each m and n is independently an integer of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q , wherein each Q is independently selected from: (a) deuterium, cyano, halo, nitro, and oxo; (b) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a ; and (c) $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^{bR^c}$, $-\text{C}(\text{O})\text{SR}^a$, $-\text{C}(\text{NR}^a)\text{NR}^{bR^c}$, $-\text{C}(\text{S})\text{R}^a$, $-\text{C}(\text{S})\text{OR}^a$, $-\text{C}(\text{S})\text{NR}^{bR^c}$, $-\text{OR}^a$, $-\text{OC}(\text{O})\text{R}^a$, $-\text{OC}(\text{O})\text{OR}^a$, $-\text{OC}(\text{O})\text{NR}^{bR^c}$, $-\text{OC}(\text{O})\text{SR}^a$, $-\text{OC}(\text{NR}^a)\text{NR}^{bR^c}$, $-\text{OC}(\text{S})\text{R}^a$, $-\text{OC}(\text{S})\text{OR}^a$, $-\text{OC}(\text{S})\text{NR}^{bR^c}$, $-\text{OP}(\text{O})(\text{OR}^b)\text{OR}^c$, $-\text{OS}(\text{O})\text{R}^a$, $-\text{OS}(\text{O})_2\text{R}^a$, $-\text{OS}(\text{O})\text{NR}^{bR^c}$, $-\text{OS}(\text{O})_2\text{NR}^{bR^c}$, $-\text{NR}^{bR^c}$, $-\text{NR}^a\text{C}(\text{O})\text{R}^d$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^d$, $-\text{NR}^a\text{C}(\text{O})\text{NR}^{bR^c}$, $-\text{NR}^a\text{C}(\text{O})\text{SR}^d$, $-\text{NR}^a\text{C}(\text{NR}^d)\text{NR}^{bR^c}$, $-\text{NR}^a\text{C}(\text{S})\text{R}^d$, $-\text{NR}^a\text{C}(\text{S})\text{OR}^d$, $-\text{NR}^a\text{C}(\text{S})\text{NR}^{bR^c}$, $-\text{NR}^a\text{S}(\text{O})\text{R}^d$, $-\text{NR}^a\text{S}(\text{O})_2\text{R}^d$, $-\text{NR}^a\text{S}(\text{O})\text{NR}^{bR^c}$, $-\text{NR}^a\text{S}(\text{O})_2\text{NR}^{bR^c}$, $-\text{SR}^a$, $-\text{S}(\text{O})\text{R}^a$, $-\text{S}(\text{O})_2\text{R}^a$, $-\text{S}(\text{O})_2\text{OR}^a$, $-\text{S}(\text{O})\text{NR}^{bR^c}$, and $-\text{S}(\text{O})_2\text{NR}^{bR^c}$, wherein each R^a , R^b , R^c , and R^d is independently (i) hydrogen or deuterium; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a ; or (iii) R^b and R^c together with the N atom to which they are

attached form heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a ;

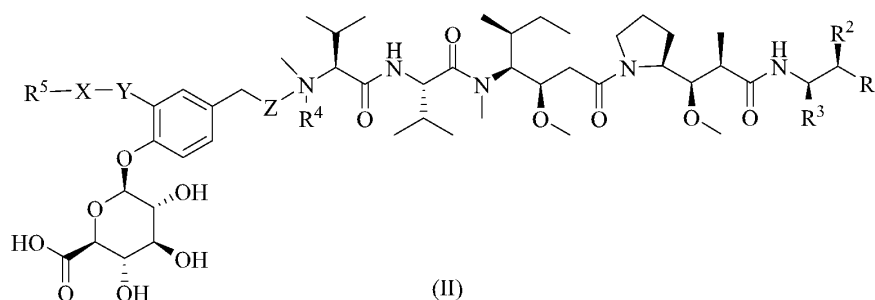
wherein each Q^a is independently selected from: (a) deuterium, cyano, halo, nitro, and oxo; (b) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^fR^g$, $-C(O)SR^e$, $-C(NR^e)NR^fR^g$, $-C(S)R^e$, $-C(S)OR^e$, $-C(S)NR^fR^g$, $-OR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)NR^fR^g$, $-OC(O)SR^e$, $-OC(NR^e)NR^fR^g$, $-OC(S)R^e$, $-OC(S)OR^e$, $-OC(S)NR^fR^g$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^fR^g$, $-OS(O)_2NR^fR^g$, $-NR^eR^g$, $-NR^eC(O)R^h$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^fR^g$, $-NR^eC(O)SR^f$, $-NR^eC(NR^h)NR^fR^g$, $-NR^eC(S)R^h$, $-NR^eC(S)OR^f$, $-NR^eC(S)NR^fR^g$, $-NR^eS(O)R^h$, $-NR^eS(O)_2R^h$, $-NR^eS(O)NR^fR^g$, $-NR^eS(O)_2NR^fR^g$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)_2OR^e$, $-S(O)NR^fR^g$, and $-S(O)_2NR^fR^g$; wherein each R^e , R^f , R^g , and R^h is independently (i) hydrogen or deuterium; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl.

2. The compound of claim 1, wherein L is a self-immolative linker cleavable by a glucuronidase.

3. The compound of claim 1, wherein L is a self-immolative linker cleavable by a galactosidase.

4. The compound of claim 1, wherein L is a self-immolative linker cleavable by a cathepsin.

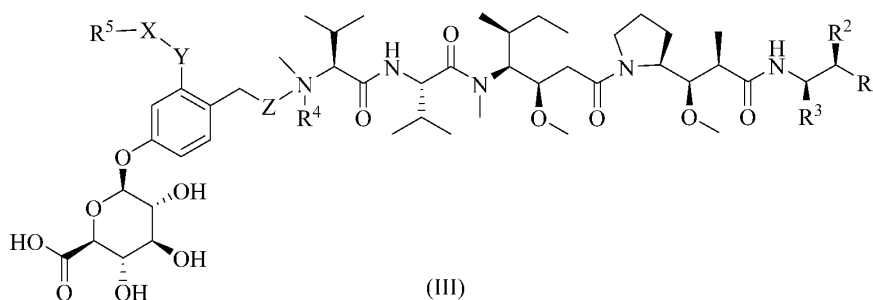
5. The compound of claim 1 or 2, having the structure of Formula (II):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more

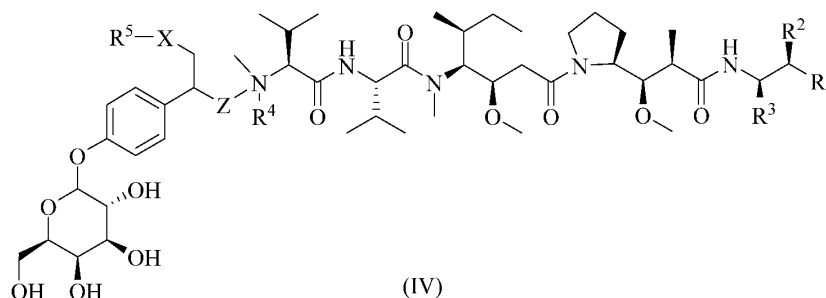
diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein X is a divalent linker; Y is a bond, $-O-$, or $-N(R^{1b})-$; Z is a bond or $-OC(O)-$.

6. The compound of claim 1 or 2, having the structure of Formula (III):



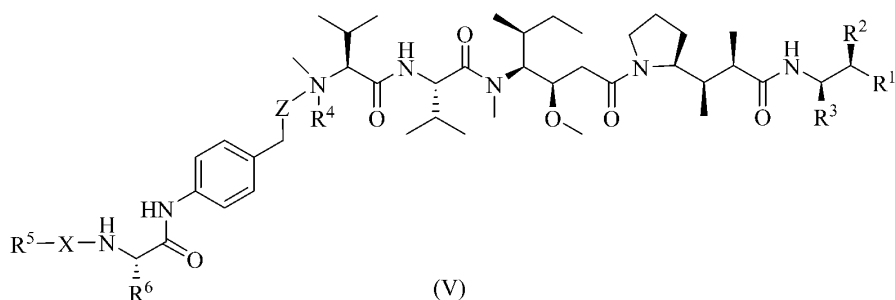
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein X is a divalent linker; Y is a bond, $-O-$, or $-N(R^{1b})-$; Z is a bond or $-OC(O)-$.

7. The compound of claim 1 or 3, having the structure of Formula (IV):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein X is a divalent linker; and Z is a bond or $-OC(O)-$.

8. The compound of claim 1 or 4, having the structure of Formula (V):



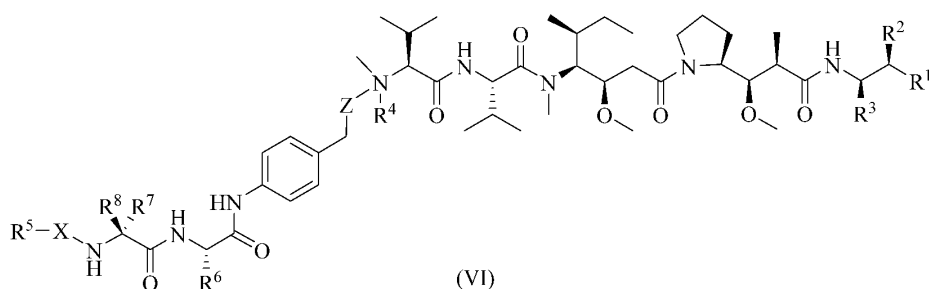
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

R^6 is (i) hydrogen or deuterium; or (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents Q;

X is a divalent linker; and

Z is a bond or $-OC(O)-$.

9. The compound of claim 1 or 4, having the structure of Formula (VI):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

R^6 is (i) hydrogen or deuterium; or (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents Q;

R^7 and R^8 are each independently (i) hydrogen or deuterium; or (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents Q; or R^7 and R^8 together

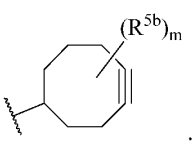
with the carbon atom to which they are attached form C₃₋₁₀ cycloalkylene or heterocyclylene, each optionally substituted with one or more substituents Q;

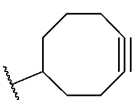
X is a divalent linker; and

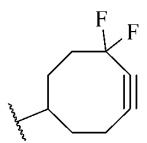
Z is a bond or $-\text{OC}(\text{O})-$.

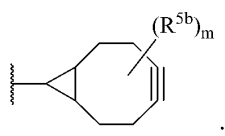
10. The compound of any one of claims 1 to 9, wherein R⁵ is $-\text{C}\equiv\text{CR}^{5a}$.

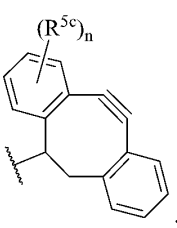
11. The compound of any one of claims 1 to 10, wherein R⁵ is ethynyl.

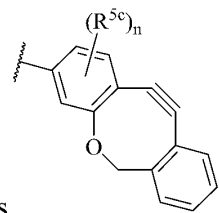
12. The compound of any one of claims 1 to 9, wherein R⁵ is .

13. The compound of any one of claims 1 to 9 and 12, wherein R⁵ is  or

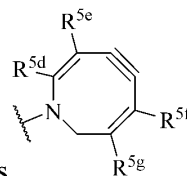


14. The compound of any one of claims 1 to 9, wherein R⁵ is .

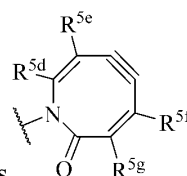
15. The compound of any one of claims 1 to 9, wherein R⁵ is .



16. The compound of any one of claims 1 to 9, wherein R⁵ is



17. The compound of any one of claims 1 to 9, wherein R⁵ is



18. The compound of any one of claims 1 to 9, wherein R⁵ is

19. The compound of claim 17 or 18, wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form C₆₋₁₄ arylene, optionally substituted with one or more substituents Q.

20. The compound of claim 17 or 18, wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form phenylene, optionally substituted with one or more substituents Q.

21. The compound of claim 17 or 18, wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form heteroarylene, optionally substituted with one or more substituents Q.

22. The compound of claim 17 or 18, wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form monocyclic heteroarylene, optionally substituted with one or more substituents Q.

23. The compound of claim 17 or 18, wherein R^{5d} and R^{5e} together with the carbon atoms to which they are attached form 5- or 6-membered heteroarylene, each optionally

substituted with one or more substituents Q.

24. The compound of any one of claims 17 to 23, wherein R^{5f} and R^{5g} together with the carbon atoms to which they are attached form C₆₋₁₄ arylene, optionally substituted with one or more substituents Q.

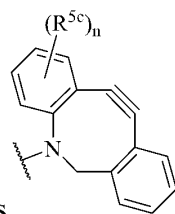
25. The compound of any one of claims 17 to 23, wherein R^{5f} and R^{5g} together with the carbon atoms to which they are attached form phenylene, optionally substituted with one or more substituents Q.

26. The compound of any one of claims 17 to 23, wherein R^{5f} and R^{5g} together with the carbon atoms to which they are attached form heteroarylene, optionally substituted with one or more substituents Q.

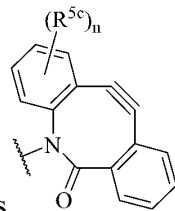
27. The compound of any one of claims 17 to 23, wherein R^{5f} and R^{5g} together with the carbon atoms to which they are attached form monocyclic heteroarylene, optionally substituted with one or more substituents Q.

28. The compound of any one of claims 17 to 23, wherein R^{5f} and R^{5g} together with the carbon atoms to which they are attached form 5- or 6-membered heteroarylene, each optionally substituted with one or more substituents Q.

29. The compound of any one of claims 1 to 9 and 17, wherein R^5 is



30. The compound of any one of claims 1 to 9 and 18, wherein R^5 is



31. The compound of any one of claims 1 to 30, wherein R^4 is absent.

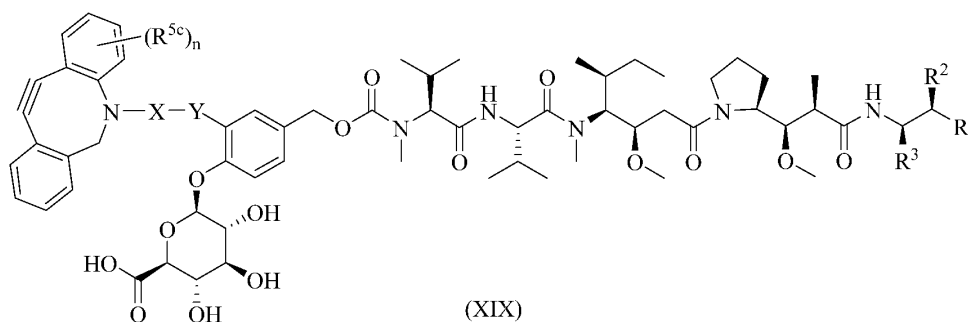
32. The compound of any one of claims 1 to 30, wherein R^4 is C_{1-6} alkyl, optionally substituted with one or more substituents Q; and the N atom to which R^4 is attached is positively charged.

33. The compound of any one of claims 1 to 30 and 32, wherein R^4 is methyl; and the N atom to which R^4 is attached is positively charged.

34. The compound of any one of claims 5 to 33, wherein Z is a bond.

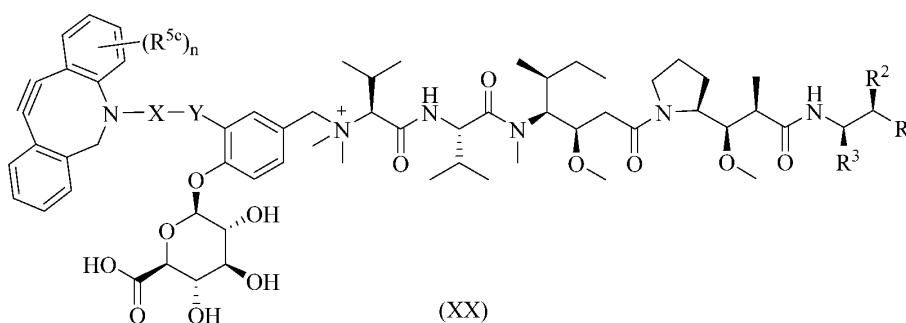
35. The compound of any one of claims 5 to 33, wherein Z is $-OC(O)-$.

36. The compound of claim 5, having the structure of Formula (XIX):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

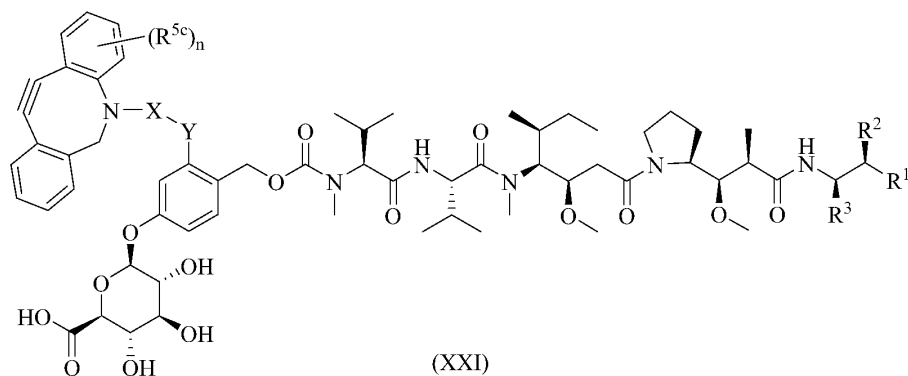
37. The compound of claim 5, having the structure of Formula (XX):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or

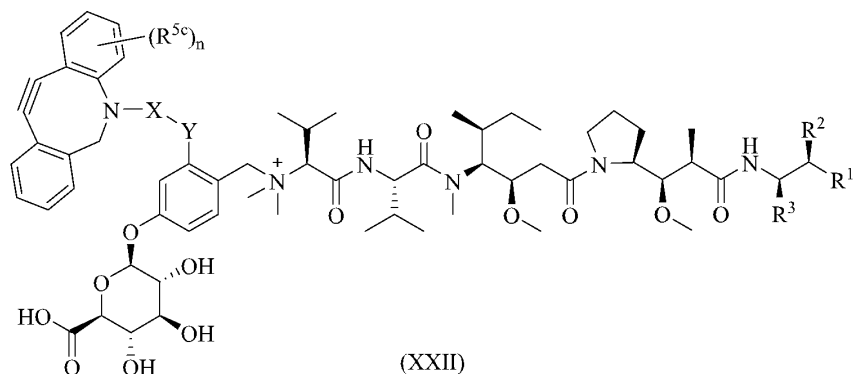
a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

38. The compound of claim 6, having the structure of Formula (XXI):



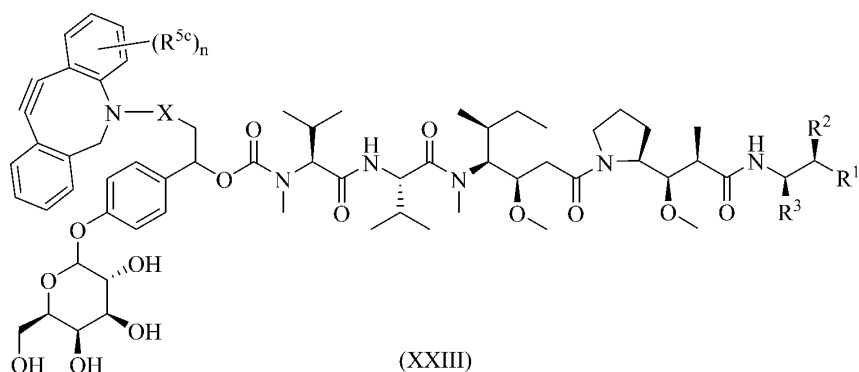
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

39. The compound of claim 6, having the structure of Formula (XXII):



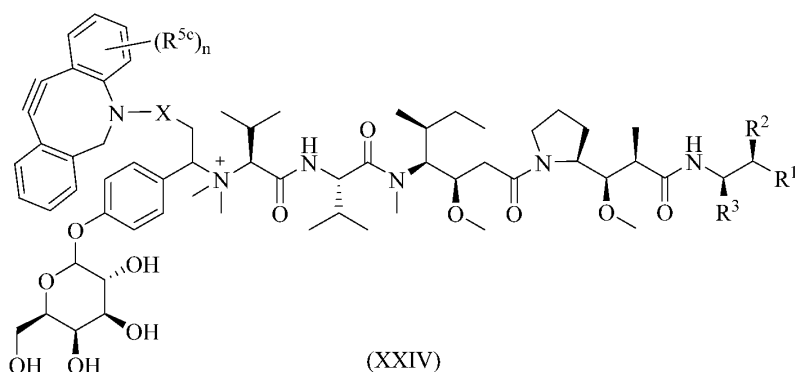
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

40. The compound of claim 7, having the structure of Formula (XXIII):



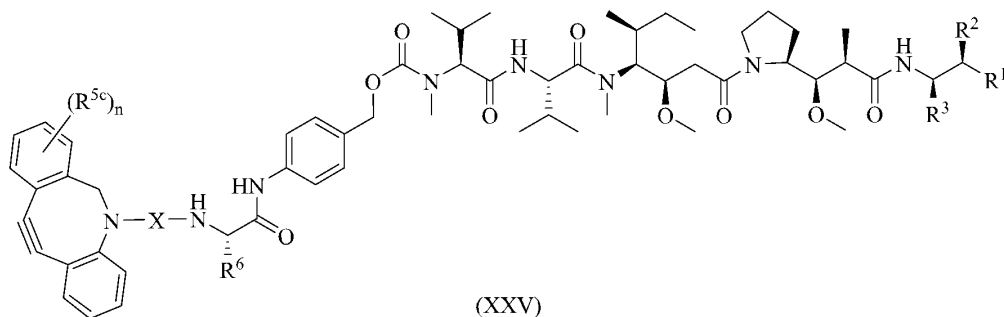
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

41. The compound of claim 7, having the structure of Formula (XXIV):



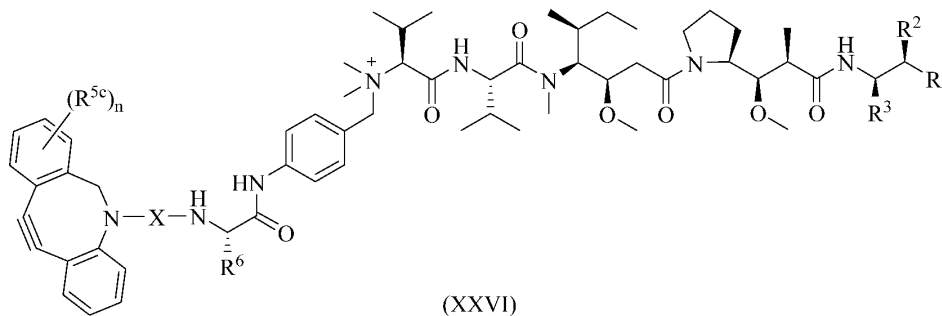
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

42. The compound of claim 8, having the structure of Formula (XXV):



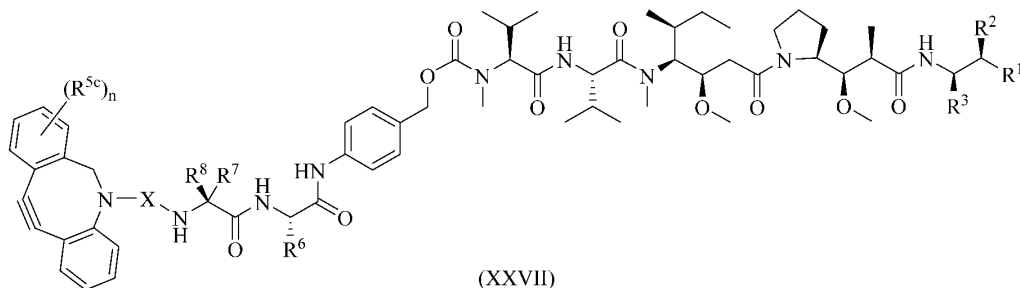
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

43. The compound of claim 8, having the structure of Formula (XXVI):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein X is a divalent linker; and Z is a bond or $-\text{OC}(\text{O})-$.

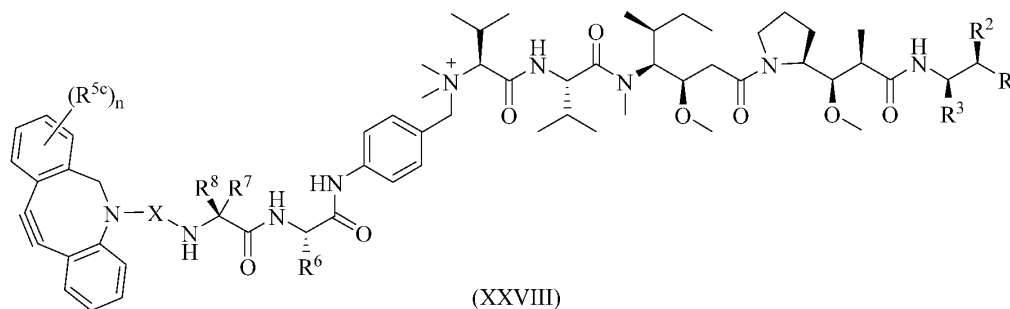
44. The compound of claim 9, having the structure of Formula (XXVII):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more

diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

45. The compound of claim 9, having the structure of Formula (XXVIII):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

46. The compound of any one of claims 15, 16, and 29 to 45, wherein n is an integer of 0, 1, or 2.

47. The compound of any one of claims 15, 16, and 29 to 46, wherein n is an integer of 0.

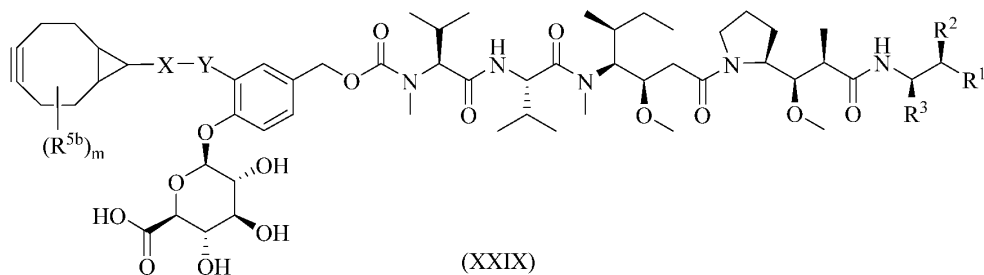
48. The compound of any one of claims 15, 16, and 29 to 46, wherein n is an integer of 1.

49. The compound of any one of claims 15, 16, and 29 to 46, wherein n is an integer of 2.

50. The compound of any one of claims 15, 16, 29 to 46, 48, and 49, wherein each R^{5c} is independently halo or nitro.

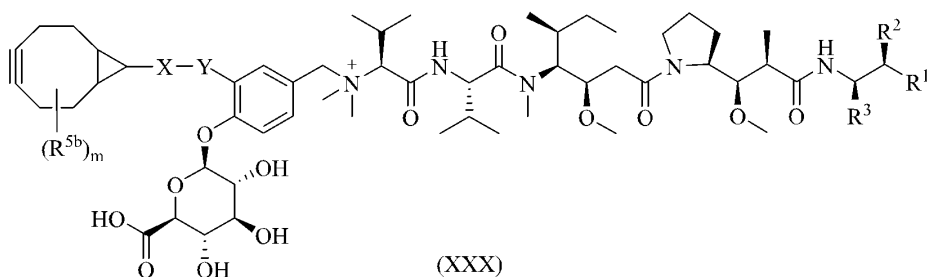
51. The compound of any one of claims 15, 16, 29 to 46, and 48 to 50, wherein each R^{5c} is independently fluoro, chloro, bromo, or nitro.

52. The compound of claim 5, having the structure of Formula (XXIX):



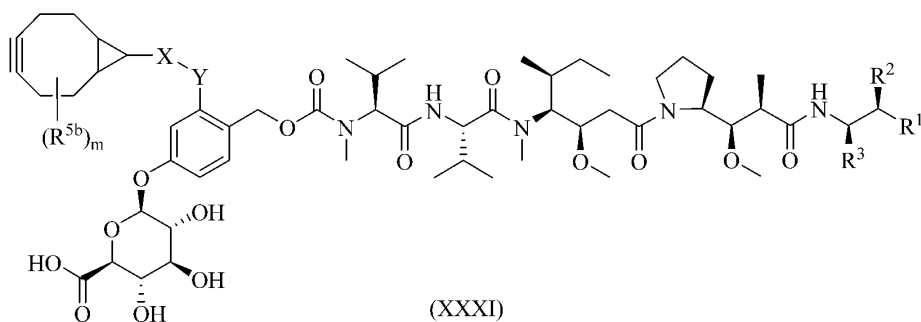
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

53. The compound of claim 5, having the structure of Formula (XXX):



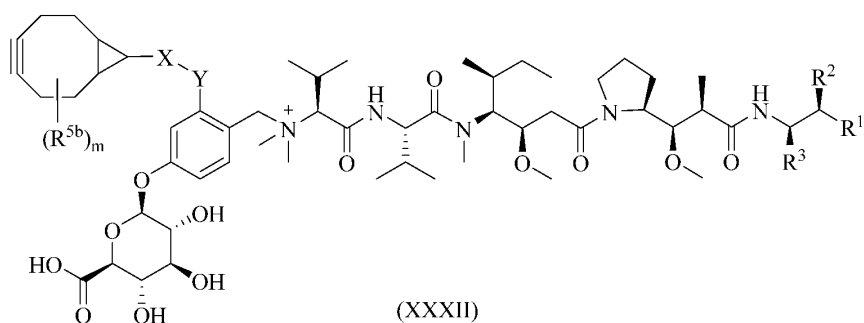
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

54. The compound of claim 6, having the structure of Formula (XXXI):



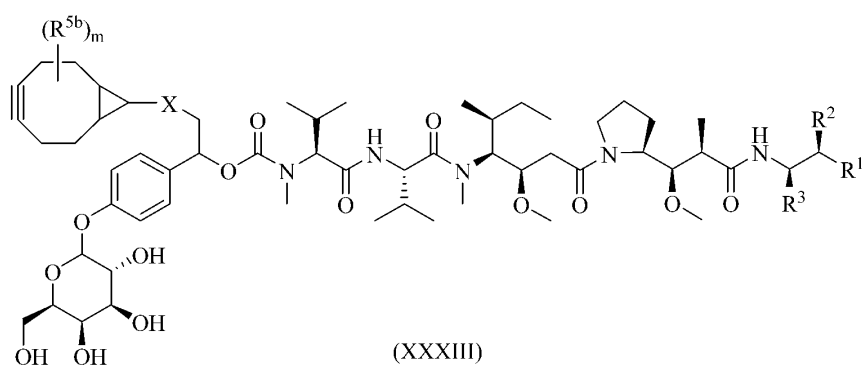
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

55. The compound of claim 6, having the structure of Formula (XXXII):



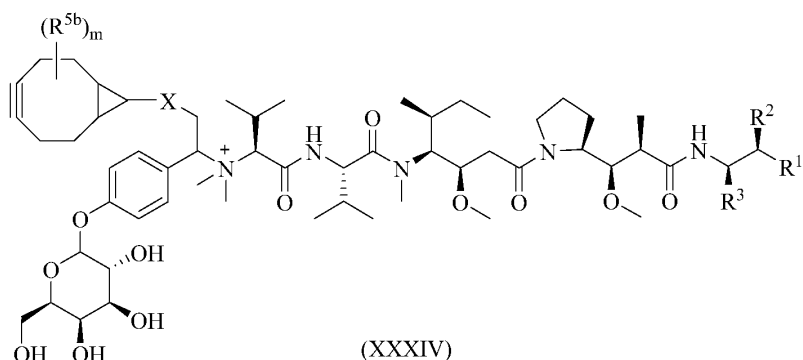
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

56. The compound of claim 7, having the structure of Formula (XXXIII):



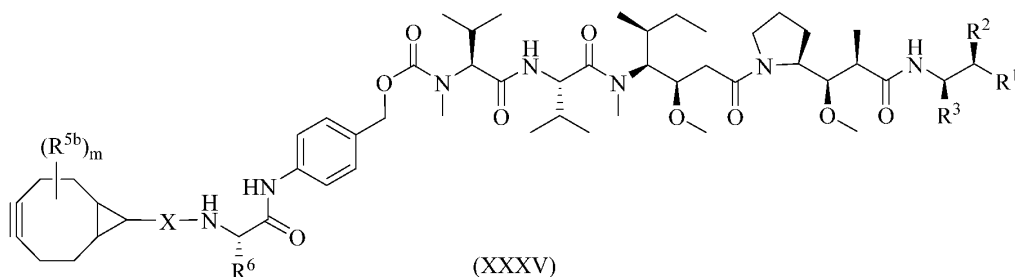
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

57. The compound of claim 7, having the structure of Formula (XXXIV):



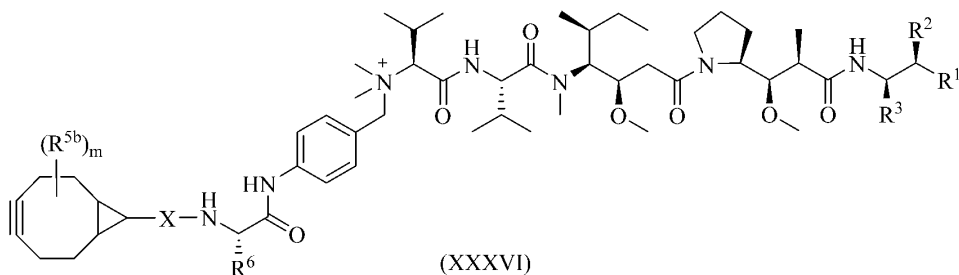
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

58. The compound of claim 8, having the structure of Formula (XXXV):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

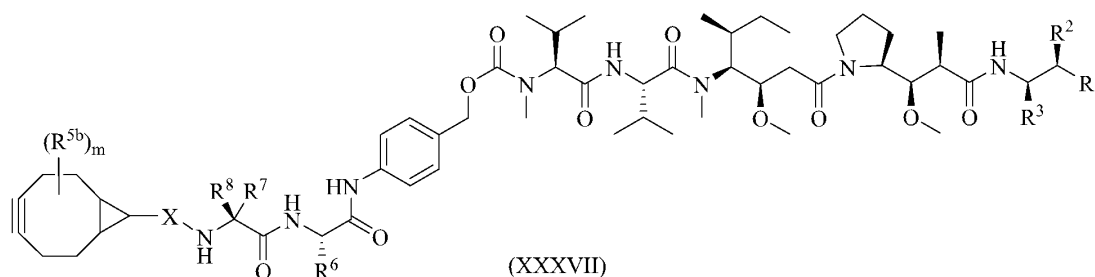
59. The compound of claim 8, having the structure of Formula (XXXVI):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or

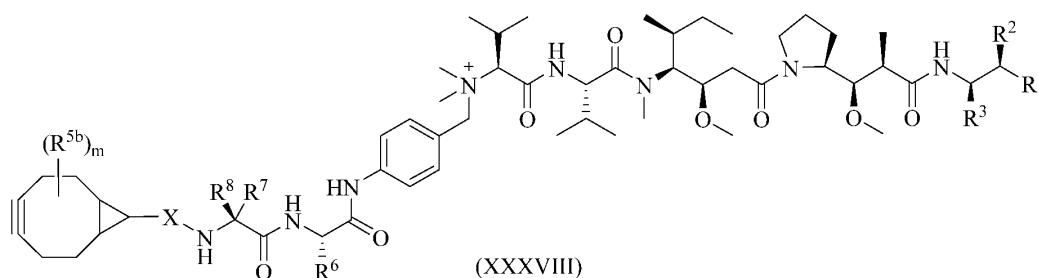
a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein X is a divalent linker; and Z is a bond or $-\text{OC}(\text{O})-$.

60. The compound of claim 9, having the structure of Formula (XXXVII):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

61. The compound of claim 9, having the structure of Formula (XXXVIII):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

62. The compound of any one of claims 12, 14, 31 to 35, and 52 to 61, wherein m is an integer of 0, 1, or 2.

63. The compound of any one of claims 12, 14, 31 to 35, and 52 to 62, wherein m is an integer of 0.

64. The compound of any one of claims 12, 14, 31 to 35, and 52 to 62, wherein m is an integer of 1.

65. The compound of any one of claims 12, 14, 31 to 35, and 52 to 62, wherein m is an integer of 2.

66. The compound of any one of claims 12, 14, 31 to 35, 52 to 62, 64, and 65, wherein each R^{5b} is independently halo.

67. The compound of any one of claims 12, 14, 31 to 35, 52 to 62, and 64 to 66, wherein each R^{5b} is independently fluoro, chloro, or bromo.

68. The compound of any one of claims 8 to 35, 42 to 51, and 58 to 67, wherein R^6 is (i) hydrogen; or (ii) C_{1-6} alkyl, optionally substituted with one or more substituents Q .

69. The compound of any one of claims 8 to 35, 42 to 51, and 58 to 68, wherein R^6 is C_{1-6} alkyl, optionally substituted with one or more substituents Q .

70. The compound of any one of claims 8 to 35, 42 to 51, and 58 to 69, wherein R^6 is C_{1-6} alkyl, optionally substituted with a substituent, which is (i) C_{6-14} aryl or heteroaryl, each optionally substituted with one or more substituents Q ; or (ii) $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-OR^{1a}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, or $-SR^{1a}$.

71. The compound of any one of claims 8 to 35, 42 to 51, and 58 to 70, wherein R^6 is methyl, ethyl, propyl, or butyl, each optionally substituted with a substituent, which is phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NH_2$, $-NHC(O)NH_2$, $-NHC(NH)NH_2$, $-SH$, or $-SCH_3$.

72. The compound of any one of claims 8 to 35, 42 to 51, and 58 to 71, wherein R^6 is methyl, isopropyl, isobutyl, *sec*-butyl, benzyl, 4-hydroxybenzyl, imidazol-4-ylmethyl, indol-3-ylmethyl, carboxymethyl, 2-carboxyethyl, aminocarbonylmethyl, 2-aminocarbonylethyl, hydroxymethyl, 1-hydroxyethyl, 3-aminopropyl, 4-aminobutyl, 3-ureidopropyl, 3-guanidinylpropyl, mercapto-methyl, or 2-methylthioethyl.

73. The compound of any one of claims 8 to 35, 42 to 51, and 58 to 72, wherein R^6 is 3-aminopropyl, 4-aminobutyl, 3-ureidopropyl, or 3-guanidinylpropyl.

74. The compound of any one of claims 8 to 35, 42 to 51, and 58 to 73, wherein R^6 is

4-aminobutyl.

75. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 74, wherein R^7 is (i) hydrogen; or (ii) C_{1-6} alkyl, optionally substituted with one or more substituents Q.

76. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 75, wherein R^7 is hydrogen.

77. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 76, wherein R^8 is (i) hydrogen; or (ii) C_{1-6} alkyl, optionally substituted with one or more substituents Q.

78. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 77, wherein R^8 is C_{1-6} alkyl, optionally substituted with one or more substituents Q.

79. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 78, wherein R^8 is C_{1-6} alkyl, optionally substituted with a substituent, which is (i) C_{6-14} aryl or heteroaryl, each optionally substituted with one or more substituents Q; or (ii) $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-OR^{1a}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, or $-SR^{1a}$.

80. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 79, wherein R^8 is methyl, ethyl, propyl, or butyl, each optionally substituted with a substituent, which is phenyl, 4-hydroxyphenyl, imidazol-4-yl, indol-3-yl, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NH_2$, $-NHC(O)NH_2$, $-NHC(NH)NH_2$, $-SH$, or $-SCH_3$.

81. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 80, wherein R^8 is methyl, isopropyl, isobutyl, *sec*-butyl, benzyl, 4-hydroxybenzyl, imidazol-4-ylmethyl, indol-3-ylmethyl, carboxymethyl, 2-carboxyethyl, aminocarbonylmethyl, 2-aminocarbonylethyl, hydroxymethyl, 1-hydroxyethyl, 3-aminopropyl, 4-aminobutyl, 3-ureidopropyl, 3-guanidinylpropyl, mercaptomethyl, or 2-methylthioethyl.

82. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 81, wherein R^8 is methyl, isopropyl, or benzyl.

83. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 74, wherein R^7 and R^8 together with the carbon atom to which they are attached form C_{3-10} cycloalkylene,

optionally substituted with one or more substituents Q.

84. The compound of any one of claims 9 to 35, 44 to 51, 60 to 74, and 83, wherein R^7 and R^8 together with the carbon atom to which they are attached form monocyclic C_{3-10} cycloalkylene, optionally substituted with one or more substituents Q.

85. The compound of any one of claims 9 to 35, 44 to 51, 60 to 74, 83, and 84, wherein R^7 and R^8 together with the carbon atom to which they are attached form monocyclic C_{3-10} cycloalkylene, optionally substituted with one or more substituents Q.

86. The compound of any one of claims 9 to 35, 44 to 51, 60 to 74, and 83 to 85, wherein R^7 and R^8 together with the carbon atom to which they are attached form cyclopropane-1,1-diyl, cyclobutane-1,1-diyl, cyclopentane-1,1-diyl, or cyclohexane-1,1-diyl, each optionally substituted with one or more substituents Q.

87. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 67, wherein R^6 is methyl; R^7 is hydrogen; and R^8 is isopropyl.

88. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 67, wherein R^6 is 3-ureidopropyl; R^7 is hydrogen; and R^8 is isopropyl.

89. The compound of any one of claims 9 to 35, 44 to 51, and 60 to 67, wherein R^6 is 3-ureidopropyl; and R^7 and R^8 together with the carbon atom to which they are attached form cyclobutane-1,1-diyl.

90. The compound of any one of claims 1 to 89, wherein R^1 is C_{6-14} aryl, optionally substituted with one or more substituents Q.

91. The compound of any one of claims 1 to 90, wherein R^1 is phenyl, optionally substituted with one or more substituents Q.

92. The compound of any one of claims 1 to 89, wherein R^1 is heteroaryl, optionally substituted with one or more substituents Q.

93. The compound of any one of claims 1 to 89 and 92, wherein R^1 is monocyclic

heteroaryl, optionally substituted with one or more substituents Q.

94. The compound of any one of claims 1 to 89, 92, and 93, wherein R¹ is 5- or 6-membered heteroaryl, each optionally substituted with one or more substituents Q.

95. The compound of any one of claims 1 to 89 and 92 to 94, wherein R¹ is pyridinyl.

96. The compound of any one of claims 1 to 95, wherein R² is hydrogen.

97. The compound of any one of claims 1 to 95, wherein R² is -OR^{1a}.

98. The compound of any one of claims 1 to 95 and 97, wherein R² is hydroxyl.

99. The compound of any one of claims 1 to 98, wherein R³ is hydrogen.

100. The compound of any one of claims 1 to 98, wherein R³ is C₁₋₆ alkyl, optionally substituted with one or more substituents Q.

101. The compound of any one of claims 1 to 98 and 100, wherein R³ is methyl.

102. The compound of any one of claims 1 to 98, wherein R³ is heteroaryl, optionally substituted with one or more substituents Q.

103. The compound of any one of claims 1 to 98 and 102, wherein R³ is monocyclic heteroaryl, optionally substituted with one or more substituents Q.

104. The compound of any one of claims 1 to 98, 102, and 103, wherein R³ is 5- or 6-membered heteroaryl, each optionally substituted with one or more substituents Q.

105. The compound of any one of claims 1 to 98 and 102 to 104, wherein R³ is thiazolyl.

106. The compound of any one of claims 1 to 98, wherein R³ is -C(O)OR^{1a}.

107. The compound of any one of claims 1 to 98 and 106, wherein R³ is carboxy or methoxycarbonyl.

108. The compound of any one of claims 1 to 98, 106, and 107, wherein R³ is carboxy.
109. The compound of any one of claims 1 to 89, wherein R¹ is phenyl; R² is hydroxyl; and R³ is methyl.
110. The compound of any one of claims 1 to 89, wherein R¹ is phenyl; R² is hydrogen; and R³ is carboxy.
111. The compound of any one of claims 1 to 89, wherein R¹ is phenyl; R² is hydrogen; and R³ is thiazol-2-yl.
112. The compound of any one of claims 5 to 111, wherein X is a divalent linker comprising sulfo.
113. The compound of any one of claims 5 to 112, wherein X is a divalent linker having the structure of $-Z^n-(R^n-Z^n)_z-$, wherein:
each Rⁿ is independently C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene, each of which is optionally substituted with one or more substituents Q;
each Zⁿ is independently a bond, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{1b}-$, $-C(O)S-$, $-C(NR^{1a})NR^{1b}-$, $-C(S)-$, $-C(S)O-$, $-C(S)NR^{1b}-$, $-O-$, $-OC(O)O-$, $-OC(O)NR^{1b}-$, $-OC(O)S-$, $-OC(NR^{1a})NR^{1b}-$, $-OC(S)O-$, $-OC(S)NR^{1b}-$, $-OS(O)-$, $-OS(O)_2-$, $-OS(O)NR^{1b}-$, $-OS(O)_2NR^{1b}-$, $-NR^{1b}-$, $-NR^{1a}C(O)NR^{1b}-$, $-NR^{1a}C(O)S-$, $-NR^{1a}C(NR^{1d})NR^{1b}-$, $-NR^{1a}C(S)NR^{1b}-$, $-NR^{1a}S(O)NR^{1b}-$, $-NR^{1a}S(O)_2NR^{1b}-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{1b}-$, or $-S(O)_2NR^{1b}-$; wherein each R^{1a}, R^{1b}, and R^{1d} is as defined herein; and
z is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.
114. The compound of claim 113, wherein each Rⁿ is independently C₁₋₆ alkylene, C₃₋₆ cycloalkylene, or heterocyclylene, each optionally substituted with one or more substituents Q.
115. The compound of claim 113 or 114, wherein Rⁿ is independently C₁₋₆ alkylene, optionally substituted with one or more substituents Q.
116. The compound of any one of claims 113 to 115, wherein Rⁿ is independently methanediyl, ethanediyl, propanediyl, butanediyl, pentanediyl, or hexanediyl, each optionally

substituted with one or more substituents Q.

117. The compound of any one of claims 113 to 116, wherein R^n is independently methanediyl, ethane-1,2-diyl, propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl, or hexane-1,6-diyl, each optionally substituted with one or more substituents Q.

118. The compound of any one of claims 113 to 117, wherein R^n is independently methanediyl, ethane-1,2-diyl, or 1-sulfoethane-1,2-diyl.

119. The compound of any one of claims 113 to 118, wherein each Z^n is independently a bond, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{1b}-$, $-O-$, $-OC(O)NR^{1b}-$, $-NR^{1b}-$, $-NR^{1a}C(O)NR^{1b}-$, $-NR^{1a}S(O)NR^{1b}-$, $-NR^{1a}S(O)_2NR^{1b}-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{1b}-$, or $-S(O)_2NR^{1b}-$.

120. The compound of any one of claims 113 to 119, wherein each Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NR^{1b}-$, $-OC(O)NR^{1b}-$, or $-O-$.

121. The compound of any one of claims 113 to 120, wherein each Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)NH-$, or $-O-$.

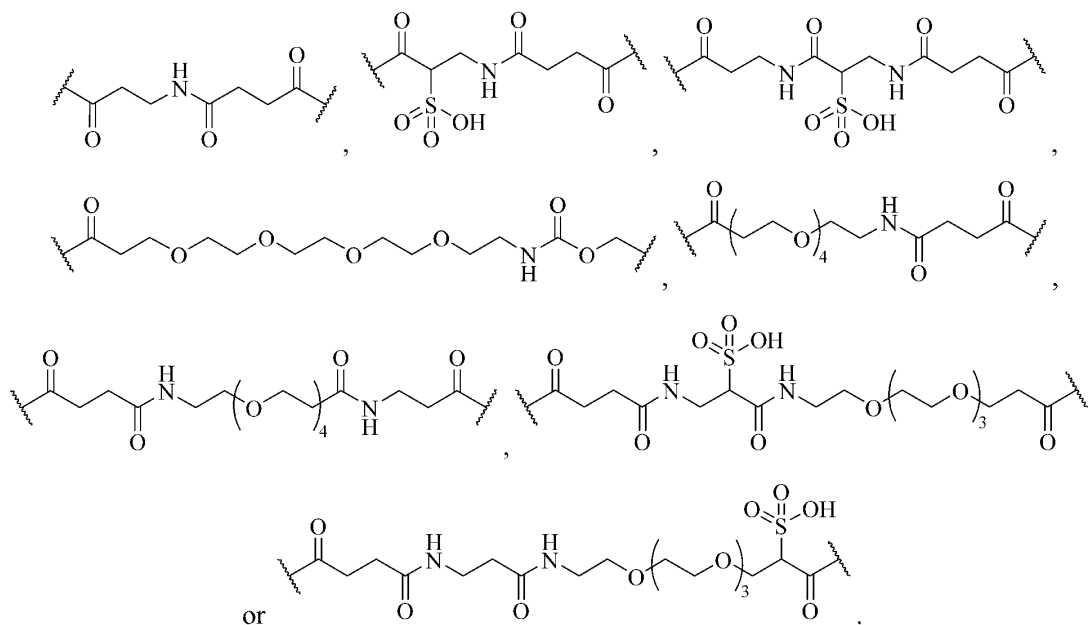
122. The compound of claim 113, wherein each R^n is independently C_{1-6} alkylene, optionally substituted with one or more substituents Q; each Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NR^{1b}-$, $-OC(O)NR^{1b}-$, or $-O-$; and z is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

123. The compound of claim 113 or 122, wherein each R^n is independently methanediyl, ethanediyl, propanediyl, butanediyl, pentanediyl, or hexanediyl, each optionally substituted with one or more substituents Q; each Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)NH-$, or $-O-$; and z is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

124. The compound of any one of claims 113, 122, and 123, wherein each R^n is independently methanediyl, ethane-1,2-diyl, propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl, or hexane-1,6-diyl, each optionally substituted with one or more substituents Q; each Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)NH-$, or $-O-$; and z is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

125. The compound of any one of claims 113 and 122 to 124, wherein each R^n is independently methanediyl, ethane-1,2-diyl or 1-sulfoethane-1,2-diyl; each Z^n is independently $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)NH-$, or $-O-$; and z is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

126. The compound of any one of claims 5 to 113, wherein X is:



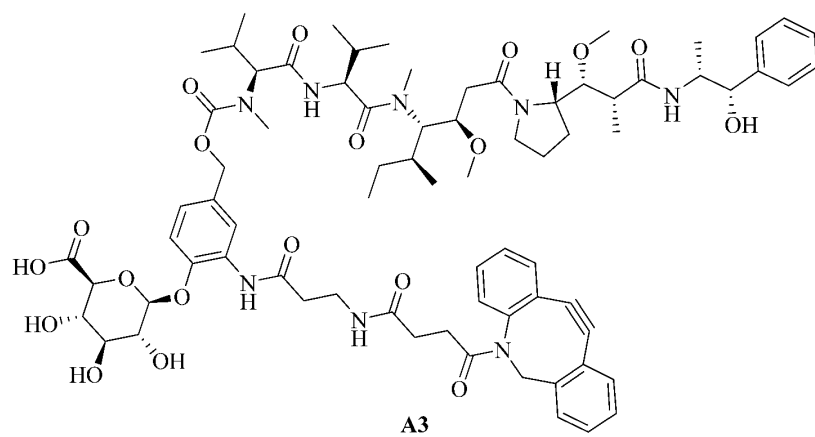
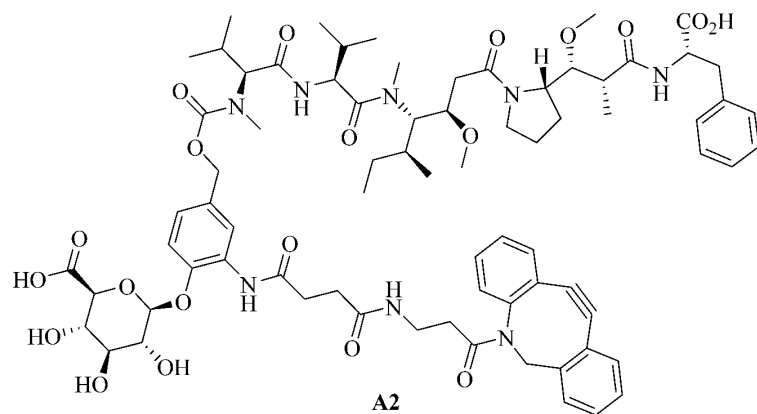
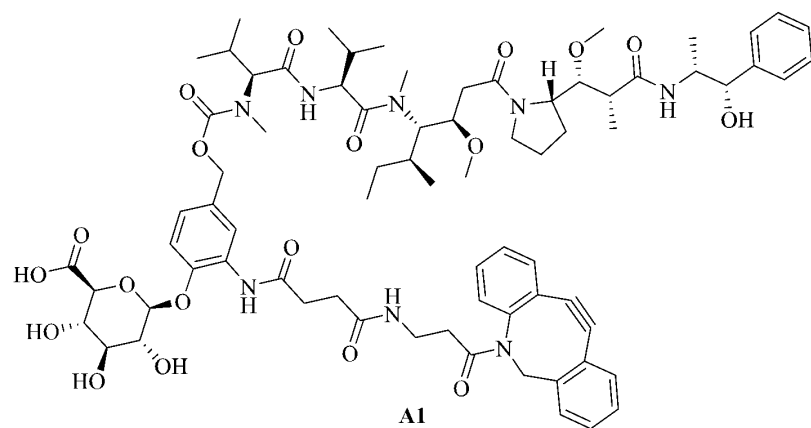
127. The compound of any one of claims 5, 6, 10 to 39, 46 to 55, and 62 to 126, wherein Y is a bond.

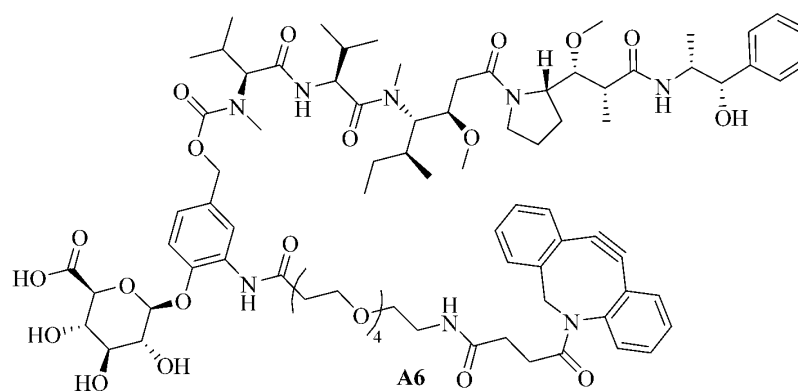
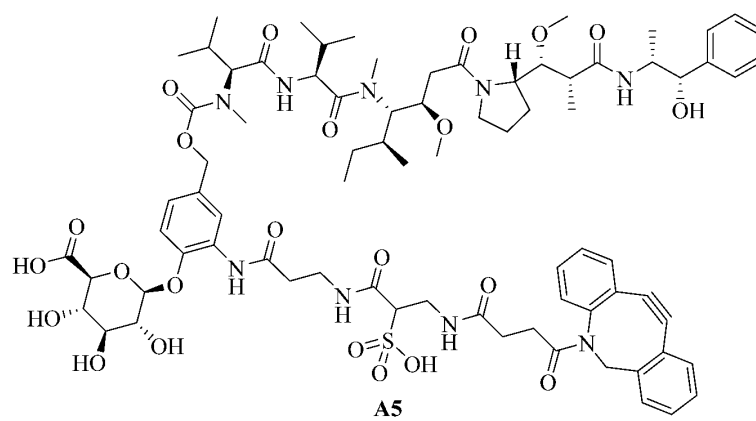
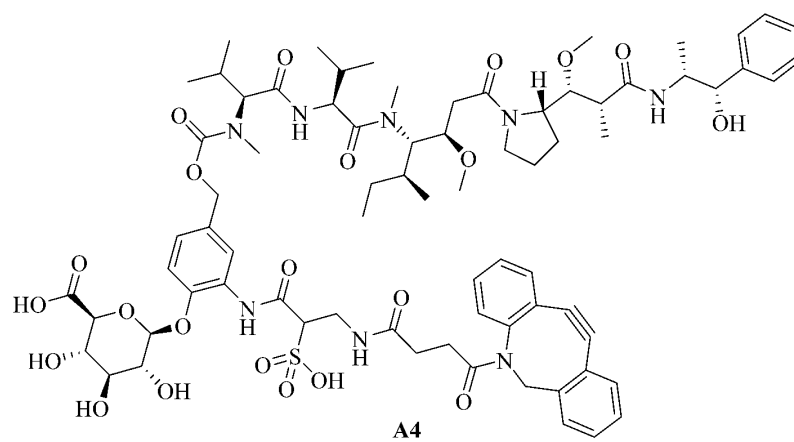
128. The compound of any one of claims 5, 6, 10 to 39, 46 to 55, and 62 to 126, wherein Y is $-O-$.

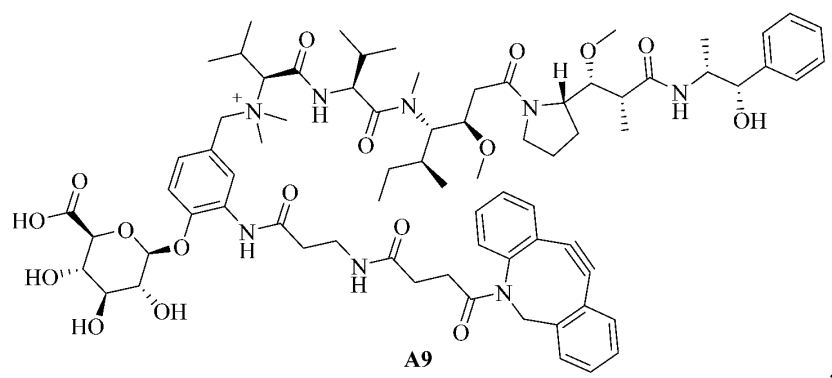
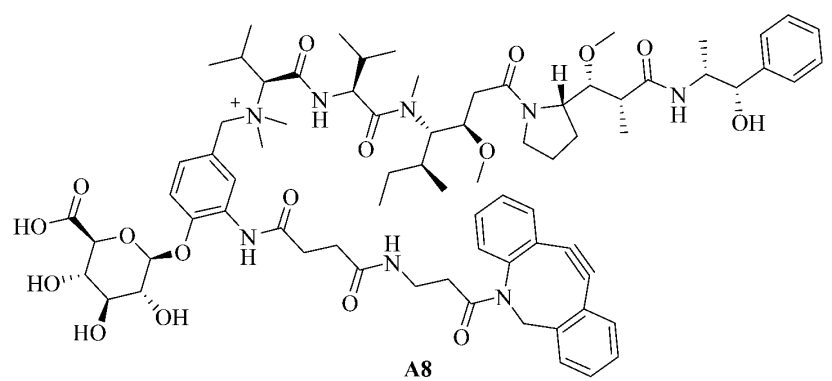
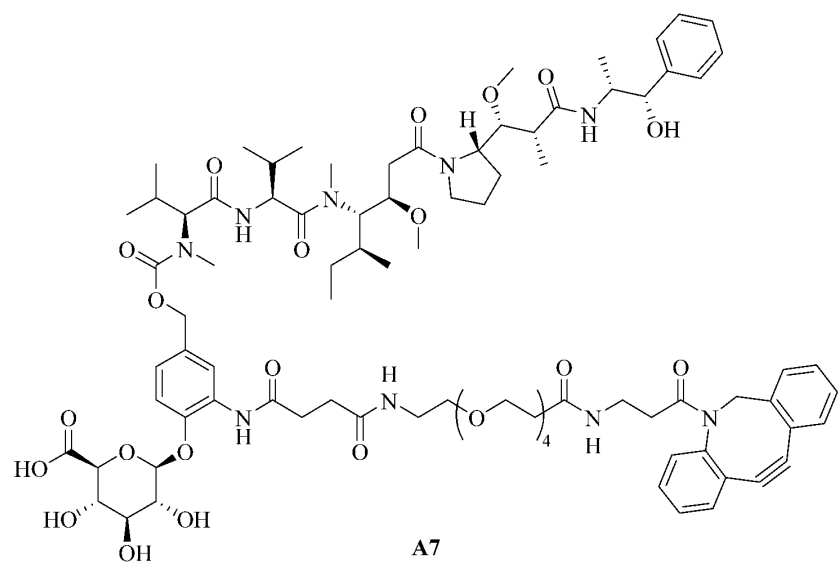
129. The compound of any one of claims 5, 6, 10 to 39, 46 to 55, and 62 to 126, wherein Y is $-N(R^{1b})-$.

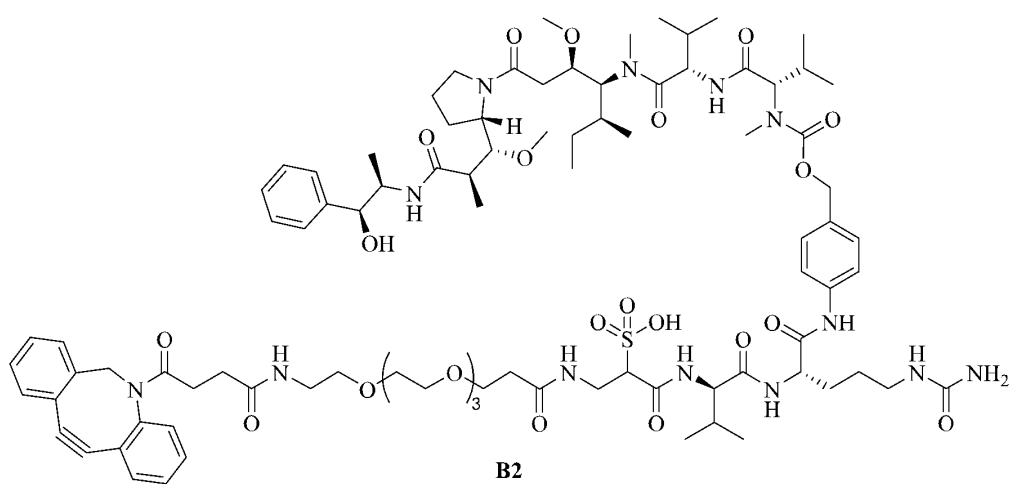
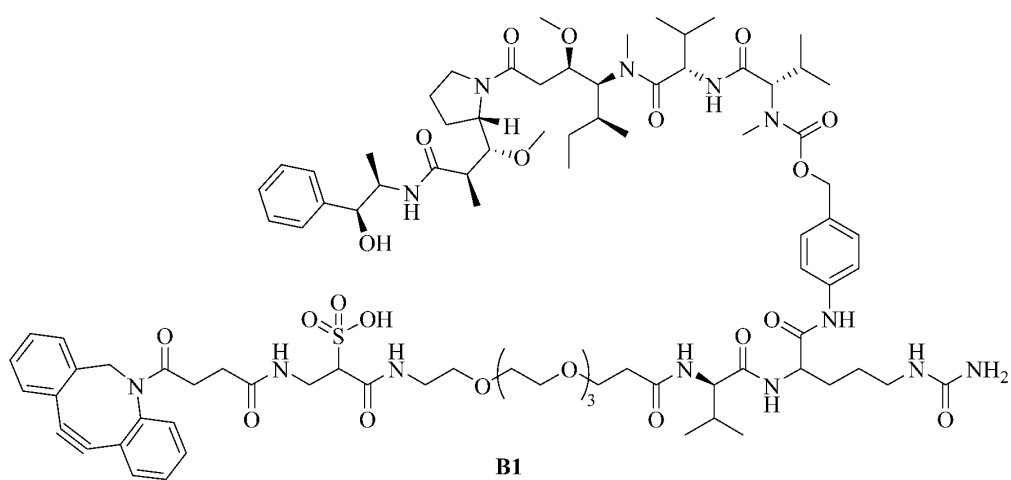
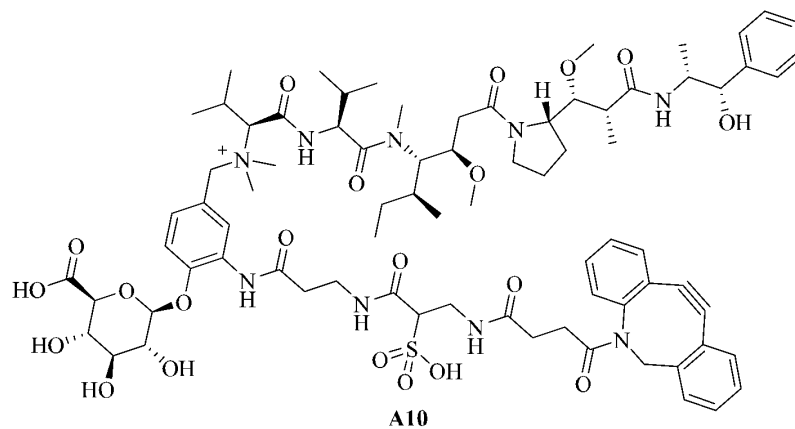
130. The compound of any one of claims 5, 6, 10 to 39, 46 to 55, 62 to 126, and 129, wherein Y is $-N(H)-$.

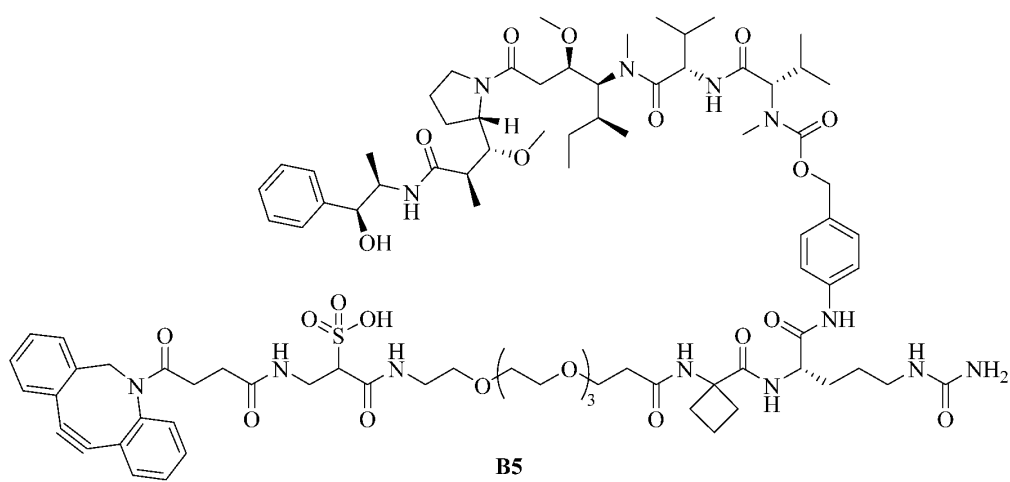
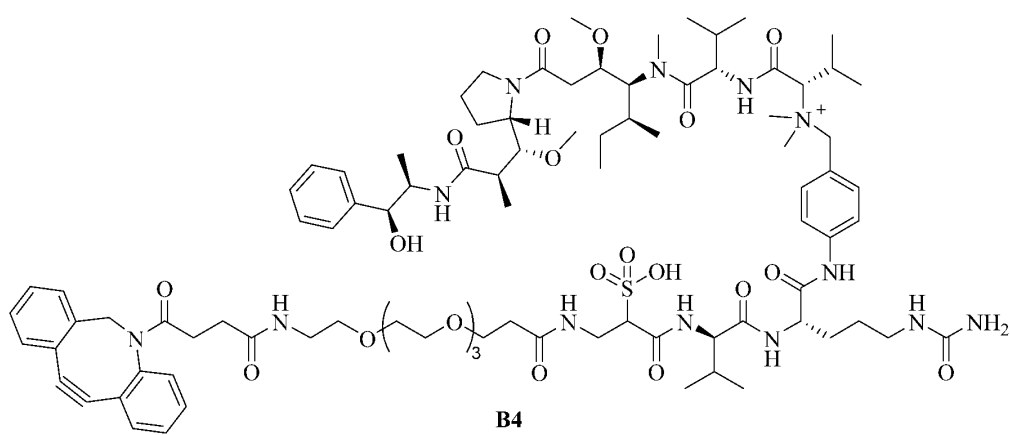
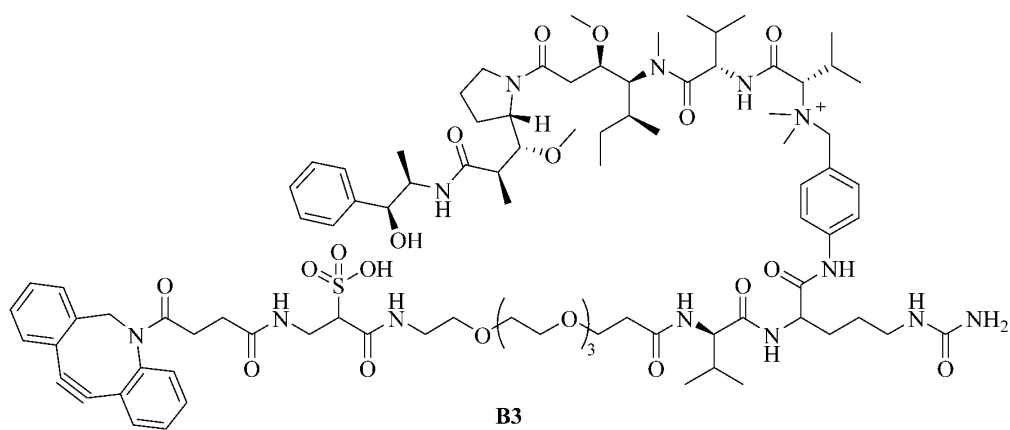
131. The compound of claim 1, wherein the compound is:

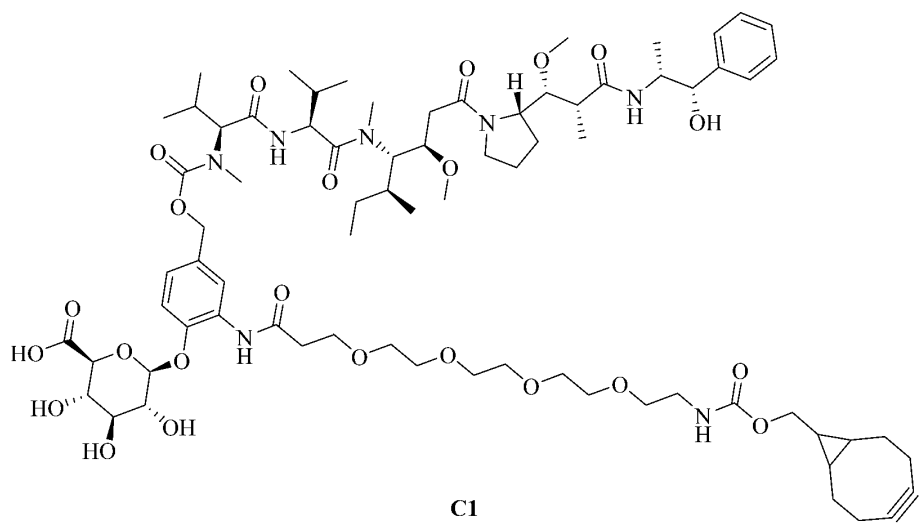
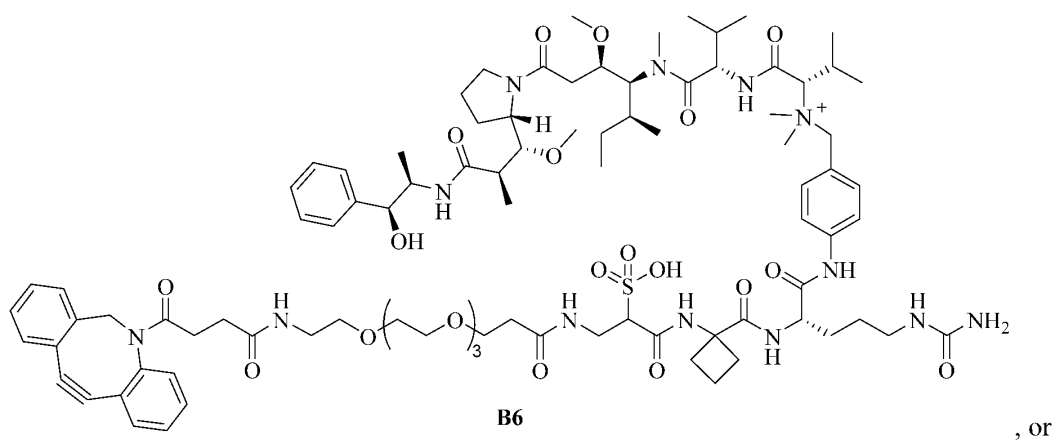












or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

132. A pharmaceutical composition comprising the compound of any one of claims 1 to 131, or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and a pharmaceutically acceptable excipient.

133. The pharmaceutical composition of claim 132, wherein the composition is in single dosage form.

134. The pharmaceutical composition of claim 132 or 133, wherein the composition is in an oral, parenteral, or intravenous dosage form.

135. A method of treating, treating, preventing, or ameliorating one or more symptoms of a proliferative disease in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 131 or a pharmaceutical composition of any one of claims 132 to 134.

136. The method of claim 135, wherein the proliferative disease is cancer.

137. The method of claim 136, wherein the cancer is azido-labelled.

138. The method of claim 136 or 137, wherein the cancer is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)-tetrahydro-2*H*-pyran-2-yl, (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy, (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yl, (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy, ((3*S*,4*R*,5*S*,6*S*)-6-(azidomethyl)-2,4,5-trihydroxytetrahydro-2*H*-pyran-3-yl)oxy, (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl, (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy, (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl, (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy, (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl, or (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy.

139. The method of any one of claims 136 or 138, wherein the cancer is breast cancer, melanoma, or ovarian cancer.

140. The method of any one of claims 136 or 139, wherein the cancer is relapsed or refractory.

141. The method of any one of claims 136 or 140, wherein the cancer is metastatic.

142. The method of any one of claims 136 or 141, wherein the cancer is drug-resistant.
143. The method of any one of claims 135 or 142, wherein the subject is a human.
144. A method of inhibiting the growth of a cell, comprising contacting the cell with an effective amount of a compound of any one of claims 1 to 131 or a pharmaceutical composition of any one of claims 132 to 134.
145. The method of claim 144, wherein the cell is a cancerous cell.
146. The method of claim 144 or 145, wherein the cell is azido-labelled.
147. The method of any one of claims 144 to 146, wherein the cell is azido-labelled with (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yl, (4*S*,5*R*,6*R*)-5-(2-azidoacetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy, (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yl, (4*S*,5*R*,6*R*)-5-(acetamido)-4-hydroxy-2-carboxy-6-((1*R*,2*R*)-3-azido-1,2-dihydroxypropyl)tetrahydro-2*H*-pyran-2-yloxy, ((3*S*,4*R*,5*S*,6*S*)-6-(azidomethyl)-2,4,5-trihydroxytetrahydro-2*H*-pyran-3-yl)oxy, (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl, (3*R*,4*R*,5*R*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy, (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl, (3*R*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy, (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl, or (3*S*,4*R*,5*S*,6*R*)-3-(2-azidoacetamido)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy.