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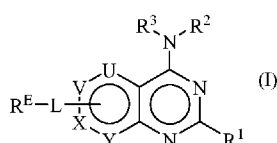
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SOS1 PROTEIN DEGRADERS, PHARMACEUTICAL COMPOSITIONS THEREOF, AND THEIR THERAPEUTIC APPLICATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of the priority of U.S. Provisional Application Nos. 63/079,467, filed September 16, 2020, and 63/196,665, filed June 3, 2021; the disclosure of each of which is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein are SOS1 protein degraders and pharmaceutical compositions thereof. Also provided herein are methods of their use for treating, preventing, or ameliorating one or more symptoms of an SOS1-mediated disorder, disease, or condition.

BACKGROUND

[0003] The three *RAS* oncogenes, *KRAS*, *HRAS*, and *NRAS*, are from the most frequently mutated oncogene family in cancer. Milburn *et al*, *Science* **1990**, 247, 939-45; Cox *et al.*, *Nat. Rev. Drug Discov.* **2014**, 13, 828-51; Papke and Der, *Science* **2017**, 355, 1158-63. *RAS* mutations have been detected in up to 30% of all human cancer. Cox *et al.*, *Nat. Rev. Drug Discov.* **2014**, 13, 828-51. *RAS* mutations are found in about 95% of pancreatic ductal adenocarcinomas (PDACs), about 50% of colorectal adenocarcinomas (CRCs), and about 30% of lung adenocarcinomas (CACs). Papke and Der, *Science* **2017**, 355, 1158-63. Among the three, *KRAS* mutations are the most common and alone account for about a million death per year worldwide. Cox *et al.*, *Nat. Rev. Drug Discov.* **2014**, 13, 828-51; Simanshu *et al.*, *Cell* **2017**, 170, 17-33.

[0004] A *RAS* protein is a small GTPase encoded by a *RAS* oncogene. Papke and Der, *Science* **2017**, 355, 1158-63. The *RAS* protein functions as a molecular switch cycling between the active guanosine triphosphate (GTP)-bound and inactive guanosine diphosphate (GDP)-bound states. Milburn *et al*, *Science* **1990**, 247, 939-45. The GTP-bound active *RAS* activates downstream effector pathways, including rat fibrosarcoma/mitogen-activated protein kinase kinase/extracellular regulated kinase (RAF/MEK/ERK) and phosphoinositide 3-kinase/protein

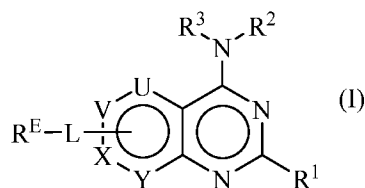
kinase B/mechanistic target of rapamycin kinase (PI3K/AKT/mTOR). Rebocho and Marais, *Cancer Discov.* **2011**, *1*, 98-9. Oncogenic mutations in RAS proteins impair their ability for GTP hydrolysis, resulting in the accumulation of GTP-bound active RAS and hyperactivation of downstream signaling cascades that lead to uncontrolled cell proliferation and survival. Uras *et al.*, *Int. J. Mol. Sci.* **2020**, *21*, 4325.

[0005] The RAS signaling is tightly regulated by guanine nucleotide exchange factor (GEF) proteins, which catalyze the exchange of GDP for GTP, and GTPase-activating proteins (GAPs), which increase the rate of GTP hydrolysis to GDP. Simanshu *et al.*, *Cell* **2017**, *170*, 17-33. In other words, the RAS GTP/GDP cycle is regulated negatively by GAPs and positively by GEFs. Bos, *Cell* **2007**, *129*, 865-77. The son of sevenless homolog 1 (SOS1) is a GEF that binds to RAS to promote nucleotide exchange and formation of GTP-bound active RAS. Wang *et al.*, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5766-76. Small molecule SOS1 inhibitors have been shown to be effective in downregulating active RAS in tumor cells with wild-type KRAS as well as tumor cells bearing a KRAS mutation. Hillig *et al.*, *Proc. Nat. Acad. Sci.* **2019**, *114*, 2551-60. By preventing formation of the KRAS-SOS1 complex, the SOS1 inhibitors block reloading of KRAS with GTP, leading to antiproliferative activity. *Id.*

[0006] Despite the advances in cancer treatment, cancer remains a major worldwide public health problem. It was estimated that there will be 1,898,160 new cancer cases diagnosed and 608,570 cancer deaths in the US alone in 2021. *Cancer Facts & Figures* 2021. Therefore, there is a need for an effective therapy for cancer treatment.

SUMMARY OF THE DISCLOSURE

[0007] 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:

one of U, V, X, and Y is $-C=$ or $-N=$; and the remaining three of U, V, X, and Y are each independently $-C(R^4)=$ or $-N=$;

L is a linker;

R^E is an E3 ubiquitin ligase binding moiety;

R^1 and R^3 are each independently hydrogen, deuterium, 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;

R^2 is 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, heteroaryl- C_{1-6} alkylene, or heterocyclyl;

each R^4 is independently (i) hydrogen, deuterium, cyano, halo, nitro, or oxo; (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) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and

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, or heterocyclyl;

wherein each alkyl, alkylene, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl 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, imino, 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) $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^bR^c$, $-C(O)SR^a$, $-C(NR^a)NR^bR^c$, $-C(S)R^a$, $-C(S)OR^a$, $-C(S)NR^bR^c$, $-OR^a$, $-OC(O)R^a$, $-OC(O)OR^a$, $-OC(O)NR^bR^c$, $-OC(O)SR^a$, $-OC(NR^a)NR^bR^c$, $-OC(S)R^a$, $-OC(S)OR^a$, $-OC(S)NR^bR^c$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-OS(O)NR^bR^c$, $-OS(O)_2NR^bR^c$, $-NR^bR^c$, $-NR^aC(O)R^d$, $-NR^aC(O)OR^d$, $-NR^aC(O)NR^bR^c$, $-NR^aC(O)SR^d$, $-NR^aC(NR^d)NR^bR^c$, $-NR^aC(S)R^d$, $-NR^aC(S)OR^d$, $-NR^aC(S)NR^bR^c$,

$-\text{NR}^a\text{S}(\text{O})\text{R}^d$, $-\text{NR}^a\text{S}(\text{O})_2\text{R}^d$, $-\text{NR}^a\text{S}(\text{O})\text{NR}^b\text{R}^c$, $-\text{NR}^a\text{S}(\text{O})_2\text{NR}^b\text{R}^c$, $-\text{SR}^a$, $-\text{S}(\text{O})\text{R}^a$, $-\text{S}(\text{O})_2\text{R}^a$, $-\text{S}(\text{O})\text{NR}^b\text{R}^c$, and $-\text{S}(\text{O})_2\text{NR}^b\text{R}^c$, 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, imino, 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) $-\text{C}(\text{O})\text{R}^e$, $-\text{C}(\text{O})\text{OR}^e$, $-\text{C}(\text{O})\text{NR}^f\text{R}^g$, $-\text{C}(\text{O})\text{SR}^e$, $-\text{C}(\text{NR}^e)\text{NR}^f\text{R}^g$, $-\text{C}(\text{S})\text{R}^e$, $-\text{C}(\text{S})\text{OR}^e$, $-\text{C}(\text{S})\text{NR}^f\text{R}^g$, $-\text{OR}^e$, $-\text{OC}(\text{O})\text{R}^e$, $-\text{OC}(\text{O})\text{OR}^e$, $-\text{OC}(\text{O})\text{NR}^f\text{R}^g$, $-\text{OC}(\text{O})\text{SR}^e$, $-\text{OC}(\text{NR}^e)\text{NR}^f\text{R}^g$, $-\text{OC}(\text{S})\text{R}^e$, $-\text{OC}(\text{S})\text{OR}^e$, $-\text{OC}(\text{S})\text{NR}^f\text{R}^g$, $-\text{OS}(\text{O})\text{R}^e$, $-\text{OS}(\text{O})_2\text{R}^e$, $-\text{OS}(\text{O})\text{NR}^f\text{R}^g$, $-\text{OS}(\text{O})_2\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{R}^g$, $-\text{NR}^e\text{C}(\text{O})\text{R}^h$, $-\text{NR}^e\text{C}(\text{O})\text{OR}^f$, $-\text{NR}^e\text{C}(\text{O})\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{C}(\text{O})\text{SR}^f$, $-\text{NR}^e\text{C}(\text{NR}^h)\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{C}(\text{S})\text{R}^h$, $-\text{NR}^e\text{C}(\text{S})\text{OR}^f$, $-\text{NR}^e\text{C}(\text{S})\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{S}(\text{O})\text{R}^h$, $-\text{NR}^e\text{S}(\text{O})_2\text{R}^h$, $-\text{NR}^e\text{S}(\text{O})\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{S}(\text{O})_2\text{NR}^f\text{R}^g$, $-\text{SR}^e$, $-\text{S}(\text{O})\text{R}^e$, $-\text{S}(\text{O})_2\text{R}^e$, $-\text{S}(\text{O})\text{NR}^f\text{R}^g$, and $-\text{S}(\text{O})_2\text{NR}^f\text{R}^g$; 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.

[0008] 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.

[0009] Additionally provided herein is a method of treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition mediated by a loss of sevenless homolog 1 (SOS1) 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.

[0010] Furthermore, provided herein is a method of treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition mediated by a Ras 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.

[0011] Provided herein is a method of 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.

[0012] Provided herein is a method of inhibiting the growth of a cell, comprising contacting the cell with 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.

[0013] Provided herein is a method of inducing degradation of an SOS1, comprising contacting the SOS1 with 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.

DETAILED DESCRIPTION

[0014] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] 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.

[0021] 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.

[0022] The term “IC₅₀” or “EC₅₀” refers to an amount, concentration, or dosage of a compound that is required for 50% inhibition of a maximal response in an assay that measures such a response.

[0023] 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*, 1st ed.; Gibson Ed.; CRC Press, 2015.

[0024] 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.

[0025] 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 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 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 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).

[0026] 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, C₁₋₆ 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 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 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 heteroalkyl groups are also referred as “lower heteroalkyl.” Examples of heteroalkyl groups include, but are not limited to, -OCH₃, -OCH₂CH₃, -CH₂OCH₃, -NHCH₃, -ONHCH₃, -NHCH₃, -NHCH₃, -NHCH₃, -SCH₃, -CH₂NHCH₂CH₃, and -NHCH₂CH₂CH₃. Examples of substituted heteroalkyl groups include, but are not limited to, -CH₂NHC(O)CH₃ and -NHC(O)CH₂CH₃.

[0027] 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, $-\text{C}(\text{O})\text{CH}_2-$, $-\text{C}(\text{O})(\text{CH}_2)_2-$, $-\text{C}(\text{O})(\text{CH}_2)_3-$, $-\text{C}(\text{O})(\text{CH}_2)_4-$, $-\text{C}(\text{O})(\text{CH}_2)_5-$, $-\text{C}(\text{O})(\text{CH}_2)_6-$, $-\text{C}(\text{O})(\text{CH}_2)_7-$, $-\text{C}(\text{O})(\text{CH}_2)_8-$, $-\text{C}(\text{O})(\text{CH}_2)_9-$, $-\text{C}(\text{O})(\text{CH}_2)_{10}-$, $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})-$, $-\text{C}(\text{O})(\text{CH}_2)_2\text{C}(\text{O})-$, $-\text{C}(\text{O})(\text{CH}_2)_3\text{C}(\text{O})-$, $-\text{C}(\text{O})(\text{CH}_2)_4\text{C}(\text{O})-$, or $-\text{C}(\text{O})(\text{CH}_2)_5\text{C}(\text{O})-$.

[0028] 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, C₁₋₆ 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 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 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 heteroalkylene groups are also referred to as “lower heteroalkylene.” Examples of heteroalkylene groups include, but are not

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

[0029] 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, C_{2-6} 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 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 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 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).

[0030] 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, C_{2-6} 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 (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 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).

[0031] The terms “heteroalkenylene” and “heteroalkenediyl” 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), and which contains one or more heteroatoms each independently selected from O, S, and N in the hydrocarbon chain. The heteroalkenylene is optionally substituted with one or more substituents Q as described herein. The term “heteroalkenylene” 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, C_{2-6} heteroalkenylene 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 heteroalkenylene is a linear divalent hydrocarbon radical of 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 divalent hydrocarbon radical of 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 heteroalkenylene groups include, but are not limited to, $-CH=CHO-$, $-CH=CHOCH_2-$, $-CH=CHCH_2O-$, $-CH=CHS-$, $-CH=CHSCH_2-$, $-CH=CHCH_2S-$, or $-CH=CHCH_2NH-$.

[0032] 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, C₂₋₆ 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 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 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 alkynyl groups include, but are not limited to, ethynyl (–C≡CH), propynyl (including all isomeric forms, *e.g.*, 1-propynyl (–C≡CCH₃) and propargyl (–CH₂C≡CH)), butynyl (including all isomeric forms, *e.g.*, 1-butyne-1-yl and 2-butyne-1-yl), pentynyl (including all isomeric forms, *e.g.*, 1-pentyne-1-yl and 1-methyl-2-butyne-1-yl), and hexynyl (including all isomeric forms, *e.g.*, 1-hexyne-1-yl and 2-hexyne-1-yl).

[0033] 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, C₂₋₆ 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).

[0034] The terms “heteroalkynylene” and “heteroalkynediyl” 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), and which contains one or more heteroatoms in its main chain, each independently selected from O, S, and N. A heteroalkynylene group does not contain a carbon-carbon double bond. The heteroalkynylene is optionally substituted with one or more substituents Q as described herein. For example, C₂₋₆ heteroalkynylene 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 heteroalkynylene 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 heteroalkynylene groups include, but are not limited to, $-\text{C}\equiv\text{CCH}_2\text{O}-$, $-\text{C}\equiv\text{CCH}_2\text{S}-$, or $-\text{C}\equiv\text{CCH}_2\text{NH}-$.

[0035] 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.

[0036] 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), cyclopentanediy (including all isomeric forms, *e.g.*, cyclopentane-1,1-diyl, cyclopentane-1,2-diyl, and cyclopentane-1,3-diyl), cyclohexanediy (including all isomeric forms, *e.g.*, cyclohexane-1,1-diyl, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl, and cyclohex-1,4-diyl), cycloheptanediy (including all isomeric forms, *e.g.*, cycloheptane-1,1-diyl, cycloheptane-1,2-diyl, cycloheptane-1,3-diyl, and cycloheptane-1,4-diyl), decalinediy (including all isomeric forms, *e.g.*, decaline-1,1-diyl, decaline-1,2-diyl, and decaline-1,8-diyl), and adamantdiy (including all isomeric forms, *e.g.*, adamant-1,2-diyl, adamant-1,3-diyl, and adamant-1,8-diyl).

[0037] 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 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.

[0038] The terms “arylene” and “arenediy” 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 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.

[0039] 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 (C₇₋₃₀), from 7 to 20 (C₇₋₂₀), or from 7 to 16 (C₇₋₁₆) 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.

[0040] 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 (C₇₋₃₀), from 7 to 20 (C₇₋₂₀), or from 7 to 16 (C₇₋₁₆) 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.

[0041] 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, furopyridyl (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, indolizynyl, indolyl, isobenzofuranyl, isobenzothienyl (*i.e.*, benzo[*c*]thienyl), isoindolyl, isoquinolynyl, 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), quinolynyl, quinoxalynyl, 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-

phenanthrolyl, 1,9-phenanthrolyl, and 2,10-phenanthrolyl), phenarsaziny, phenaziny, phenothiaziny, phenoxaziny, and xanthy. In certain embodiments, the heteroaryl is optionally substituted with one or more substituents Q as described herein.

[0042] 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.

[0043] 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, dihydrobenzisoxazinyl (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, dihydropyranal, dihydropyrazolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, imidazolidinyl, imidazolyl, indolinyl, isochromanyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl,

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.

[0044] 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, dihydrobenzisoithiazoldiyl, dihydrobenzisoiazindiyl (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, dihydrofurdiyl, 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, tetrahydrofurdiyl, 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.

[0045] The term “halogen”, “halide,” or “halo” refers to fluoro, chloro, bromo, and/or iodo.

[0046] The term “optionally substituted” is intended to mean that a group or substituent, such as an alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, alkynylene, heteroalkynylene, 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, imino (=NH), 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^bOR^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)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.”

[0047] In one embodiment, each Q^a is independently selected from: (a) deuterium, cyano, halo, imino, 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,

$-\text{OC}(\text{O})\text{OR}^e$, $-\text{OC}(\text{O})\text{NR}^f\text{R}^g$, $-\text{OC}(\text{O})\text{SR}^e$, $-\text{OC}(\text{NR}^e)\text{NR}^f\text{R}^g$, $-\text{OC}(\text{S})\text{R}^e$, $-\text{OC}(\text{S})\text{OR}^e$,
 $-\text{OC}(\text{S})\text{NR}^f\text{R}^g$, $-\text{OP}(\text{O})(\text{OR}^f)\text{OR}^g$, $-\text{OS}(\text{O})\text{R}^e$, $-\text{OS}(\text{O})_2\text{R}^e$, $-\text{OS}(\text{O})\text{NR}^f\text{R}^g$, $-\text{OS}(\text{O})_2\text{NR}^f\text{R}^g$,
 $-\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{C}(\text{O})\text{R}^h$, $-\text{NR}^e\text{C}(\text{O})\text{OR}^f$, $-\text{NR}^e\text{C}(\text{O})\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{C}(\text{O})\text{SR}^f$, $-\text{NR}^e\text{C}(\text{NR}^h)\text{NR}^f\text{R}^g$,
 $-\text{NR}^e\text{C}(\text{S})\text{R}^h$, $-\text{NR}^e\text{C}(\text{S})\text{OR}^f$, $-\text{NR}^e\text{C}(\text{S})\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{S}(\text{O})\text{R}^h$, $-\text{NR}^e\text{S}(\text{O})_2\text{R}^h$, $-\text{NR}^e\text{S}(\text{O})\text{NR}^f\text{R}^g$,
 $-\text{NR}^e\text{S}(\text{O})_2\text{NR}^f\text{R}^g$, $-\text{SR}^e$, $-\text{S}(\text{O})\text{R}^e$, $-\text{S}(\text{O})_2\text{R}^e$, $-\text{S}(\text{O})\text{NR}^f\text{R}^g$, and $-\text{S}(\text{O})_2\text{NR}^f\text{R}^g$; 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.

[0048] 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.

[0049] 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*.

[0050] 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.

[0051] 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.

[0052] The term “isotopic enrichment factor” refers the ratio between the isotopic abundance in an isotopically enriched compound and the natural abundance of a specific isotope.

[0053] 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%.

[0054] 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%).

[0055] 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%.

[0056] 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%).

[0057] 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.

[0058] 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.

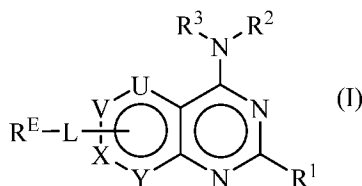
[0059] For a divalent group described herein, no orientation is implied by the direction in which the divalent group is presented. For example, unless a particular orientation is specified,

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

[0060] The phrase “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” has the same meaning as the phrase “(i) 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 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 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

[0061] 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:

one of U, V, X, and Y is $-\text{C}=\text{O}$ or $-\text{N}=\text{O}$; and the remaining three of U, V, X, and Y are each independently $-\text{C}(\text{R}^4)=$ or $-\text{N}=\text{O}$;

L is a linker;

R^E is an E3 ubiquitin ligase binding moiety;

R^1 and R^3 are each independently hydrogen, deuterium, 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;

R^2 is 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, heteroaryl- C_{1-6} alkylene, or heterocyclyl;

each R^4 is independently (i) hydrogen, deuterium, cyano, halo, nitro, or oxo; (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) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and

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, or heterocyclyl;

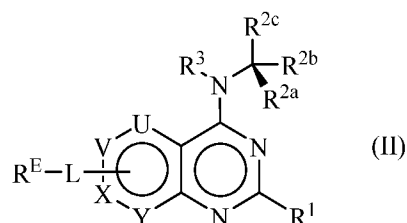
wherein each alkyl, alkylene, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q, wherein each Q is independently selected from: (a) deuterium, cyano, halo, imino, 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) $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^bR^c$, $-C(O)SR^a$, $-C(NR^a)NR^bR^c$, $-C(S)R^a$, $-C(S)OR^a$, $-C(S)NR^bR^c$, $-OR^a$, $-OC(O)R^a$, $-OC(O)OR^a$, $-OC(O)NR^bR^c$, $-OC(O)SR^a$, $-OC(NR^a)NR^bR^c$, $-OC(S)R^a$, $-OC(S)OR^a$, $-OC(S)NR^bR^c$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-OS(O)NR^bR^c$, $-OS(O)_2NR^bR^c$, $-NR^bR^c$, $-NR^aC(O)R^d$, $-NR^aC(O)OR^d$, $-NR^aC(O)NR^bR^c$, $-NR^aC(O)SR^d$, $-NR^aC(NR^d)NR^bR^c$, $-NR^aC(S)R^d$, $-NR^aC(S)OR^d$, $-NR^aC(S)NR^bR^c$, $-NR^aS(O)R^d$, $-NR^aS(O)_2R^d$, $-NR^aS(O)NR^bR^c$, $-NR^aS(O)_2NR^bR^c$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^bR^c$, 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, imino, 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) $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^fR^g$,

$-\text{C}(\text{O})\text{SR}^e$, $-\text{C}(\text{NR}^e)\text{NR}^f\text{R}^g$, $-\text{C}(\text{S})\text{R}^e$, $-\text{C}(\text{S})\text{OR}^e$, $-\text{C}(\text{S})\text{NR}^f\text{R}^g$, $-\text{OR}^e$, $-\text{OC}(\text{O})\text{R}^e$, $-\text{OC}(\text{O})\text{OR}^e$,
 $-\text{OC}(\text{O})\text{NR}^f\text{R}^g$, $-\text{OC}(\text{O})\text{SR}^e$, $-\text{OC}(\text{NR}^e)\text{NR}^f\text{R}^g$, $-\text{OC}(\text{S})\text{R}^e$, $-\text{OC}(\text{S})\text{OR}^e$, $-\text{OC}(\text{S})\text{NR}^f\text{R}^g$,
 $-\text{OS}(\text{O})\text{R}^e$, $-\text{OS}(\text{O})_2\text{R}^e$, $-\text{OS}(\text{O})\text{NR}^f\text{R}^g$, $-\text{OS}(\text{O})_2\text{NR}^f\text{R}^g$, $-\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{C}(\text{O})\text{R}^h$, $-\text{NR}^e\text{C}(\text{O})\text{OR}^f$,
 $-\text{NR}^e\text{C}(\text{O})\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{C}(\text{O})\text{SR}^f$, $-\text{NR}^e\text{C}(\text{NR}^h)\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{C}(\text{S})\text{R}^h$, $-\text{NR}^e\text{C}(\text{S})\text{OR}^f$,
 $-\text{NR}^e\text{C}(\text{S})\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{S}(\text{O})\text{R}^h$, $-\text{NR}^e\text{S}(\text{O})_2\text{R}^h$, $-\text{NR}^e\text{S}(\text{O})\text{NR}^f\text{R}^g$, $-\text{NR}^e\text{S}(\text{O})_2\text{NR}^f\text{R}^g$, $-\text{SR}^e$,
 $-\text{S}(\text{O})\text{R}^e$, $-\text{S}(\text{O})_2\text{R}^e$, $-\text{S}(\text{O})\text{NR}^f\text{R}^g$, and $-\text{S}(\text{O})_2\text{NR}^f\text{R}^g$; 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.

[0062] In certain embodiments, R^2 is C_{1-6} alkyl, C_{7-15} aralkyl, or heteroaryl- C_{1-6} alkylene,
wherein each alkyl, alkylene, aralkyl, and heteroaryl is optionally substituted with one or more
substituents Q. In certain embodiments, R^2 is C_{1-6} alkyl, optionally substituted with one or more
substituents Q. In certain embodiments, R^2 is C_{1-6} alkyl substituted with heteroaryl, *i.e.*,
heteroaryl- C_{1-6} alkylene, where the heteroaryl and alkylene are each optionally substituted with
one or more substituents Q. In certain embodiments, R^2 is monocyclic heteroaryl- C_{1-6} alkylene,
where the heteroaryl and alkylene are each optionally substituted with one or more substituents
Q. In certain embodiments, R^2 is 5- or 6-membered heteroaryl- C_{1-6} alkylene, where the
heteroaryl and alkylene are each optionally substituted with one or more substituents Q. In
certain embodiments, R^2 is 5-membered heteroaryl- C_{1-6} alkylene, where the heteroaryl and
alkylene are each optionally substituted with one or more substituents Q. In certain
embodiments, R^2 is bicyclic heteroaryl- C_{1-6} alkylene, where the heteroaryl and alkylene are each
optionally substituted with one or more substituents Q. In certain embodiments, R^2 is 5,6-fused
or 6,6-fused heteroaryl- C_{1-6} alkylene, where the heteroaryl and alkylene are each optionally
substituted with one or more substituents Q. In certain embodiments, R^2 is C_{7-15} aralkyl,
optionally substituted with one or more substituents Q. In certain embodiments, R^2 is
monocyclic C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain
embodiments, R^2 is bicyclic C_{9-15} aralkyl, optionally substituted with one or more substituents Q.

[0063] 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:

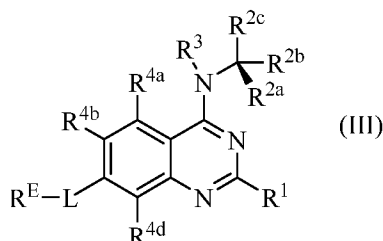
R^{2a} and R^{2b} are each independently hydrogen, deuterium, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, or heterocyclyl;

R^{2c} is C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, or heterocyclyl; and

R^1 , R^3 , R^E , L, U, V, X, and Y are each as defined herein;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

[0064] In yet another embodiment, provided herein is a compound of Formula (III):



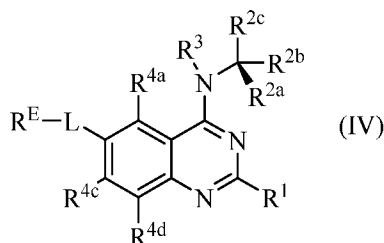
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

R^{4a} , R^{4b} , and R^{4d} are each independently (i) hydrogen, 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, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$,

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

R^1 , R^3 , R^{1a} , R^{1b} , R^{1c} , R^{1d} , R^{2a} , R^{2b} , R^{2c} , R^E , and L are each as defined herein.

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



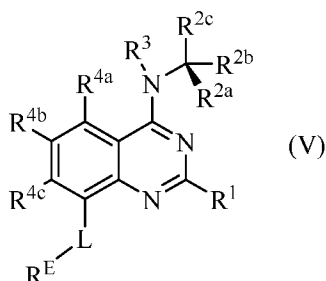
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

R^{4c} is (i) hydrogen, 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, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q ; or (iii) $-\text{C}(\text{O})\text{R}^{1a}$, $-\text{C}(\text{O})\text{OR}^{1a}$, $-\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{C}(\text{O})\text{SR}^{1a}$, $-\text{C}(\text{NR}^{1a})\text{NR}^{1b}\text{R}^{1c}$, $-\text{C}(\text{S})\text{R}^{1a}$, $-\text{C}(\text{S})\text{OR}^{1a}$, $-\text{C}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OR}^{1a}$, $-\text{OC}(\text{O})\text{R}^{1a}$, $-\text{OC}(\text{O})\text{OR}^{1a}$, $-\text{OC}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OC}(\text{O})\text{SR}^{1a}$, $-\text{OC}(\text{NR}^{1a})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OC}(\text{S})\text{R}^{1a}$, $-\text{OC}(\text{S})\text{OR}^{1a}$, $-\text{OC}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS}(\text{O})\text{R}^{1a}$, $-\text{OS}(\text{O})_2\text{R}^{1a}$, $-\text{OS}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{SR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{NR}^{1d})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{R}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{SR}^{1a}$, $-\text{S}(\text{O})\text{R}^{1a}$, $-\text{S}(\text{O})_2\text{R}^{1a}$, $-\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, or $-\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$; and

R^1 , R^3 , R^{1a} , R^{1b} , R^{1c} , R^{1d} , R^{2a} , R^{2b} , R^{2c} , R^{4a} , R^{4d} , R^E , and L are each as defined

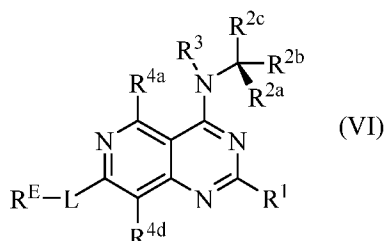
herein.

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



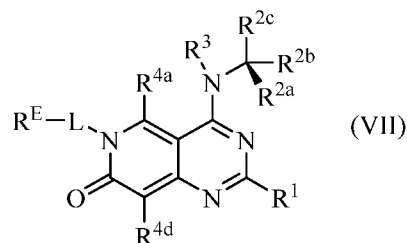
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{2c}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

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



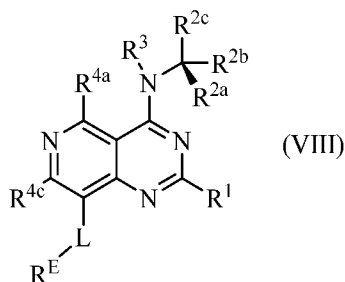
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{2c}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

[0068] In yet another 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^3 , R^{2a} , R^{2b} , R^{2c} , R^{4a} , R^{4d} , R^E , and L are each as defined herein.

[0069] In yet 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^3 , R^{2a} , R^{2b} , R^{2c} , R^{4a} , R^{4c} , R^E , and L are each as defined herein.

[0070] In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is C_{6-14} aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one, two, or three substituents Q . In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is C_{6-14} aryl, optionally substituted with one, two, or three substituents Q . In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is phenyl, optionally substituted with one, two, or three substituents Q . In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is phenyl, optionally substituted with one, two, or three substituents, each of which is independently (i) halo or nitro; (ii) C_{1-6} alkyl, heteroaryl, or heterocyclyl, each optionally substituted with one, two, three, or four substituents Q^a ; or (iii) $-NR^bR^c$, where R^b and R^c are each as defined herein. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is phenyl, optionally substituted with one, two, or three substituents, each of which is independently fluoro, chloro, bromo, iodo, nitro, methyl, difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, 1-hydroxyethyl, 1-hydroxy-1-methylethyl, 2-hydroxy-1,1-difluoroethyl, 3-hydroxyoxetan-3-yl, pyrazol-4-yl, or amino. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is phenyl, 3-bromophenyl, 3-methylphenyl, 3-difluoromethylphenyl, 3-trifluoromethylphenyl, 3-(2,2,2-trifluoroethyl)phenyl, 3-(1-hydroxyethyl)phenyl, 3-(1-hydroxy-1-methylethyl)phenyl, 3-(2-hydroxy-1,1-difluoroethyl)phenyl, 3-(3-hydroxyoxetan-3-yl)phenyl, 3-(1*H*-pyrazol-4-yl)phenyl, 2-fluoro-3-methylphenyl, 2-fluoro-3-difluoromethylphenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-3-(1,1-difluoroethyl)phenyl, 2-methyl-3-difluoromethylphenyl, 2-methyl-3-trifluoromethylphenyl, 3-trifluoromethyl-5-aminophenyl, 2-

fluoro-3-trifluoromethyl-5-aminophenyl, or 2-methyl-3-trifluoromethyl-5-aminophenyl. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is bicyclic C_{9-14} aryl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is 5,6- or 6,6-fused C_{9-14} aryl, each optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is 2,3-dihydro-1*H*-indenyl or naphthyl, each optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is 2,3-dihydro-1*H*-inden-5-yl or naphtha-1-yl, each optionally substituted with one, two, or three substituents Q.

[0071] In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is heteroaryl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is monocyclic heteroaryl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is 5- or 6-membered heteroaryl, each optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is thienyl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is thien-2-yl or thien-3-yl, each optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is thien-2-yl, substituted with C_{6-14} aryl or heteroaryl, where the aryl and heteroaryl are each optionally further substituted with one, two, or three substituents Q^a . In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is thieny-2-yl, 5-(2-hydroxymethylphenyl)thien-2-yl, 5-(2-aminomethylphenyl)-thien-2-yl, 4-(2-methylaminomethylphenyl)thien-2-yl, 5-(2-(2-aminoethyl)-phenyl)thien-2-yl, or 5-(6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl)thien-2-yl. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is 5-(2-hydroxymethylphenyl)thien-2-yl, 5-(2-aminomethylphenyl)-thien-2-yl, 4-(2-methylaminomethylphenyl)thien-2-yl, 5-(2-(2-aminoethyl)phenyl)thien-2-yl, or 5-(6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl)thien-2-yl. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is bicyclic heteroaryl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is 5,5-, 5,6-, or 6,6-fused heteroaryl, each optionally substituted with one, two, or three substituents Q.

[0072] In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is heterocyclyl,

optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is monocyclic heterocyclyl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is 3-, 4-, 5-, 6-, or 7-membered heterocyclyl, each optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is bicyclic heterocyclyl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is 5,5-, 5,6-, or 6,6-fused heterocyclyl, each optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (II) to (VIII), R^{2c} is 2,3-dihydrobenzofuranyl, optionally substituted with one, two, or three substituents Q.

[0073] In certain embodiments, in any one of Formulae (III) to (VIII),
 R¹ is hydrogen, methyl, trifluoromethyl, or dimethylamino;
 R³ is hydrogen;
 R^{2a} and R^{2b} are each independently hydrogen, deuterium, methyl, or ethyl;
 R^{2c} is phenyl, 2,3-dihydroindenyl, naphthyl, thienyl, or 2,3-dihydrobenzofuranyl, each of which is optionally substituted with one, two, or three substituents, wherein each substituent is independently fluoro, chloro, bromo, iodo, nitro, methyl, difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, 1-hydroxyethyl, 1-hydroxy-1-methylethyl, 2-hydroxy-1,1-difluoroethyl, 2-hydroxymethylphenyl, 2-aminomethylphenyl, 2-methylaminomethylphenyl, 2-(2-aminoethyl)phenyl, 3-hydroxyoxetan-3-yl, pyrazol-4-yl, 6,7-dihydro-5H-pyrrolo[1,2-a]imidazolyl, or amino;
 R^{4a}, if present, is hydrogen;
 R^{4b}, if present, is cyclopropyl, cyclobutyl, cyclohexyl, cyclohexenyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, methoxy, tetrahydrofuryloxy, or pyrrolidinyl, each of which is optionally substituted with one, two, or three substituents, wherein each substituent is independently fluoro, oxo, imino, methyl, difluoromethyl, hydroxycarbonylmethyl, dimethylcarbamoylmethyl, isopropyl, tetrahydrofur-3-yl, acetyl, propionyl, 2-methoxyacetyl, 2-dimethylaminoacetyl, cyclopropylcarbonyl, 3-cyanoazetidin-1-ylcarbonyl, 3-fluoroazetidin-1-ylcarbonyl, 3-methoxyazetidin-1-ylcarbonyl, 3-hydroxypyrrolidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-(2-methoxyethyl)piperazin-1-ylcarbonyl, hydroxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, dimethylcarbamoyl, (methyl)(ethyl)-

carbamoyl, (2-hydroxyethyl)(methyl)carbamoyl, (2-hydroxypropyl)(methyl)carbamoyl, (2-hydroxy-2-methylpropyl)(methyl)carbamoyl, (2,3-dihydroxypropyl)(methyl)carbamoyl, (2-methoxyethyl)(methyl)carbamoyl, (methyl)(oxetan-3-yl)carbamoyl, (methyl)(tetrahydrofuran-3-yl)carbamoyl, hydroxyl, or acetoxy;

R^{4c} , if present, is hydrogen or methoxy; and

R^{4d} , if present, is hydrogen, fluoro, or methyl.

[0074] In certain embodiments, in any one of Formulae (III) to (VIII),

R^1 is hydrogen, methyl, trifluoromethyl, or dimethylamino;

R^3 is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{2c} is phenyl, 3-bromophenyl, 3-methylphenyl, 3-difluoromethylphenyl, 3-trifluoromethylphenyl, 3-(2,2,2-trifluoroethyl)phenyl, 3-(1-hydroxyethyl)phenyl, 3-(1-hydroxy-1-methylethyl)phenyl, 3-(2-hydroxy-1,1-difluoroethyl)phenyl, 3-(3-hydroxyoxetan-3-yl)phenyl, 3-(1*H*-pyrazol-4-yl)phenyl, 2-fluoro-3-methylphenyl, 2-fluoro-3-difluoromethylphenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-3-(1,1-difluoroethyl)phenyl, 2-methyl-3-difluoromethylphenyl, 2-methyl-3-trifluoromethylphenyl, 3-trifluoromethyl-5-aminophenyl, 2-fluoro-3-trifluoromethyl-5-aminophenyl, 2-methyl-3-trifluoromethyl-5-aminophenyl, 3,3-difluoro-2,3-dihydro-1*H*-inden-5-yl, naphth-1-yl, thien-2-yl, 5-(2-hydroxymethylphenyl)thien-2-yl, 5-(2-aminomethylphenyl)thien-2-yl, 4-(2-methylaminomethylphenyl)thien-2-yl, 5-(2-(2-aminoethyl)phenyl)thien-2-yl, 5-(6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl)thien-2-yl, or 3,3-difluoro-2,3-dihydrobenzofuran-5-yl;

R^{4a} , if present, is hydrogen;

R^{4b} , if present, is 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, 4-hydroxycyclohexyl, 4-hydroxycarbonylcyclohexyl, 4-ethoxycarbonylcyclohexyl, 4-(3-cyanoazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-fluoroazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-methoxyazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-hydroxypyrrolidin-1-yl)carbonylcyclohexyl, 4-morpholin-4-ylcarbonylcyclohexyl, 4-(4-methylpiperazin-1-yl)carbonylcyclohexyl, 4-(4-(2-methoxyethyl)piperazin-1-yl)carbonylcyclohexyl, 4-dimethylcarbamoylcyclohexyl, 4-(methyl)(ethyl)carbamoylcyclohexyl, 4-(2-hydroxyethyl)(methyl)carbamoylcyclohexyl, 4-(2-hydroxypropyl)(methyl)carbamoyl-

cyclohexyl, 4-(2-hydroxy-2-methylpropyl)(methyl)-carbamoylcyclohexyl, 4-(2,3-dihydroxypropyl)(methyl)carbamoylcyclohexyl, 4-(2-methoxyethyl)(methyl)carbamoylcyclohexyl, 4-(methyl)(oxetan-3-yl)carbamoylcyclohexyl, 4-(methyl)(tetrahydrofuran-3-yl)carbamoylcyclohexyl, 4-acetoxy-1-hydroxycyclohexyl, 1,4-dihydroxycyclohexyl, 4-hydroxycarbonyl-1-hydroxycyclohexyl, 4-ethoxycarbonyl-1-hydroxycyclohexyl, 4-dimethylcarbamoyl-1-hydroxycyclohexyl, 4-(2-hydroxyethyl)(methyl)-carbamoyl-1-hydroxycyclohexyl, 4-(2-hydroxypropyl)(methyl)-carbamoyl-1-hydroxy-cyclohexyl, bicyclo[1.1.1]pentan-1-yl, 4-fluorobicyclo[2.2.2]octan-1-yl, 3-methyltetrahydrofuran-3-yl, piperidin-4-yl, 1-isopropylpiperidin-4-yl, 1-(hydroxycarbonylmethyl)piperidin-4-yl, 1-(dimethylcarbamoylmethyl)piperidin-4-yl, 1-tetrahydrofuran-3-ylpiperidin-4-yl, 1-acetyl piperidin-4-yl, 1-(2-methoxyacetyl)piperidin-4-yl, 1-(2-dimethylaminoacetyl)piperidin-4-yl, 1-*tert*-butoxycarbonylpiperidin-4-yl, 4-hydroxypiperidin-4-yl, 1-acetyl-4-hydroxypiperidin-4-yl, 1-(2-methoxyacetyl)-4-hydroxypiperidin-4-yl, 4-hydroxy-1-*tert*-butoxycarbonylpiperidin-4-yl, 1-dimethylcarbamoyl-4-hydroxypiperidin-4-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, 1-oxotetrahydrothiopyran-4-yl, 1,1-dioxotetrahydrothiopyran-4-yl, 1-oxo-1-iminotetrahydrothiopyran-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, 3,6-dihydropyran-4-yl, 3,6-dihydrothiopyran-4-yl, 1-oxo-3,6-dihydrothiopyran-4-yl, 1,1-dioxo-3,6-dihydrothiopyran-4-yl, 1-oxo-1-imino-3,6-dihydrothiopyran-4-yl, 6-hydroxy-2-azaspiro[3.3]heptan-6-yl, 2-hydroxy-7-azaspiro[3.5]nonan-2-yl, methoxy, tetrahydrofuran-3-yloxy, (*R*)-tetrahydrofuran-3-yloxy, (*S*)-tetrahydrofuran-3-yloxy, pyrrolidin-3-yloxy, 1-acetylpyrrolidin-3-yloxy, 1-propionylpyrrolidin-3-yloxy, 1-cyclopropylcarbonylpyrrolidin-3-yloxy, or 1-*tert*-butoxycarbonylpyrrolidin-3-yloxy;

R^{4c} , if present, is hydrogen, fluoro, methyl, or methoxy; and

R^{4d} , if present, is hydrogen, fluoro, or methyl.

[0075] In certain embodiments, in any one of Formulae (III) to (VIII),

R^1 is hydrogen, methyl, trifluoromethyl, or dimethylamino;

R^3 is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{2c} is phenyl, 3-bromophenyl, 3-methylphenyl, 3-difluoromethylphenyl, 3-trifluoromethylphenyl, 3-(2,2,2-trifluoroethyl)phenyl, 3-(1-hydroxyethyl)phenyl, 3-(1-hydroxy-1-methylethyl)phenyl, 3-(2-hydroxy-1,1-difluoroethyl)phenyl, 3-(3-hydroxyoxetan-3-yl)phenyl, 3-(1*H*-pyrazol-4-yl)phenyl, 2-fluoro-3-methylphenyl, 2-fluoro-3-difluoromethylphenyl, 2-fluoro-

3-trifluoromethylphenyl, 2-fluoro-3-(1,1-difluoroethyl)phenyl, 2-methyl-3-difluoromethylphenyl, 2-methyl-3-trifluoromethylphenyl, 3-trifluoromethyl-5-aminophenyl, 2-fluoro-3-trifluoromethyl-5-aminophenyl, 2-methyl-3-trifluoromethyl-5-aminophenyl, 3,3-difluoro-2,3-dihydro-1*H*-inden-5-yl, naphth-1-yl, 5-(2-hydroxymethylphenyl)thien-2-yl, 5-(2-aminomethylphenyl)thien-2-yl, 4-(2-methylaminomethylphenyl)thien-2-yl, 5-(2-(2-aminoethyl)phenyl)thien-2-yl, 5-(6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl)thien-2-yl, or 3,3-difluoro-2,3-dihydro-benzofuran-5-yl;

R^{4a}, if present, is hydrogen;

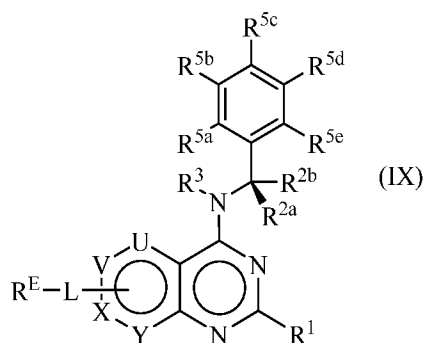
R^{4b}, if present, is 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, 4-hydroxycyclohexyl, 4-hydroxycarbonylcyclohexyl, 4-ethoxycarbonylcyclohexyl, 4-(3-cyanoazetidin-1-ylcarbonyl)-cyclohexyl, 4-(3-fluoroazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-methoxyazetidin-1-ylcarbonyl)-cyclohexyl, 4-(3-hydroxypyrrolidin-1-yl)carbonylcyclohexyl, 4-morpholin-4-ylcarbonyl-cyclohexyl, 4-(4-methylpiperazin-1-yl)carbonylcyclohexyl, 4-(4-(2-methoxyethyl)piperazin-1-yl)carbonylcyclohexyl, 4-dimethylcarbamoylcyclohexyl, 4-(methyl)(ethyl)carbamoylcyclohexyl, 4-(2-hydroxyethyl)(methyl)carbamoylcyclohexyl, 4-(2-hydroxypropyl)(methyl)carbamoyl-cyclohexyl, 4-(2-hydroxy-2-methylpropyl)(methyl)-carbamoylcyclohexyl, 4-(2,3-dihydroxypropyl)(methyl)carbamoylcyclohexyl, 4-(2-methoxyethyl)(methyl)carbamoylcyclohexyl, 4-(methyl)(oxetan-3-yl)carbamoylcyclohexyl, 4-(methyl)(tetrahydrofur-3-yl)carbamoylcyclohexyl, 4-acetoxy-1-hydroxycyclohexyl, 1,4-dihydroxycyclohexyl, 4-hydroxycarbonyl-1-hydroxy-cyclohexyl, 4-ethoxycarbonyl-1-hydroxycyclohexyl, 4-dimethylcarbamoyl-1-hydroxy-cyclohexyl, 4-(2-hydroxyethyl)(methyl)-carbamoyl-1-hydroxycyclohexyl, 4-(2-hydroxypropyl)-(methyl)carbamoyl-1-hydroxy-cyclohexyl, bicyclo[1.1.1]pentan-1-yl, 4-fluorobicyclo[2.2.2]-octan-1-yl, 3-methyltetrahydrofuran-3-yl, piperidin-4-yl, 1-isopropylpiperidin-4-yl, 1-(hydroxycarbonylmethyl)piperidin-4-yl, 1-(dimethylcarbamoylmethyl)piperidin-4-yl, 1-tetrahydrofur-3-ylpiperidin-4-yl, 1-acetyl piperidin-4-yl, 1-(2-methoxyacetyl)piperidin-4-yl, 1-(2-dimethylaminoacetyl)piperidin-4-yl, 1-*tert*-butoxycarbonylpiperidin-4-yl, 4-hydroxypiperidin-4-yl, 1-acetyl-4-hydroxypiperidin-4-yl, 1-(2-methoxyacetyl)-4-hydroxypiperidin-4-yl, 4-hydroxy-1-*tert*-butoxycarbonylpiperidin-4-yl, 1-dimethylcarbamoyl-4-hydroxypiperidin-4-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, 1-oxotetrahydrothiopyran-4-yl, 1,1-dioxotetrahydrothiopyran-4-yl, 1-oxo-1-iminotetrahydrothiopyran-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, 3,6-dihydropyran-4-yl, 3,6-

dihydrothiopyran-4-yl, 1-oxo-3,6-dihydrothiopyran-4-yl, 1,1-dioxo-3,6-dihydrothiopyran-4-yl, 1-oxo-1-imino-3,6-dihydrothiopyran-4-yl, 6-hydroxy-2-azaspiro[3.3]heptan-6-yl, 2-hydroxy-7-azaspiro[3.5]nonan-2-yl, methoxy, tetrahydrofur-3-yloxy, (*R*)-tetrahydrofur-3-yloxy, (*S*)-tetrahydrofur-3-yloxy, pyrrolidin-3-yloxy, 1-acetylpyrrolidin-3-yloxy, 1-propionylpyrrolidin-3-yloxy, 1-cyclopropylcarbonylpyrrolidin-3-yloxy, or 1-*tert*-butoxycarbonylpyrrolidin-3-yloxy;

R^{4c} , if present, is hydrogen, fluoro, methyl, or methoxy; and

R^{4d} , if present, is hydrogen, fluoro, or methyl.

[0076] 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:

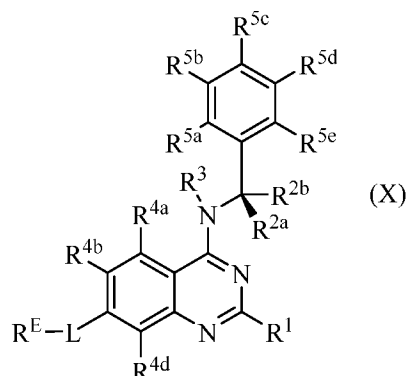
R^{5a} , R^{5b} , R^{5c} , R^{5d} , and R^{5e} are each independently (i) hydrogen, deuterium, cyano, halo, nitro, or oxo; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more, in one embodiment, one, two, or three, substituents Q; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; or

R^{5a} and R^{5b} or R^{5b} and R^{5c} together with the carbon atoms to which they are attached form C_{5-10} cycloalkyl, C_{6-14} aryl, heteroaryl, or heterocyclyl, each of which is optionally

substituted with one or more, in one embodiment, one, two, or three, substituents Q; and

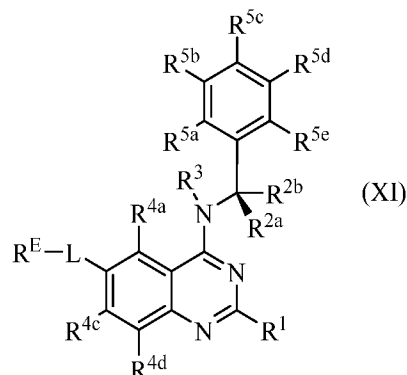
R^1 , R^3 , R^{1a} , R^{1b} , R^{1c} , R^{1d} , R^{2a} , R^{2b} , R^E , L, U, V, X, and Y are each as defined herein.

[0077] In yet another embodiment, provided herein is a compound of Formula (X):



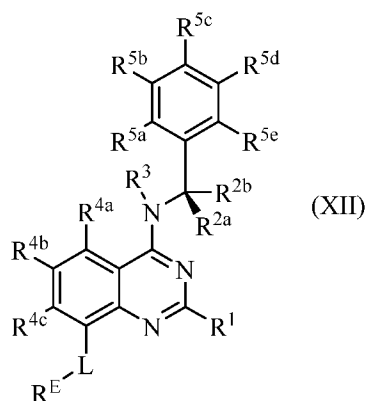
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a}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

[0078] In yet another embodiment, provided herein is a compound of Formula (XI):



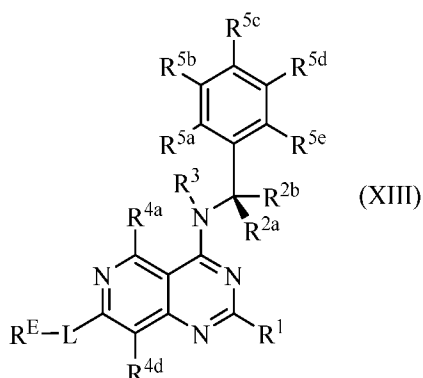
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a}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

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



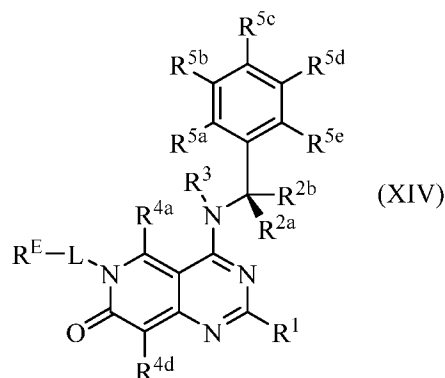
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a}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

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



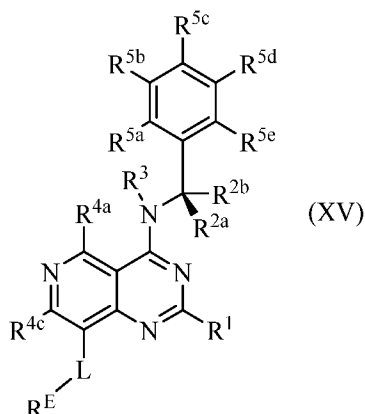
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a}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

[0081] In yet 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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^E , and L are each as defined herein.

[0082] 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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4c} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^E , and L are each as defined herein.

[0083] In certain embodiments, in any one of Formulae (X) to (XV),

R^1 is hydrogen, methyl, trifluoromethyl, or dimethylamino;

R^3 is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a} , if present, is hydrogen;

R^{4b}, if present, is cyclopropyl, cyclobutyl, cyclohexyl, cyclohexenyl, bicyclo[1.1.1]pentanyl, or bicyclo[2.2.2]octanyl, each of which is optionally substituted with one, two, or three substituents, wherein each substituent is independently fluoro, methyl, difluoromethyl, 3-cyanoazetidin-1-ylcarbonyl, 3-fluoroazetidin-1-ylcarbonyl, 3-methoxyazetidin-1-ylcarbonyl, 3-hydroxypyrrolidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-(2-methoxyethyl)piperazin-1-ylcarbonyl, hydroxycarbonyl, ethoxycarbonyl, dimethylcarbamoyl, (methyl)(ethyl)carbamoyl, (2-hydroxyethyl)(methyl)-carbamoyl, (2-hydroxypropyl)(methyl)carbamoyl, (2-hydroxy-2-methylpropyl)(methyl)-carbamoyl, (2,3-dihydroxypropyl)(methyl)carbamoyl, (2-methoxyethyl)(methyl)carbamoyl, (methyl)(oxetan-3-yl)carbamoyl, (methyl)(tetrahydrofur-3-yl)carbamoyl, hydroxyl, or acetoxy;

R^{4c}, if present, is hydrogen or methoxy;

R^{4d}, if present, is hydrogen, fluoro, or methyl;

R^{5a} is hydrogen, fluoro, or methyl;

R^{5b} is bromo, fluoromethyl, difluoromethyl, trifluoromethyl, difluoroethyl, (difluoro)(hydroxy)ethyl, or pyrazolyl;

R^{5c} and R^{5e} are each hydrogen; and

R^{5d} is hydrogen, nitro, or amino.

[0084] In certain embodiments, in any one of Formulae (X) to (XV),

R¹ is hydrogen, methyl, or trifluoromethyl;

R³ is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a}, if present, is hydrogen;

R^{4b}, if present, is 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, 4-hydroxycyclohexyl, 4-hydroxycarbonylcyclohexyl, 4-ethoxycarbonylcyclohexyl, 4-(3-cyanoazetidin-1-ylcarbonyl)-cyclohexyl, 4-(3-fluoroazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-methoxyazetidin-1-ylcarbonyl)-cyclohexyl, 4-(3-hydroxypyrrolidin-1-yl)carbonylcyclohexyl, 4-morpholin-4-ylcarbonyl-cyclohexyl, 4-(4-methylpiperazin-1-yl)carbonylcyclohexyl, 4-(4-(2-methoxyethyl)piperazin-1-yl)carbonylcyclohexyl, 4-dimethylcarbamoylcyclohexyl, 4-(methyl)(ethyl)carbamoylcyclohexyl, 4-(2-hydroxyethyl)(methyl)carbamoylcyclohexyl, 4-(2-hydroxypropyl)(methyl)carbamoyl-

cyclohexyl, 4-(2-hydroxy-2-methylpropyl)(methyl)-carbamoylcyclohexyl, 4-(2,3-dihydroxypropyl)(methyl)carbamoylcyclohexyl, 4-(2-methoxyethyl)(methyl)carbamoylcyclohexyl, 4-(methyl)(oxetan-3-yl)carbamoylcyclohexyl, 4-(methyl)(tetrahydrofuran-3-yl)-carbamoylcyclohexyl, 4-acetoxy-1-hydroxycyclohexyl, 1,4-dihydroxycyclohexyl, 4-hydroxycarbonyl-1-hydroxycyclohexyl, 4-ethoxycarbonyl-1-hydroxycyclohexyl, 4-dimethylcarbamoyl-1-hydroxycyclohexyl, 4-(2-hydroxyethyl)(methyl)-carbamoyl-1-hydroxycyclohexyl, 4-(2-hydroxypropyl)(methyl)carbamoyl-1-hydroxy-cyclohexyl, bicyclo[1.1.1]pentan-1-yl, or 4-fluorobicyclo[2.2.2]octan-1-yl;

R^{4c} , if present, is hydrogen or methoxy;

R^{4d} , if present, is hydrogen, fluoro, or methyl;

R^{5a} is hydrogen, fluoro, or methyl;

R^{5b} is bromo, difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, 1,1-difluoro-2-hydroxyethyl, or pyrazol-4-yl;

R^{5c} and R^{5e} are each hydrogen; and

R^{5d} is hydrogen, nitro, or amino.

[0085] In certain embodiments, in any one of Formulae (X) to (XV),

R^1 is hydrogen, methyl, trifluoromethyl, or dimethylamino;

R^3 is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a} , if present, is hydrogen;

R^{4b} , if present, is tetrahydrofuryl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydropyridinyl, dihydropyranyl, dihydrothiopyranyl, azaspiro[3.3]heptanyl, or 7-azaspiro[3.5]nonanyl, each of which is optionally substituted with one, two, or three substituents, wherein each substituent is independently oxo, imino, isopropyl, hydroxycarbonylmethyl, dimethylcarbamoylmethyl, tetrahydrofuran-3-yl, acetyl, 2-methoxy-acetyl, 2-dimethylaminoacetyl, *tert*-butoxycarbonyl, or hydroxyl;

R^{4c} , if present, is hydrogen or methoxy;

R^{4d} , if present, is hydrogen, fluoro, or methyl;

R^{5a} is hydrogen, fluoro, or methyl;

R^{5b} is bromo, fluoromethyl, difluoromethyl, trifluoromethyl, difluoroethyl,

(difluoro)(hydroxy)ethyl, or pyrazolyl;

R^{5c} and R^{5e} are each hydrogen; and

R^{5d} is hydrogen, nitro, or amino.

[0086] In certain embodiments, in any one of Formulae (X) to (XV),

R^1 is hydrogen, methyl, or trifluoromethyl;

R^3 is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a} , if present, is hydrogen;

R^{4b} , if present, is 3-methyltetrahydrofuran-3-yl, piperidin-4-yl, 1-isopropyl-piperidin-4-yl, 1-(hydroxycarbonylmethyl)piperidin-4-yl, 1-(dimethylcarbamoyl-methyl)-piperidin-4-yl, 1-tetrahydrofur-3-ylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-(2-methoxyacetyl)-piperidin-4-yl, 1-(2-dimethylaminoacetyl)piperidin-4-yl, 1-*tert*-butoxycarbonyl-piperidin-4-yl, 4-hydroxypiperidin-4-yl, 1-acetyl-4-hydroxypiperidin-4-yl, 1-(2-methoxyacetyl)-4-hydroxy-piperidin-4-yl, 4-hydroxy-1-*tert*-butoxycarbonylpiperidin-4-yl, 1-dimethyl-carbamoyl-4-hydroxypiperidin-4-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, 1-oxotetrahydrothiopyran-4-yl, 1,1-dioxotetrahydrothiopyran-4-yl, 1-oxo-1-iminotetrahydrothiopyran-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, 3,6-dihydropyran-4-yl, 3,6-dihydrothiopyran-4-yl, 1-oxo-3,6-dihydrothiopyran-4-yl, 1,1-dioxo-3,6-dihydrothiopyran-4-yl, 1-oxo-1-imino-3,6-dihydrothiopyran-4-yl, 6-hydroxy-2-azaspiro[3.3]heptan-6-yl, or 2-hydroxy-7-azaspiro[3.5]nonan-2-yl;

R^{4c} , if present, is hydrogen or methoxy;

R^{4d} , if present, is hydrogen, fluoro, or methyl;

R^{5a} is hydrogen, fluoro, or methyl;

R^{5b} is bromo, difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, 1,1-difluoro-2-hydroxyethyl, or pyrazol-4-yl;

R^{5c} and R^{5e} are each hydrogen; and

R^{5d} is hydrogen, nitro, or amino.

[0087] In certain embodiments, in any one of Formulae (X) to (XV),

R^1 is hydrogen, methyl, trifluoromethyl, or dimthylamino;

R^3 is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a}, if present, is hydrogen;

R^{4b}, if present, is tetrahydrofuryloxy or pyrrolidinyloxy, each of which is optionally substituted with acetyl, propionyl, cyclopropylcarbonyl, or *tert*-butoxycarbonyl;

R^{4c}, if present, is hydrogen or methoxy;

R^{4d}, if present, is hydrogen, fluoro, or methyl;

R^{5a} is hydrogen, fluoro, or methyl;

R^{5b} is bromo, fluoromethyl, difluoromethyl, trifluoromethyl, difluoroethyl, (difluoro)(hydroxy)ethyl, or pyrazolyl;

R^{5c} and R^{5e} are each hydrogen; and

R^{5d} is hydrogen, nitro, or amino.

[0088] In certain embodiments, in any one of Formulae (X) to (XV),

R¹ is hydrogen, methyl, or trifluoromethyl;

R³ is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a}, if present, is hydrogen;

R^{4b}, if present, is tetrahydrofur-3-yloxy, (*R*)-tetrahydrofur-3-yloxy, (*S*)-tetrahydrofur-3-yloxy, pyrrolidin-3-yloxy, 1-acetylpyrrolidin-3-yloxy, 1-propionylpyrrolidin-3-yloxy, 1-cyclopropylcarbonylpyrrolidin-3-yloxy, or 1-*tert*-butoxycarbonylpyrrolidin-3-yloxy;

R^{4c}, if present, is hydrogen or methoxy;

R^{4d}, if present, is hydrogen, fluoro, or methyl;

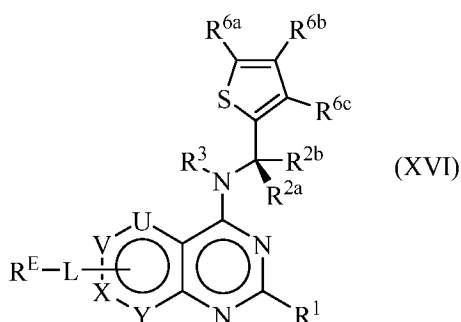
R^{5a} is hydrogen, fluoro, or methyl;

R^{5b} is bromo, difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, 1,1-difluoro-2-hydroxyethyl, or pyrazol-4-yl;

R^{5c} and R^{5e} are each hydrogen; and

R^{5d} is hydrogen, nitro, or amino.

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

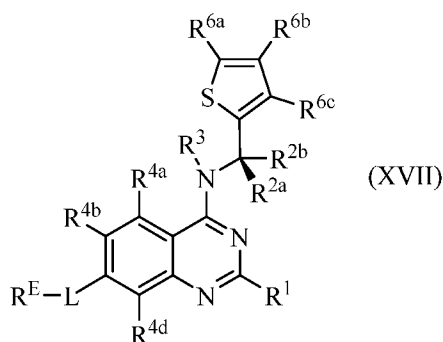


or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

R^{6a} , R^{6b} , and R^{6c} are each independently (i) hydrogen, deuterium, cyano, halo, nitro, or oxo; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, alkyl, 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, or three, substituents Q; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and

R^1 , R^3 , R^{1a} , R^{1b} , R^{1c} , R^{1d} , R^{2a} , R^{2b} , R^E , L, U, V, X, and Y are each as defined herein.

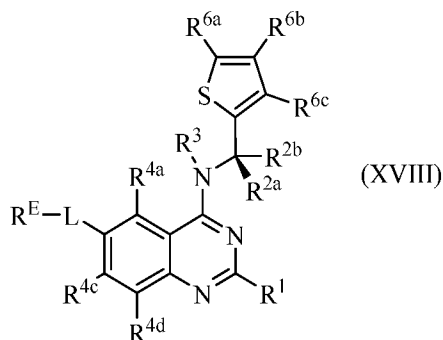
[0090] In yet another embodiment, provided herein is a compound of Formula (XVII):



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

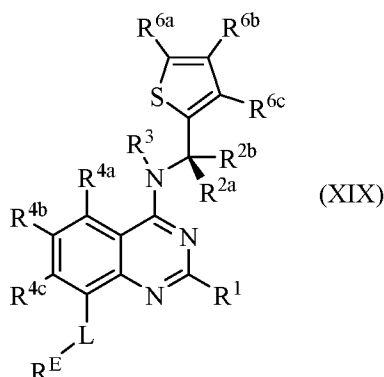
diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^E , and L are each as defined herein.

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



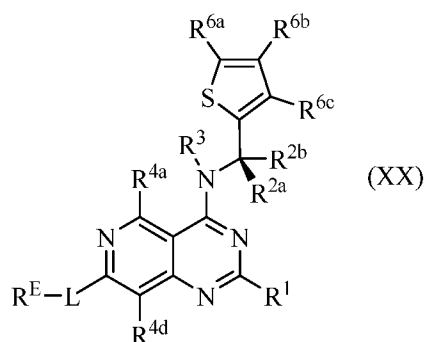
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a}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

[0092] In yet another embodiment, provided herein is a compound of Formula (XIX):



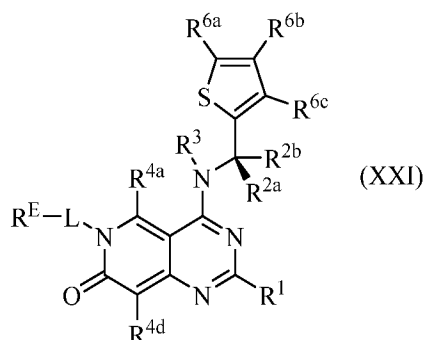
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a}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

[0093] In yet another embodiment, provided herein is a compound of Formula (XX):



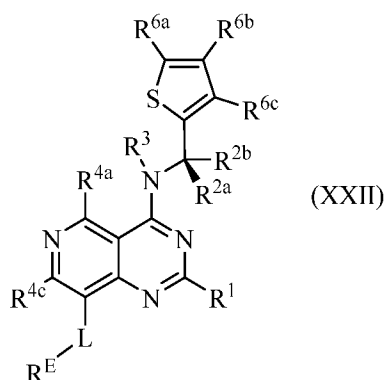
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a}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

[0094] 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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^E , and L are each as defined herein.

[0095] In still 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 R¹, R³, R^{2a}, R^{2b}, R^{4a}, R^{4c}, R^{6a}, R^{6b}, R^{6c}, R^E, and L are each as defined herein.

[0096] In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is (i) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more, in one embodiment, one, two, or three, substituents Q; or (ii) –OR^{1a}, where R^{1a} is as defined herein. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is C₁₋₆ alkyl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is C₂₋₆ alkenyl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is C₆₋₁₄ aryl, optionally substituted with one, two, or three substituents Q.

[0097] In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is C₃₋₁₀ cycloalkyl, optionally substituted with one or more, in one embodiment, one, two, or three, substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is monocyclic C₃₋₁₀ cycloalkyl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is bicyclic C₄₋₁₀ cycloalkyl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is cyclopropyl, cyclobutyl, cyclohexyl, cyclohexenyl, bicyclo[1.1.1]pentanyl, or bicyclo[2.2.2]octanyl, each of which is optionally substituted with one, two, or three substituents Q, where each substituent is independently (i) C₁₋₆ alkyl,

optionally substituted with one or more substituents Q^a ; or (ii) $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^bR^c$, $-OR^a$, or $-OC(O)R^a$, where each R^a , R^b , and R^c is as defined herein. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is cyclopropyl, cyclobutyl, cyclohexyl, cyclohexenyl, bicyclo[1.1.1]pentanyl, or bicyclo[2.2.2]octanyl, each of which is optionally substituted with one, two, or three substituents, where each substituent is independently fluoro, methyl, difluoromethyl, 3-cyanoazetidin-1-ylcarbonyl, 3-fluoroazetidin-1-ylcarbonyl, 3-methoxyazetidin-1-ylcarbonyl, 3-hydroxypyrrolidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-(2-methoxyethyl)piperazin-1-ylcarbonyl, hydroxycarbonyl, ethoxycarbonyl, dimethylcarbamoyl, (methyl)(ethyl)carbamoyl, (2-hydroxyethyl)(methyl)carbamoyl, (2-hydroxypropyl)(methyl)carbamoyl, (2-hydroxy-2-methylpropyl)(methyl)carbamoyl, (2,3-dihydroxypropyl)(methyl)carbamoyl, (2-methoxyethyl)(methyl)carbamoyl, (methyl)(oxetan-3-yl)carbamoyl, (methyl)(tetrahydrofuran-3-yl)carbamoyl, hydroxyl, or acetoxy. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 3-fluoro-cyclobutyl, 3,3-difluorocyclobutyl, 4-hydroxycyclohexyl, 4-hydroxycarbonylcyclohexyl, 4-ethoxycarbonylcyclohexyl, 4-(3-cyanoazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-fluoroazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-methoxyazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-hydroxypyrrolidin-1-yl)carbonylcyclohexyl, 4-morpholin-4-ylcarbonylcyclohexyl, 4-(4-methylpiperazin-1-yl)carbonylcyclohexyl, 4-(4-(2-methoxyethyl)piperazin-1-yl)carbonylcyclohexyl, 4-dimethylcarbamoylcyclohexyl, 4-(methyl)(ethyl)carbamoylcyclohexyl, 4-(2-hydroxyethyl)(methyl)carbamoylcyclohexyl, 4-(2-hydroxypropyl)(methyl)carbamoylcyclohexyl, 4-(2-hydroxy-2-methylpropyl)(methyl)carbamoylcyclohexyl, 4-(2,3-dihydroxypropyl)(methyl)carbamoylcyclohexyl, 4-(2-methoxyethyl)(methyl)carbamoylcyclohexyl, 4-(methyl)(oxetan-3-yl)carbamoylcyclohexyl, 4-(methyl)(tetrahydrofuran-3-yl)carbamoylcyclohexyl, 4-acetoxy-1-hydroxycyclohexyl, 1,4-dihydroxycyclohexyl, 4-hydroxycarbonyl-1-hydroxycyclohexyl, 4-ethoxycarbonyl-1-hydroxycyclohexyl, 4-dimethylcarbamoyl-1-hydroxycyclohexyl, 4-(2-hydroxyethyl)(methyl)carbamoyl-1-hydroxycyclohexyl, 4-(2-hydroxypropyl)(methyl)carbamoyl-1-hydroxycyclohexyl, bicyclo[1.1.1]pentan-1-yl, or 4-fluorobicyclo[2.2.2]octan-1-yl.

[0098] In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is heteroaryl, optionally substituted with one or more, in one embodiment, one, two,

or three, substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is monocyclic heteroaryl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is 5- or 6-membered heteroaryl, each optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is pyrazolyl or pyridinyl, each optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is pyrazol-4-yl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each optionally substituted with one, two, or three substituents Q.

[0099] In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is monocyclic heterocyclyl, optionally substituted with one, two, or three, substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is 5- or 6-membered heterocyclyl, each optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is bicyclic heterocyclyl, optionally substituted with one, two, or three, substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is tetrahydrofuryl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydropyridinyl, dihydropyranyl, dihydrothiopyranyl, azaspiro[3.3]heptanyl, or 7-azaspiro[3.5]nonanyl, each of which is optionally substituted with one, two, or three substituents, where each substituent is independently oxo, imino, isopropyl, hydroxycarbonylmethyl, dimethylcarbamoylmethyl, tetrahydrofur-3-yl, acetyl, 2-methoxyacetyl, 2-dimethylaminoacetyl, *tert*-butoxycarbonyl, or hydroxyl. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is 3-methyltetrahydrofuran-3-yl, piperidin-4-yl, 1-isopropylpiperidin-4-yl, 1-(hydroxycarbonyl-methyl)piperidin-4-yl, 1-(dimethylcarbamoylmethyl)piperidin-4-yl, 1-tetrahydrofur-3-ylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-(2-methoxyacetyl)piperidin-4-yl, 1-(2-dimethylamino-acetyl)piperidin-4-yl, 1-*tert*-butoxycarbonylpiperidin-4-yl, 4-hydroxypiperidin-4-yl, 1-acetyl-4-hydroxypiperidin-4-yl, 1-(2-methoxyacetyl)-4-hydroxypiperidin-4-yl, 4-hydroxy-1-*tert*-butoxy-carbonylpiperidin-4-yl, 1-dimethylcarbamoyl-4-hydroxypiperidin-4-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, 1-oxotetrahydrothiopyran-4-yl, 1,1-dioxotetrahydro-

thiopyran-4-yl, 1-oxo-1-iminotetrahydrothiopyran-4-yl, 1,2,3,6-tetrahydro-pyridin-4-yl, 3,6-dihydropyran-4-yl, 3,6-dihydrothiopyran-4-yl, 1-oxo-3,6-dihydrothiopyran-4-yl, 1,1-dioxo-3,6-dihydrothiopyran-4-yl, 1-oxo-1-imino-3,6-dihydrothiopyran-4-yl, 6-hydroxy-2-azaspiro[3.3]heptan-6-yl, or 2-hydroxy-7-azaspiro[3.5]nonan-2-yl.

[00100] In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is $-OR^{1a}$, where R^{1a} is as defined herein. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is $-O-C_{1-6}$ alkyl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is methoxy. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is $-O$ -heterocyclyl, optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is $-O$ -(monocyclic heterocyclyl), optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is $-O$ -(5- or 6-membered heterocyclyl), each optionally substituted with one, two, or three substituents Q. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is $-O$ -(5-membered heterocyclyl), optionally substituted with $-C(O)R^a$ or $-C(O)OR^a$, where each R^a is as defined herein. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is methoxy, tetrahydrofuryloxy, or pyrrolidinyloxy, each of which is optionally substituted with $-C(O)R^a$ or $-C(O)OR^a$, where each R^a is as defined herein. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is methoxy, tetrahydrofuryloxy, or pyrrolidinyloxy, each of which is optionally substituted with acetyl, propionyl, cyclopropylcarbonyl, or *tert*-butoxycarbonyl. In certain embodiments, in any one of Formulae (III), (V), (X), (XII), (XVII), and (XIX), R^{4b} is methoxy, tetrahydrofur-3-yloxy, (*R*)-tetrahydrofur-3-yloxy, (*S*)-tetrahydrofur-3-yloxy, pyrrolidin-3-yloxy, 1-acetylpyrrolidin-3-yloxy, 1-propionylpyrrolidin-3-yloxy, 1-cyclopropylcarbonylpyrrolidin-3-yloxy, or 1-*tert*-butoxycarbonylpyrrolidin-3-yloxy.

[00101] In certain embodiments, in any one of Formulae (XVII) to (XXII),
 R^1 is hydrogen, methyl, trifluoromethyl, or dimethylamino;
 R^3 is hydrogen;
 R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a}, if present, is hydrogen;

R^{4b}, if present, is cyclopropyl, cyclobutyl, cyclohexyl, cyclohexenyl, bicyclo[1.1.1]pentanyl, or bicyclo[2.2.2]octanyl, each of which is optionally substituted with one, two, or three substituents, wherein each substituent is independently fluoro, methyl, difluoromethyl, 3-cyanoazetidin-1-ylcarbonyl, 3-fluoroazetidin-1-ylcarbonyl, 3-methoxyazetidin-1-ylcarbonyl, 3-hydroxypyrrolidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-(2-methoxyethyl)piperazin-1-ylcarbonyl, hydroxycarbonyl, ethoxycarbonyl, dimethylcarbamoyl, (methyl)(ethyl)carbamoyl, (2-hydroxyethyl)(methyl)-carbamoyl, (2-hydroxypropyl)(methyl)carbamoyl, (2-hydroxy-2-methylpropyl)(methyl)-carbamoyl, (2,3-dihydroxypropyl)(methyl)carbamoyl, (2-methoxyethyl)(methyl)carbamoyl, (methyl)(oxetan-3-yl)carbamoyl, (methyl)(tetrahydrofur-3-yl)carbamoyl, hydroxyl, or acetoxy;

R^{4c}, if present, is hydrogen or methoxy;

R^{4d}, if present, is hydrogen, fluoro, or methyl;

R^{6a} and R^{6b} are each independently hydrogen, hydroxymethylphenyl, aminomethylphenyl, methylaminomethylphenyl, (aminoethyl)phenyl, or 6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazolyl; and

R^{6c} is hydrogen.

[00102] In certain embodiments, in any one of Formulae (XVII) to (XXII),

R¹ is hydrogen, methyl, or trifluoromethyl;

R³ is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a}, if present, is hydrogen;

R^{4b}, if present, is 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, 4-hydroxycyclohexyl, 4-hydroxycarbonylcyclohexyl, 4-ethoxycarbonylcyclohexyl, 4-(3-cyanoazetidin-1-ylcarbonyl)-cyclohexyl, 4-(3-fluoroazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-methoxyazetidin-1-ylcarbonyl)-cyclohexyl, 4-(3-hydroxypyrrolidin-1-yl)carbonylcyclohexyl, 4-morpholin-4-ylcarbonyl-cyclohexyl, 4-(4-methylpiperazin-1-yl)carbonylcyclohexyl, 4-(4-(2-methoxyethyl)-piperazin-1-yl)carbonylcyclohexyl, 4-dimethyl-carbamoylcyclohexyl, 4-(methyl)(ethyl)-carbamoyl-

cyclohexyl, 4-(2-hydroxyethyl)(methyl)carbamoylcyclohexyl, 4-(2-hydroxypropyl)-(methyl)-carbamoylcyclohexyl, 4-(2-hydroxy-2-methylpropyl)(methyl)carbamoylcyclohexyl, 4-(2,3-dihydroxypropyl)(methyl)carbamoylcyclohexyl, 4-(2-methoxyethyl)(methyl)carbamoylcyclohexyl, 4-(methyl)(oxetan-3-yl)carbamoylcyclohexyl, 4-(methyl)(tetrahydrofuran-3-yl)-carbamoylcyclohexyl, 4-acetoxy-1-hydroxycyclohexyl, 1,4-dihydroxycyclohexyl, 4-hydroxycarbonyl-1-hydroxycyclohexyl, 4-ethoxycarbonyl-1-hydroxycyclohexyl, 4-dimethyl-carbamoyl-1-hydroxycyclohexyl, 4-(2-hydroxyethyl)(methyl)carbamoyl-1-hydroxycyclohexyl, 4-(2-hydroxypropyl)(methyl)carbamoyl-1-hydroxycyclohexyl, bicyclo[1.1.1]pentan-1-yl, or 4-fluorobicyclo[2.2.2]octan-1-yl;

R^{4c} , if present, is hydrogen or methoxy;

R^{4d} , if present, is hydrogen, fluoro, or methyl;

R^{6a} and R^{6b} are each independently hydrogen, 2-hydroxymethylphenyl, 2-aminomethylphenyl, 2-methylaminomethylphenyl, 2-(2-aminoethyl)phenyl, or 6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazol-3-yl; and

R^{6c} is hydrogen.

[00103] In certain embodiments, in any one of Formulae (XVII) to (XXII),

R^1 is hydrogen, methyl, trifluoromethyl, or dimethylamino;

R^3 is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a} , if present, is hydrogen;

R^{4b} , if present, is tetrahydrofuryl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydropyridinyl, dihydropyranyl, dihydrothiopyranyl, azaspiro[3.3]heptanyl, or 7-azaspiro[3.5]nonanyl, each of which is optionally substituted with one, two, or three substituents, wherein each substituent is independently oxo, imino, isopropyl, hydroxycarbonylmethyl, dimethylcarbamoylmethyl, tetrahydrofuran-3-yl, acetyl, 2-methoxy-acetyl, 2-dimethylaminoacetyl, *tert*-butoxycarbonyl, or hydroxyl;

R^{4c} , if present, is hydrogen or methoxy;

R^{4d} , if present, is hydrogen, fluoro, or methyl;

R^{6a} and R^{6b} are each independently hydrogen, hydroxymethylphenyl, aminomethylphenyl, methylaminomethylphenyl, (aminoethyl)phenyl, or 6,7-dihydro-5H-

pyrrolo[1,2-*a*]imidazolyl; and

R^{6c} is hydrogen.

[00104] In certain embodiments, in any one of Formulae (XVII) to (XXII),

R^1 is hydrogen, methyl, or trifluoromethyl;

R^3 is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a} , if present, is hydrogen;

R^{4b} , if present, is 3-methyltetrahydrofuran-3-yl, piperidin-4-yl, 1-isopropylpiperidin-4-yl, 1-(hydroxycarbonylmethyl)piperidin-4-yl, 1-(dimethylcarbamoylmethyl)piperidin-4-yl, 1-tetrahydrofuran-3-ylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-(2-methoxyacetyl)piperidin-4-yl, 1-(2-dimethylaminoacetyl)piperidin-4-yl, 1-*tert*-butoxycarbonylpiperidin-4-yl, 4-hydroxypiperidin-4-yl, 1-acetyl-4-hydroxypiperidin-4-yl, 1-(2-methoxyacetyl)-4-hydroxypiperidin-4-yl, 4-hydroxy-1-*tert*-butoxycarbonylpiperidin-4-yl, 1-dimethylcarbamoyl-4-hydroxypiperidin-4-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, 1-oxotetrahydrothiopyran-4-yl, 1,1-dioxotetrahydrothiopyran-4-yl, 1-oxo-1-iminotetrahydrothiopyran-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, 3,6-dihydropyran-4-yl, 3,6-dihydrothiopyran-4-yl, 1-oxo-3,6-dihydrothiopyran-4-yl, 1,1-dioxo-3,6-dihydrothiopyran-4-yl, 1-oxo-1-imino-3,6-dihydrothiopyran-4-yl, 6-hydroxy-2-azaspiro[3.3]heptan-6-yl, or 2-hydroxy-7-azaspiro[3.5]nonan-2-yl;

R^{4c} , if present, is hydrogen or methoxy;

R^{4d} , if present, is hydrogen, fluoro, or methyl;

R^{6a} and R^{6b} are each independently hydrogen, 2-hydroxymethylphenyl, 2-aminomethylphenyl, 2-methylaminomethylphenyl, 2-(2-aminoethyl)phenyl, or 6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazol-3-yl; and

R^{6c} is hydrogen.

[00105] In certain embodiments, in any one of Formulae (XVII) to (XXII),

R^1 is hydrogen, methyl, trifluoromethyl, or dimethylamino;

R^3 is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a} , if present, is hydrogen;

R^{4b} , if present, is methoxy, tetrahydrofuryloxy, or pyrrolidinyloxy, each of which is optionally substituted with acetyl, propionyl, cyclopropylcarbonyl, or *tert*-butoxycarbonyl;

R^{4c} , if present, is hydrogen or methoxy;

R^{4d} , if present, is hydrogen, fluoro, or methyl;

R^{6a} and R^{6b} are each independently hydrogen, hydroxymethylphenyl, amino-methylphenyl, methylaminomethylphenyl, (aminoethyl)phenyl, or 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazolyl; and

R^{6c} is hydrogen.

[00106] In certain embodiments, in any one of Formulae (XVII) to (XXII),

R^1 is hydrogen, methyl, or trifluoromethyl;

R^3 is hydrogen;

R^{2a} is hydrogen, methyl, or ethyl;

R^{2b} is hydrogen;

R^{4a} , if present, is hydrogen;

R^{4b} , if present, is methoxy, tetrahydrofur-3-yloxy, (*R*)-tetrahydrofur-3-yloxy, (*S*)-tetrahydrofur-3-yloxy, pyrrolidin-3-yloxy, 1-acetylpyrrolidin-3-yloxy, 1-propionylpyrrolidin-3-yloxy, 1-cyclopropylcarbonylpyrrolidin-3-yloxy, or 1-*tert*-butoxycarbonylpyrrolidin-3-yloxy;

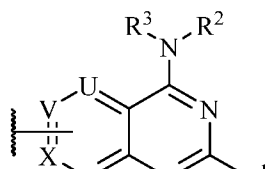
R^{4c} , if present, is hydrogen or methoxy;

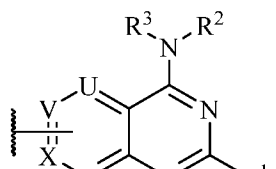
R^{4d} , if present, is hydrogen, fluoro, or methyl;

R^{6a} and R^{6b} are each independently hydrogen, 2-hydroxymethylphenyl, 2-amino-methylphenyl, 2-methylaminomethylphenyl, 2-(2-aminoethyl)phenyl, or 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl; and

R^{6c} is hydrogen.

[00107] In one embodiment, provided herein is an SOS1 protein degrader comprising an SOS1 binding moiety and an E3 ubiquitin ligase binding moiety (R^E). In another embodiment, provided herein is an SOS1 protein degrader comprising an SOS1 binding moiety, an E3 ubiquitin ligase binding moiety (R^E), and a linker (L), wherein the SOS1 binding moiety and E3 ubiquitin ligase binding moiety (R^E) are linked together *via* the linker (L). In certain

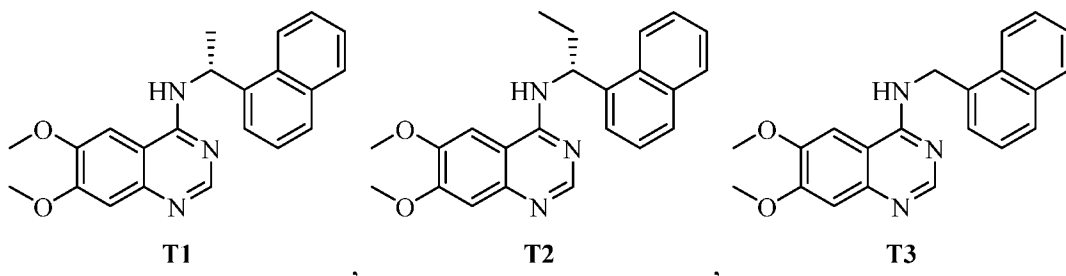


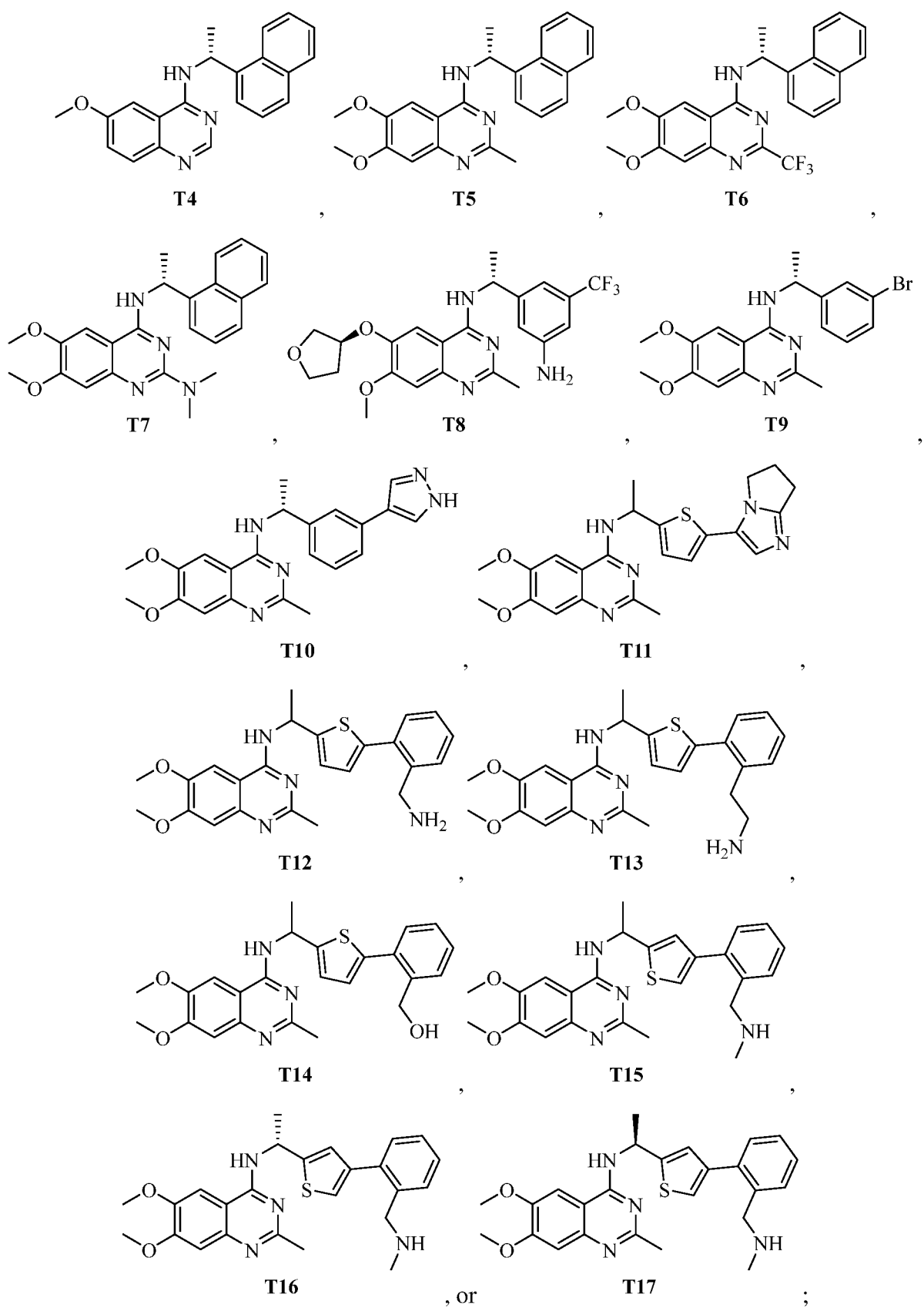
embodiments, the SOS1 binding moiety has the structure of , wherein R¹, R², and R³ are each as defined herein.

[00108] In certain embodiments, the SOS1 protein degrader provided herein is a compound of any one of Formulae (I) to (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 the SOS1 binding moiety is the structural part that is connected to the E3 ubiquitin ligase binding moiety (R^E) *via* the linker (L).

[00109] In certain embodiments, the SOS1 binding moiety is a moiety of an SOS1 inhibitor. In certain embodiments, the SOS1 binding moiety is a moiety of an SOS1 inhibitor disclosed in US 2019/0194192 A1 or US 2019/0358230 A1, the disclosure of each of which is incorporated herein by reference in its entirety. In certain embodiments, the SOS1 binding moiety is a moiety of an SOS1 inhibitor disclosed in US 2019/0194192 A1, in one embodiment, one of compounds I-1 to I-179 disclosed therein on pages 113 to 164, which are incorporated herein by reference in their entireties. In certain embodiments, the SOS1 binding moiety is a moiety of an SOS1 inhibitor disclosed in US 2019/0358230 A1, in one embodiment, one of compounds I-1 to I-384 disclosed therein on pages 79 to 189, which are incorporated herein by reference in their entireties.

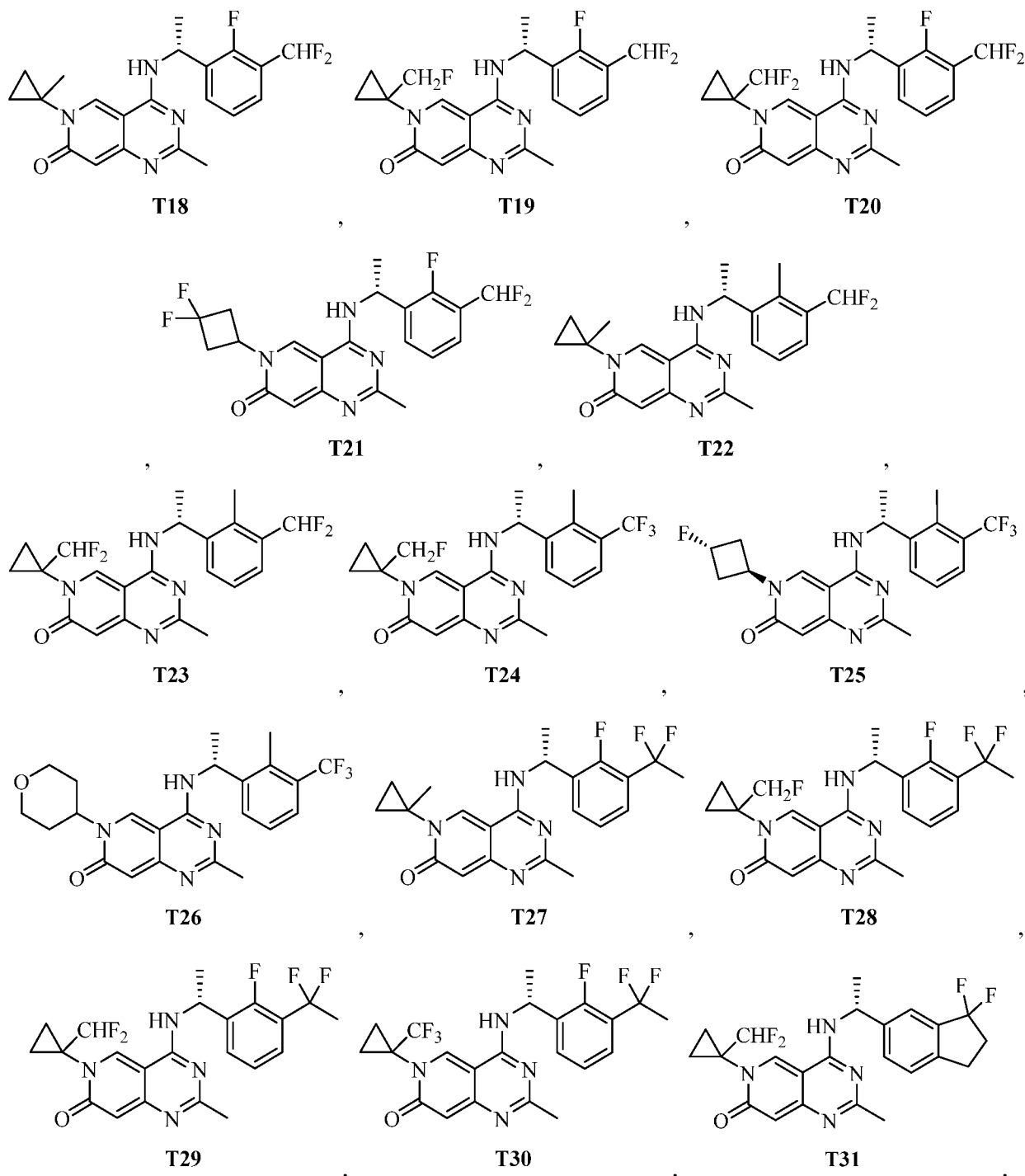
[00110] In certain embodiments, the SOS1 binding moiety is a moiety of an SOS1 inhibitor having the structure of:

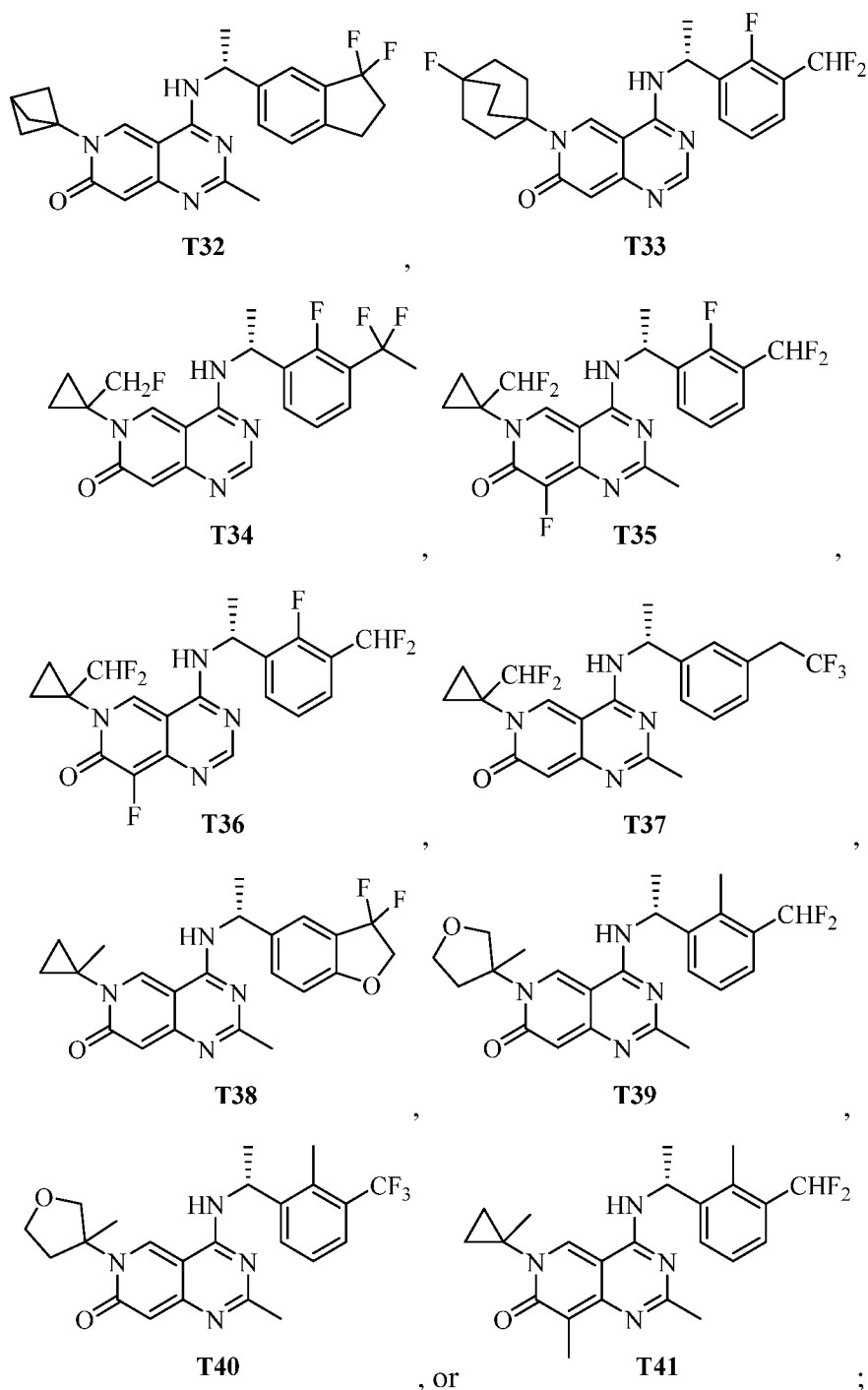




or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

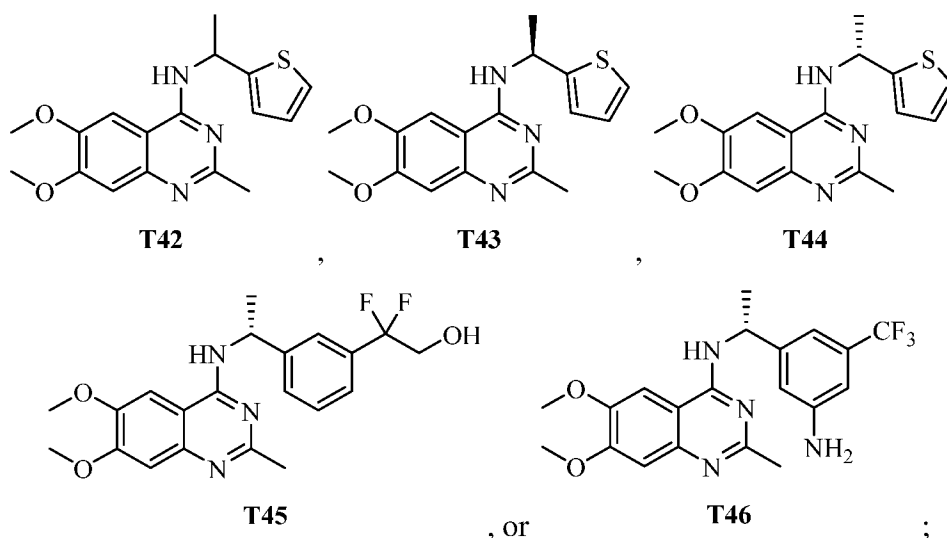
[00111] In certain embodiments, the SOS1 binding moiety is a moiety of an SOS1 inhibitor having the structure of:





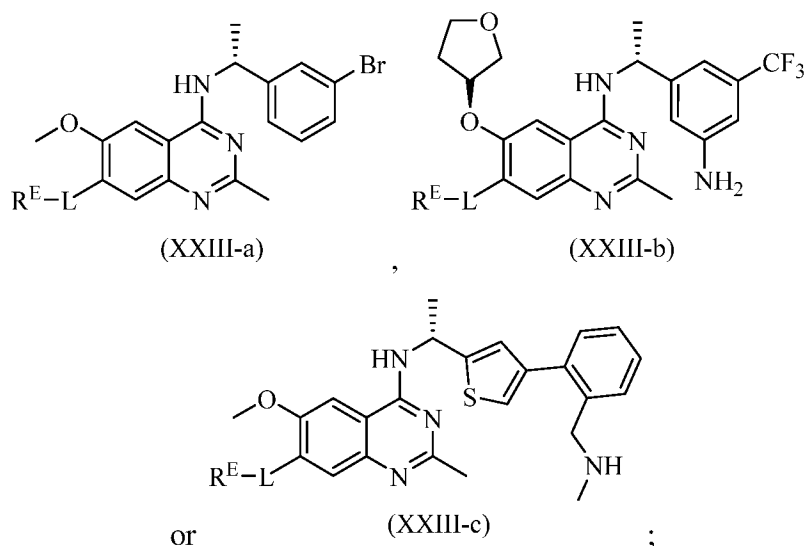
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00112] In certain embodiments, the SOS1 binding moiety is a moiety of an SOS1 inhibitor having the structure of:



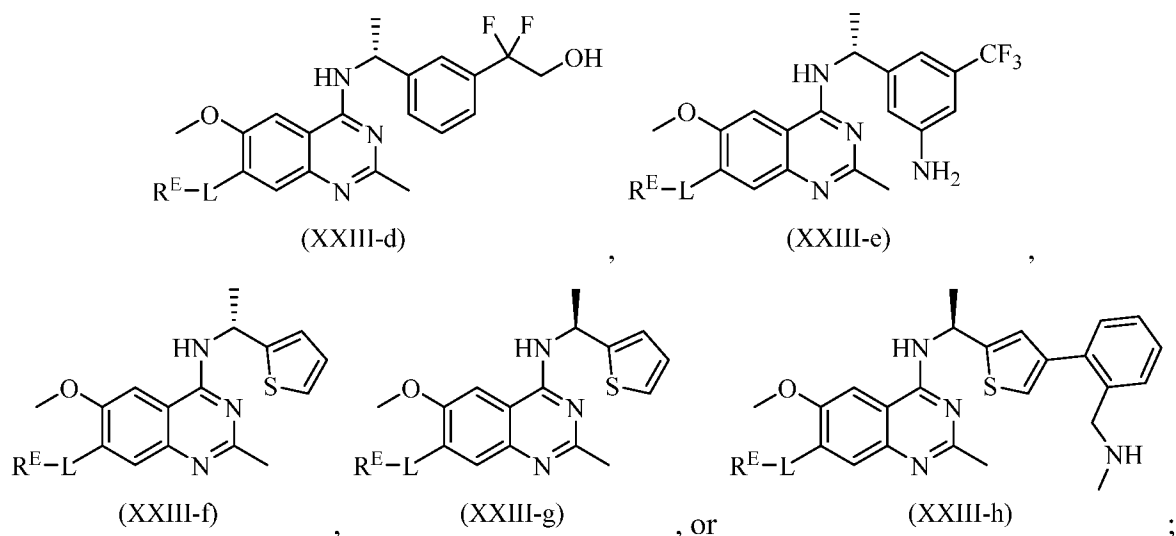
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00113] In certain embodiments, the compound provided herein has the structure of:



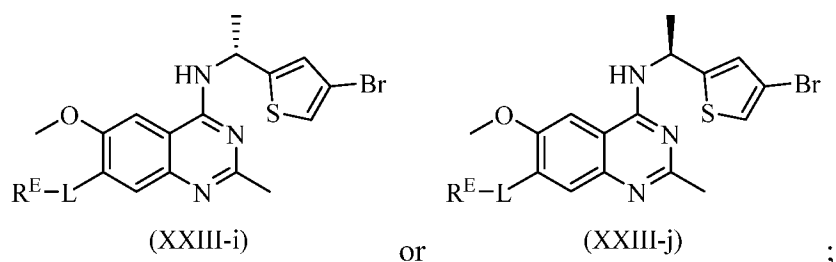
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^E and L are each as defined herein.

[00114] In certain embodiments, the compound provided herein has the structure of:



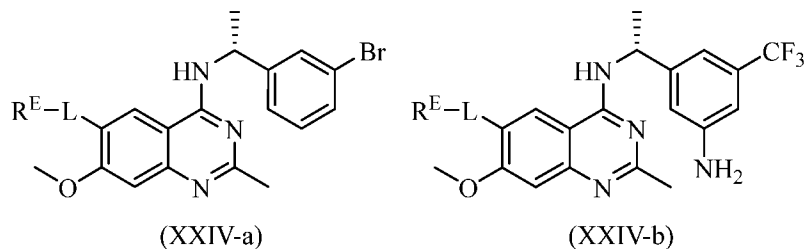
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^E and L are each as defined herein.

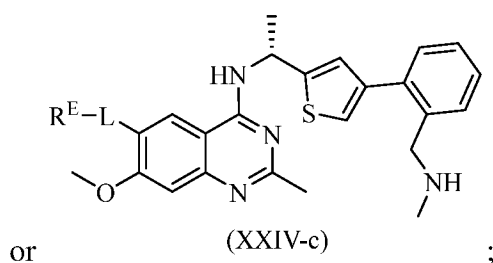
[00115] In certain embodiments, the compound provided herein has the structure of:



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^E and L are each as defined herein.

[00116] In certain embodiments, the compound provided herein has the structure of:



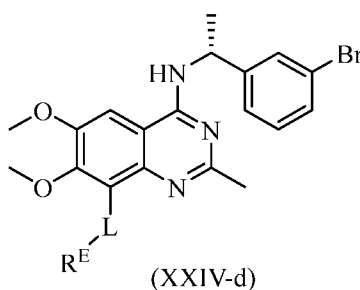


or

;

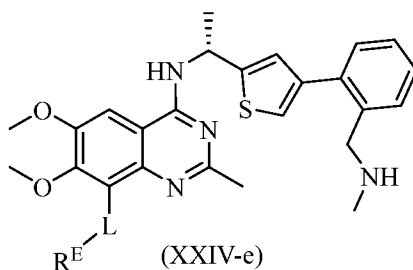
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^E and L are each as defined herein.

[00117] In certain embodiments, the compound provided herein has the structure of:



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^E and L are each as defined herein.

[00118] In certain embodiments, the compound provided herein has the structure of:

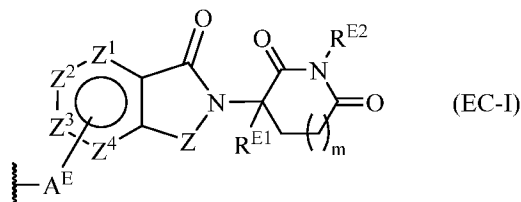


or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^E and L are each as defined herein.

[00119] In certain embodiments, R^E is a moiety of a cereblon (CRBN) E3 ligand, an inhibitors-of-apoptosis protein (IAP) E3 ligand, a mouse double minute 2 homolog (MDM2) E3 ligand, or a von Hippel-Lindau (VHL) E3 ligand.

[00120] In certain embodiments, R^E is a moiety of a CRBN E3 ligand.

[00121] In certain embodiments, R^E is a moiety having the structure of Formula (EC-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; wherein:

A^E is a bond, $-O-$, $-N(R^{1b})-$, $-S-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} heteroalkenylene, C_{2-6} alkynylene, C_{2-6} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, C_{7-15} aralkylene, heteroarylene, heterocyclylene, C_{1-6} heteroalkylene- C_{6-14} arylene, or C_{2-6} alkynylene-heterocyclylene;

Z is $-CH_2-$ or $-C(O)-$;

one of Z^1 , Z^2 , Z^3 , and Z^4 is $-C=$ and the remaining three of Z^1 , Z^2 , Z^3 , and Z^4 are each independently $-C(R^{E5})=$; or Z^1 is a bond; one of Z^2 , Z^3 , and Z^4 is $-C=$, and the remaining two of Z^2 , Z^3 , and Z^4 are each independently $-C(R^{E5})=$ or $-S-$;

m is an integer of 0, 1, or 2;

R^{E1} is hydrogen, deuterium, halo, or C_{1-6} alkyl;

R^{E2} is hydrogen or C_{1-6} alkyl;

each R^{E4} 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) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$,

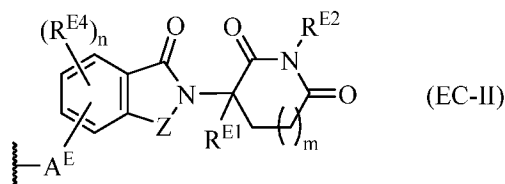
$-\text{NR}^{1a}\text{C}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$,
 $-\text{SR}^{1a}$,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

each $\text{R}^{\text{E}5}$ is independently hydrogen or $\text{R}^{\text{E}4}$; and

R^{1a} , R^{1b} , R^{1c} , and R^{1d} are each as defined herein;

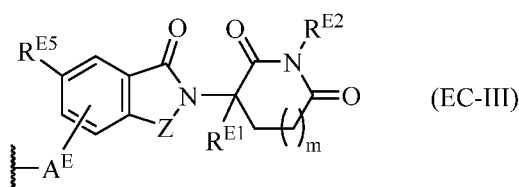
wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, alkynylene, heteroalkynylene, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, aralkylene, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

[00122] In certain embodiments, R^{E} is a moiety having the structure of Formula (EC-II):



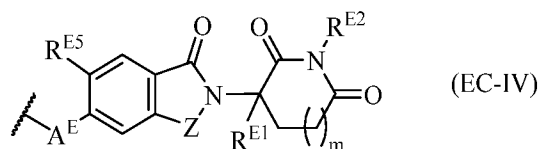
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein n is an integer of 0, 1, 2, or 3; and A^{E} , $\text{R}^{\text{E}1}$, $\text{R}^{\text{E}2}$, $\text{R}^{\text{E}4}$, Z , and m are each as defined herein.

[00123] In certain embodiments, R^{E} is a moiety having the structure of Formula (EC-III):



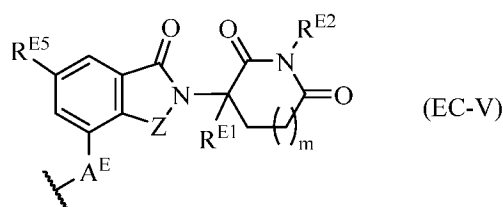
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^{E} , $\text{R}^{\text{E}1}$, $\text{R}^{\text{E}2}$, $\text{R}^{\text{E}5}$, Z , and m are each as defined herein. In one embodiment, $\text{R}^{\text{E}5}$ is hydrogen or fluoro.

[00124] In certain embodiments, R^{E} is a moiety having the structure of Formula (EC-IV):



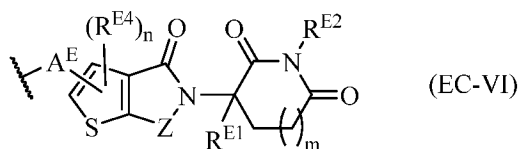
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^E , R^{E1} , R^{E2} , R^{E5} , Z , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00125] In certain embodiments, R^E is a moiety having the structure of Formula (EC-V):



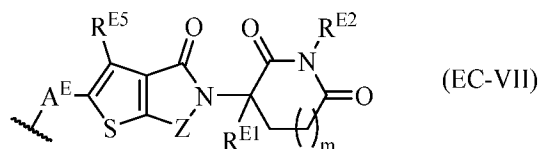
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^E , R^{E1} , R^{E2} , R^{E5} , Z , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00126] In certain embodiments, R^E is a moiety having the structure of Formula (EC-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; wherein n is an integer of 0 or 1; and A^E , R^{E1} , R^{E2} , R^{E4} , Z , and m are each as defined herein.

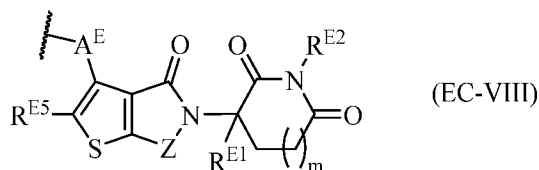
[00127] In certain embodiments, R^E is a moiety having the structure of Formula (EC-VII):



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;

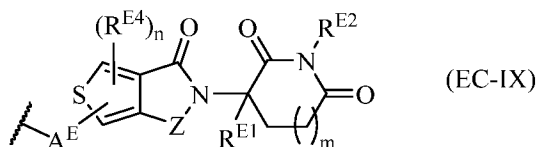
wherein A^E , R^{E1} , R^{E2} , R^{E5} , Z , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00128] In certain embodiments, R^E is a moiety having the structure of Formula (EC-VIII):



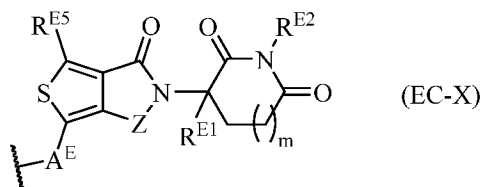
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^E , R^{E1} , R^{E2} , R^{E5} , Z , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00129] In certain embodiments, R^E is a moiety having the structure of Formula (EC-IX):



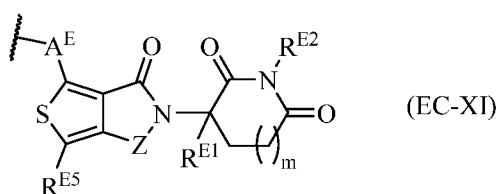
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein n is an integer of 0 or 1; and A^E , R^{E1} , R^{E2} , R^{E4} , Z , and m are each as defined herein.

[00130] In certain embodiments, R^E is a moiety having the structure of Formula (EC-X):



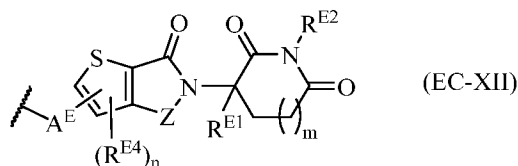
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^E , R^{E1} , R^{E2} , R^{E5} , Z , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00131] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XI):



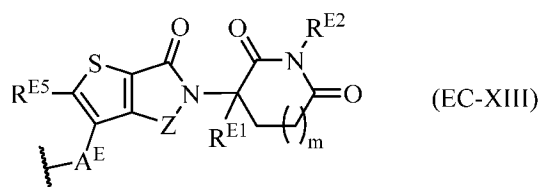
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^E , R^{E1} , R^{E2} , R^{E5} , Z , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00132] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XII):



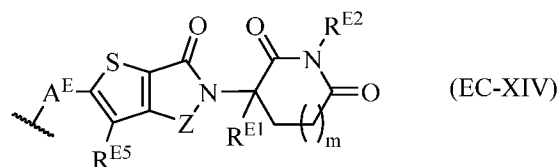
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein n is an integer of 0 or 1; and A^E , R^{E1} , R^{E2} , R^{E4} , Z , and m are each as defined herein.

[00133] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XIII):



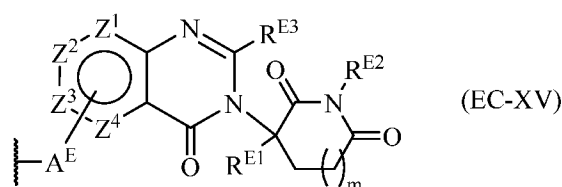
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^E , R^{E1} , R^{E2} , R^{E5} , Z , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00134] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XIV):



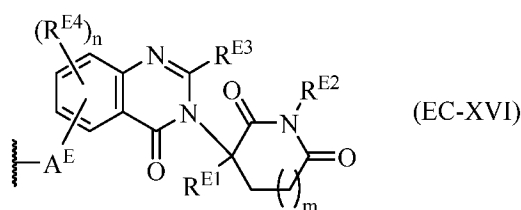
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^E , R^{E1} , R^{E2} , R^{E5} , Z , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00135] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XV):



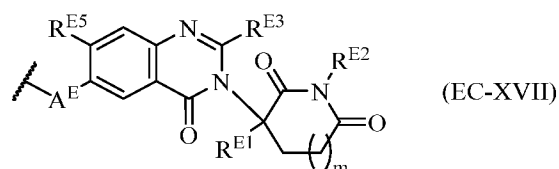
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein R^{E3} is hydrogen, deuterium, halo, or C_{1-6} alkyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q ; and A^E , R^{E1} , R^{E2} , Z^1 , Z^2 , Z^3 , Z^4 , and m are each as defined herein.

[00136] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XVI):



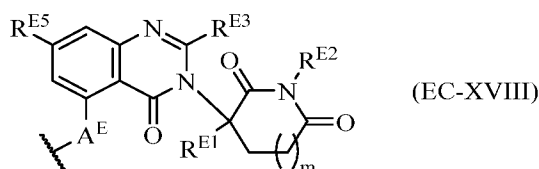
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein n is an integer of 0, 1, 2, or 3; and A^E , R^{E1} , R^{E2} , R^{E3} , R^{E4} , and m are each as defined herein.

[00137] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XVII):



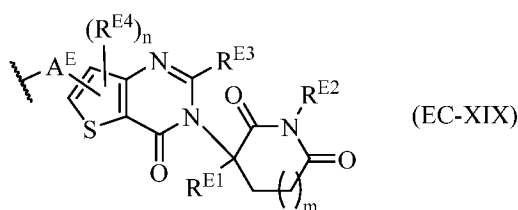
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^E , R^{E1} , R^{E2} , R^{E3} , R^{E5} , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00138] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XVIII):



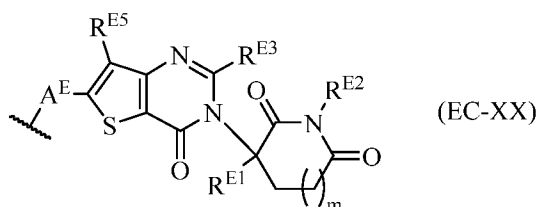
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^E , R^{E1} , R^{E2} , R^{E3} , R^{E5} , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00139] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XIX):



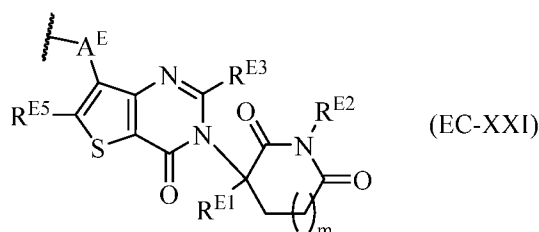
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein n is an integer of 0 or 1; and A^E , R^{E1} , R^{E2} , R^{E3} , R^{E4} , and m are each as defined herein.

[00140] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XX):



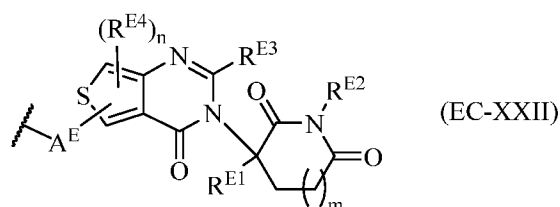
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^E , R^{E1} , R^{E2} , R^{E3} , R^{E5} , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00141] In certain embodiments, R^E is a moiety having the structure of Formula (EC-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; wherein A^E , R^{E1} , R^{E2} , R^{E3} , R^{E5} , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

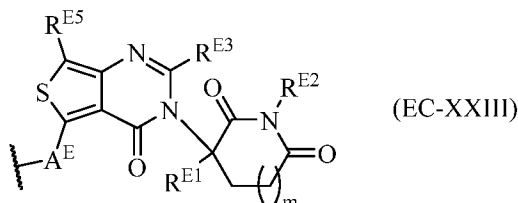
[00142] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XXII):



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; wherein n is an integer of 0 or 1; and A^E , R^{E1} , R^{E2} , R^{E3} , R^{E4} , and m are each as defined herein.

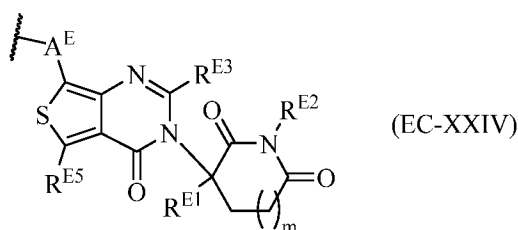
[00143] In certain embodiments, R^E is a moiety having the structure of Formula (EC-

XXIII):



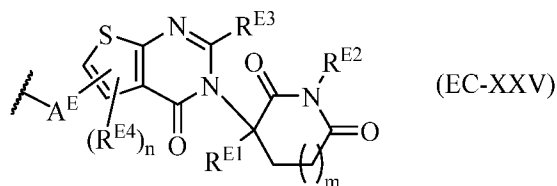
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein A^E , R^{E1} , R^{E2} , R^{E3} , R^{E5} , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00144] In certain embodiments, R^E is a moiety having the structure of Formula (EC-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; wherein A^E , R^{E1} , R^{E2} , R^{E3} , R^{E5} , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

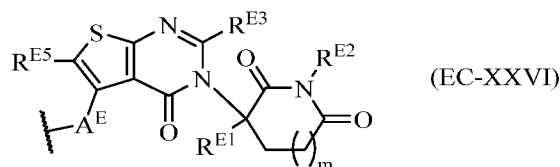
[00145] In certain embodiments, R^E is a moiety having the structure of Formula (EC-XXV):



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; wherein n is an integer of 0 or 1; and A^E , R^{E1} , R^{E2} , R^{E3} , R^{E4} , and m are each as defined herein.

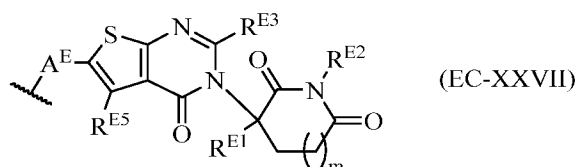
[00146] In certain embodiments, R^E is a moiety having the structure of Formula (EC-

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; wherein A^E , R^{E1} , R^{E2} , R^{E3} , R^{E5} , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00147] In certain embodiments, R^E is a moiety having the structure of Formula (EC-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; wherein A^E , R^{E1} , R^{E2} , R^{E3} , R^{E5} , and m are each as defined herein. In one embodiment, R^{E5} is hydrogen or fluoro.

[00148] In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in US 9,938,302 B2; US 10,336,771 B2; US 10,406,165 B2; US 10,513,515 B2; US 2019/0322682 A1; US 2020/0000814 A1; US 2020/0148663 A1; US 2020/0369679 A1; and WO 2019/173224 A1; the disclosure of each of which is incorporated herein by reference in its entirety. In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in US 9,938,302 B2, in one embodiment, one of compounds 1 to 57 disclosed therein in cols. 108 to 137, which are incorporated herein by reference in their entireties. In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in US 10,336,771 B2, in one embodiment, one of compounds 1 to 57 and 64 to 66 disclosed therein in cols. 113 to 161 and 169 to 172, which are incorporated herein by reference in their entireties. In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in US 10,406,165 B2, in one embodiment, one of compounds 1 to 27 disclosed therein in cols. 40 to 64, which are incorporated herein by

reference in their entireties. In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in US 10,513,515 B2, in one embodiment, one of compounds 1 to 5, 7 to 12, 14 to 16, 19, 23, and 27 disclosed therein in cols. 97 to 104, 106 to 112, 114 to 117, 122, 126, and 132, which are incorporated herein by reference in their entireties. In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in US 2019/0322682 A1, in one embodiment, one of compounds 1 to 15 disclosed therein on pages 31 to 36, which are incorporated herein by reference in their entireties. In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in US 2020/0000814 A1, in one embodiment, one of compounds 1 to 21 disclosed therein on pages 26 to 41, which are incorporated herein by reference in their entireties. In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in US 2020/0148663 A1, in one embodiment, one of compounds 1 to 21 disclosed therein on pages 18 to 34, which are incorporated herein by reference in their entireties. In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in WO 2019/173224 A1, in one embodiment, one of compounds 1 to 3 disclosed therein on pages 62 to 65 and the compounds disclosed therein on page 78, which are incorporated herein by reference in their entireties. In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in US 2020/0369679 A1, in one embodiment, one of compounds I-1 to I-106 and II-1 to II-164 disclosed therein on pages 50 to 101, which are incorporated herein by reference in their entireties.

[00149] In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in US 2020/0199073 A1, the disclosure of which is incorporated herein by reference in its entirety. In certain embodiments, R^E is a moiety of an E3 ubiquitin ligase binder disclosed in US Application No. US 2020/0199073 A1, in one embodiment, one of compounds 1 to 291 disclosed therein on pages 118 to 193, which are incorporated herein by reference in their entireties.

[00150] In certain embodiments, in any one of Formulae (EC-I) to (EC-XXVII), A^E is a bond, -O-, -N(R^{lb})-, C₂₋₆ alkynylene, heterocyclylene, C₁₋₆ heteroalkylene-C₆₋₁₄ arylene, or C₂₋₆ alkynylene-heterocyclylene, where each heteroalkylene, alkynylene, arylene, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q;

Z, if present, is $-\text{CH}_2-$ or $-\text{C}(\text{O})-$;

m is an integer of 0, 1, or 2;

R^{E1} and R^{E2} are each hydrogen; and

R^{E5} , if present, is independently hydrogen or fluoro.

[00151] In certain embodiments, in any one of Formulae (EC-I) to (EC-XXVII), A^{E} is a bond, $-\text{O}-$, $-\text{NH}-$, ethynediyl, piperidindiyl, piperazindiyl, (phendiyl)-oxymethanediyl, or (piperidindiyl)ethynediyl;

Z, if present, is $-\text{CH}_2-$ or $-\text{C}(\text{O})-$;

m is an integer of 0, 1, or 2;

R^{E1} and R^{E2} are each hydrogen; and

R^{E5} , if present, is independently hydrogen or fluoro.

[00152] In certain embodiments, in any one of Formulae (EC-I) to (EC-XXVII), A^{E} is a bond, $-\text{NH}-$, piperidin-1,3-diyl, piperidin-1,4-diyl, piperaz-1,4-diyl, (phen-1,4-diyl)oxymethanediyl, or (piperidin-1,4-diyl)ethynediyl;

Z, if present, is $-\text{CH}_2-$ or $-\text{C}(\text{O})-$;

m is an integer of 0, 1, or 2;

R^{E1} and R^{E2} are each hydrogen; and

R^{E5} , if present, is independently hydrogen or fluoro.

[00153] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^{E} is a moiety having the structure of Formula (EC-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. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^{E} is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^{E} is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In still another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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.

[00154] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and

(XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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. In still another

embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EC-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.

[00155] In one embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having

the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In still another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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.

[00156] In one embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in

a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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. In still another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EC-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.

[00157] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is

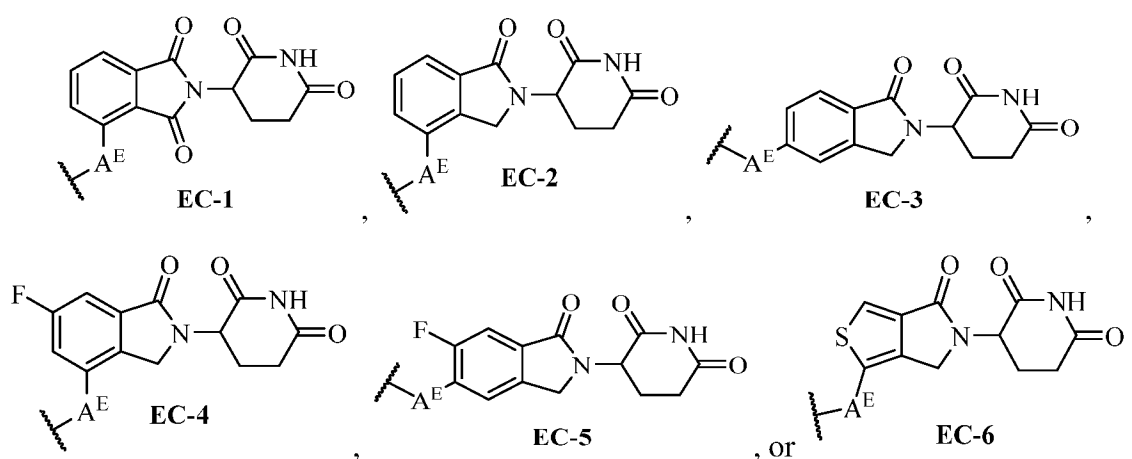
a moiety having the structure of Formula (EC-VII), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In still another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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.

[00158] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the

structure of Formula (EC-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. In still another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EC-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.

[00159] In certain embodiments, R^E is a moiety having the structure of:



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; wherein A^E is as defined herein.

[00160] In one embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is a bond, $-O-$, $-NH-$, ethynediyl, piperidindiyl, piperazindiyl, (phendiyl)oxymethanediyl, (piperidindiyl)-ethynediyl, or 3,9-diazaspiro[5.5]undecanediyl. In another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is a bond, $-O-$, $-NH-$, ethynediyl, piperidindiyl, piperazindiyl, (phendiyl)-oxymethanediyl, or (piperidindiyl)ethynediyl. In yet another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is a bond. In another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is $-O-$. In yet another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is $-NH-$. In yet another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is ethynediyl. In yet another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is piperidindiyl. In yet another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is piperazindiyl. In yet another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is (phendiyl)oxymethanediyl. In yet

another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is (piperidindiyl)ethynyl. In still another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is 3,9-diazaspiro[5.5]-undecanediyl.

[00161] In one embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is a bond, –O–, –NH–, ethynediyl, piperidin-1,3-diyl, piperidin-1,4-diyl, piperazin-1,4-diyl, (phen-1,4-diyl)oxymethanediyl, (piperidin-1,4-diyl)ethynediyl, or 3,9-diazaspiro[5.5]undecane-3,9-diyl. In another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is a bond, –O–, –NH–, ethynediyl, piperidin-1,3-diyl, piperidin-1,4-diyl, piperazin-1,4-diyl, (phen-1,4-diyl)oxymethanediyl, or (piperidin-1,4-diyl)ethynediyl. In yet another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is piperidin-1,3-diyl. In yet another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is piperidin-1,4-diyl. In yet another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is piperazin-1,4-diyl. In yet another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is (phen-1,4-diyl)oxymethanediyl. In yet another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is (piperidin-1,4-diyl)ethynediyl. In still another embodiment, in any one of Formulae **EC-1** to **EC-6**, A^E is 3,9-diazaspiro[5.5]-undecane-3,9-diyl.

[00162] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-1**, 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. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-2**, 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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-3**, 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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-4**, or an enantiomer, a mixture of

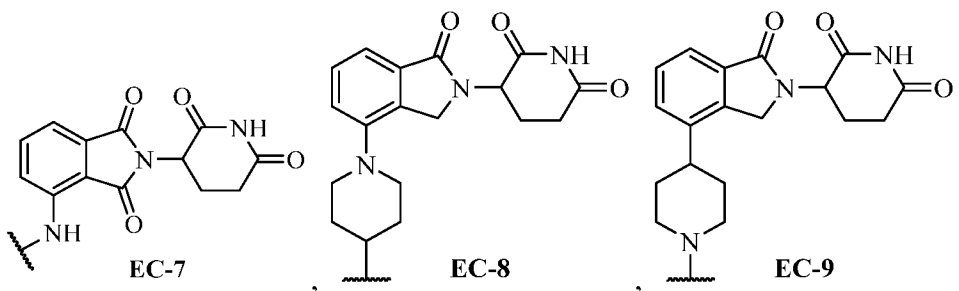
enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-5**, 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. In still another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-6**, 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.

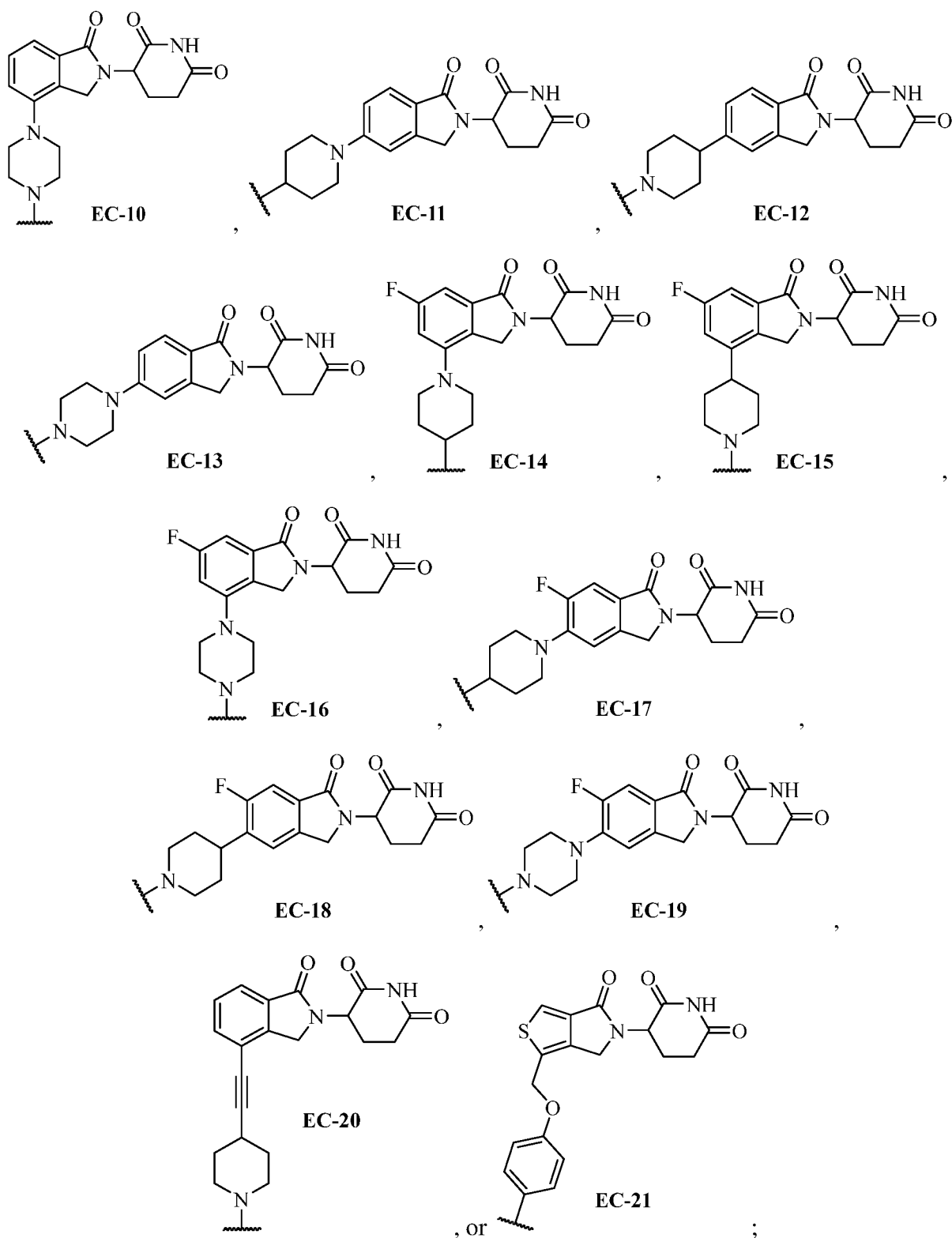
[00163] In one embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-1**, or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-2**, 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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-3**, 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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-4**, 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. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-5**, 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. In still another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-6**, 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.

[00164] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-1**, 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. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-2**, 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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-3**, 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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-4**, 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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-5**, 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. In still another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-6**, 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.

[00165] In certain embodiments, R^E is a moiety having the structure of:





or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00166] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-7**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-8**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-9**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-10**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-11**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-12**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-13**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-14**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-15**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to

(XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-16**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-17**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-18**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-19**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-20**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EC-21**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00167] In one embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-7**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-8**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-9**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-10**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In

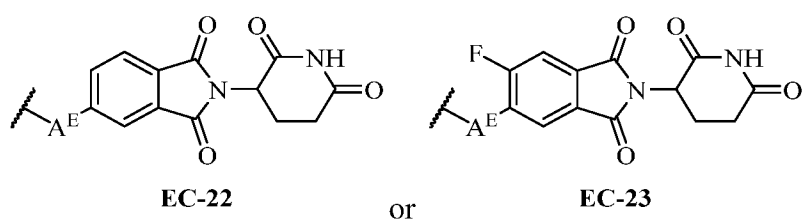
yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-11**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-12**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-13**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-14**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-15**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-16**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-17**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-18**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-19**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EC-20**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and

(XXIV-d), R^E is a moiety having the structure of Formula **EC-21**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00168] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-7**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-8**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-9**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-10**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-11**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-12**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-13**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-14**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-15**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-16**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-17**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in

a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-18**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-19**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-20**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-21**, or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00169] In certain embodiments, R^E is a moiety having the structure of:



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; wherein A^E is as defined herein.

[00170] In one embodiment, in Formula **EC-22** or **EC-23**, A^E is a bond, -O-, -NH-, ethynediyl, piperidindiyl, piperazindiyl, (phendiyl)oxymethanediyl, (piperidindiyl)-ethynediyl, or 3,9-diazaspiro[5.5]undecanediyl. In another embodiment, in Formula **EC-22** or **EC-23**, A^E is a bond, -O-, -NH-, ethynediyl, piperidindiyl, piperazindiyl, (phendiyl)oxy-methanediyl, or (piperidindiyl)ethynediyl. In another embodiment, in Formula **EC-22** or **EC-23**, A^E is a bond. In another embodiment, in Formula **EC-22** or **EC-23**, A^E is -O-. In yet another embodiment, in Formula **EC-22** or **EC-23**, A^E is -NH-. In yet another embodiment, in Formula **EC-22** or **EC-23**, A^E is ethynediyl. In yet another embodiment, in Formula **EC-22** or **EC-23**, A^E is piperidindiyl. In yet another embodiment, in Formula **EC-22** or **EC-23**, A^E is piperazindiyl. In yet another embodiment, in Formula **EC-22** or **EC-23**, A^E is (phendiyl)oxymethanediyl. In yet

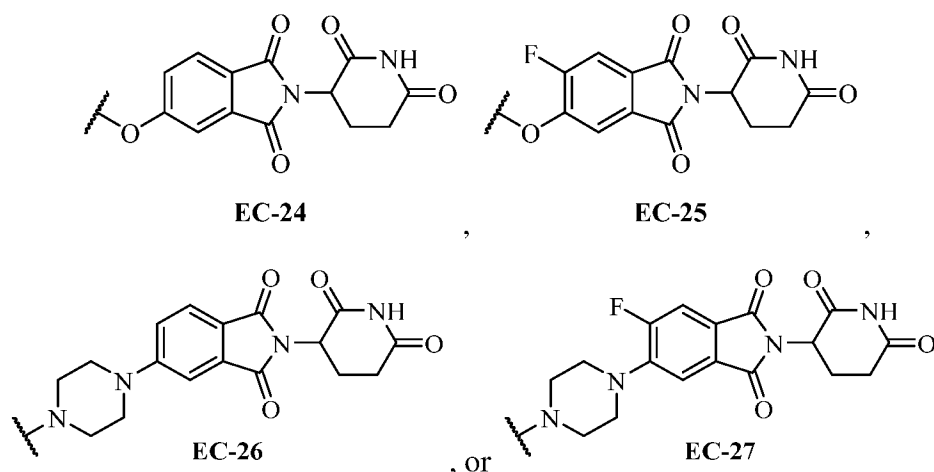
another embodiment, in Formula **EC-22** or **EC-23**, A^E is (piperidindiy)ethynyl. In still another embodiment, in Formula **EC-22** or **EC-23**, A^E is 3,9-diazaspiro[5.5]undecanediyl.

[00171] In one embodiment, in Formula **EC-22** or **EC-23**, A^E is a bond, –O–, –NH–, ethynediyl, piperidin-1,3-diyl, piperidin-1,4-diyl, piperazin-1,4-diyl, (phen-1,4-diyl)oxymethanediyl, (piperidin-1,4-diyl)ethynediyl, or 3,9-diazaspiro[5.5]undecane-3,9-diyl. In another embodiment, in Formula **EC-22** or **EC-23**, A^E is a bond, –O–, –NH–, ethynediyl, piperidin-1,3-diyl, piperidin-1,4-diyl, piperazin-1,4-diyl, (phen-1,4-diyl)oxymethanediyl, or (piperidin-1,4-diyl)ethynediyl. In another embodiment, in Formula **EC-22** or **EC-23**, A^E is piperidin-1,3-diyl. In yet another embodiment, in Formula **EC-22** or **EC-23**, A^E is piperidin-1,4-diyl. In yet another embodiment, in Formula **EC-22** or **EC-23**, A^E is piperazin-1,4-diyl. In yet another embodiment, in Formula **EC-22** or **EC-23**, A^E is (phen-1,4-diyl)oxymethanediyl. In yet another embodiment, in Formula **EC-22** or **EC-23**, A^E is (piperidin-1,4-diyl)ethynediyl. In still another embodiment, in Formula **EC-22** or **EC-23**, A^E is 3,9-diazaspiro[5.5]undecane-3,9-diyl.

[00172] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula **EC-22**, 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. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula **EC-23**, 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.

[00173] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-22**, 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. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-23**, 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.

[00174] In certain embodiments, R^E is a moiety having the structure of:



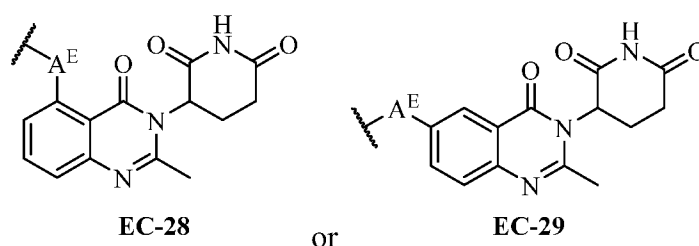
or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00175] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula **EC-24**, 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. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula **EC-25**, 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. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula **EC-26**, 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. In still another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula **EC-27**, 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.

[00176] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-24**, 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. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-25**, 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. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-26**, 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. In still another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EC-27**, 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.

[00177] In certain embodiments, R^E is a moiety having the structure of:



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; wherein A^E is as defined herein.

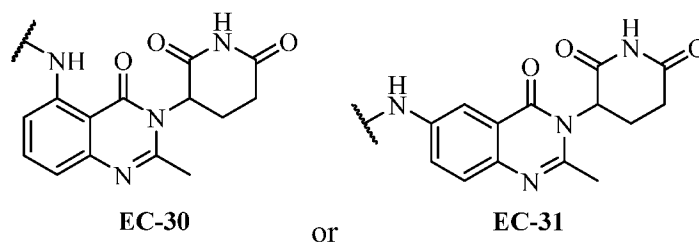
[00178] In one embodiment, in Formula **EC-28** or **EC-29**, A^E is a bond, $-O-$, $-NH-$, ethynediyl, piperidindiyl, piperazindiyl, (phendiyl)oxymethanediyl, (piperidindiyl)-ethynediyl, or 3,9-diazaspiro[5.5]undecanediyl. In another embodiment, in Formula **EC-28** or **EC-29**, A^E is a bond, $-O-$, $-NH-$, ethynediyl, piperidindiyl, piperazindiyl, (phendiyl)oxy-methanediyl, or (piperidindiyl)ethynediyl. In another embodiment, in Formula **EC-28** or **EC-29**, A^E is a bond. In another embodiment, in Formula **EC-28** or **EC-29**, A^E is $-O-$. In yet another embodiment, in Formula **EC-28** or **EC-29**, A^E is $-NH-$. In yet another embodiment, in Formula **EC-28** or **EC-29**, A^E is ethynediyl. In yet another embodiment, in Formula **EC-28** or **EC-29**, A^E is piperidindiyl. In yet another embodiment, in Formula **EC-28** or **EC-29**, A^E is piperazindiyl. In yet another embodiment, in Formula **EC-28** or **EC-29**, A^E is (phendiyl)oxymethanediyl. In yet another embodiment, in Formula **EC-28** or **EC-29**, A^E is (piperidindiyl)ethynyl. In still another

embodiment, in Formula **EC-28** or **EC-29**, A^E is 3,9-diazaspiro[5.5]undecanediyl.

[00179] In one embodiment, in Formula **EC-28** or **EC-29**, A^E is a bond, –O–, –NH–, ethynediyl, piperidin-1,3-diyl, piperidin-1,4-diyl, piperazin-1,4-diyl, (phen-1,4-diyl)oxymethanediyl, (piperidin-1,4-diyl)ethynediyl, or 3,9-diazaspiro[5.5]undecane-3,9-diyl. In another embodiment, in Formula **EC-28** or **EC-29**, A^E is a bond, –O–, –NH–, ethynediyl, piperidin-1,3-diyl, piperidin-1,4-diyl, piperazin-1,4-diyl, (phen-1,4-diyl)oxymethanediyl, or (piperidin-1,4-diyl)ethynediyl. In another embodiment, in Formula **EC-28** or **EC-29**, A^E is piperidin-1,3-diyl. In yet another embodiment, in Formula **EC-28** or **EC-29**, A^E is piperidin-1,4-diyl. In yet another embodiment, in Formula **EC-28** or **EC-29**, A^E is piperazin-1,4-diyl. In yet another embodiment, in Formula **EC-28** or **EC-29**, A^E is (phen-1,4-diyl)oxymethanediyl. In yet another embodiment, in Formula **EC-28** or **EC-29**, A^E is (piperidin-1,4-diyl)ethynediyl. In still another embodiment, in Formula **EC-28** or **EC-29**, A^E is 3,9-diazaspiro[5.5]undecane-3,9-diyl.

[00180] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-e), R^E is a moiety having the structure of Formula **EC-28**, 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. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-e), R^E is a moiety having the structure of Formula **EC-29**, 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.

[00181] In certain embodiments, R^E is a moiety having the structure of:

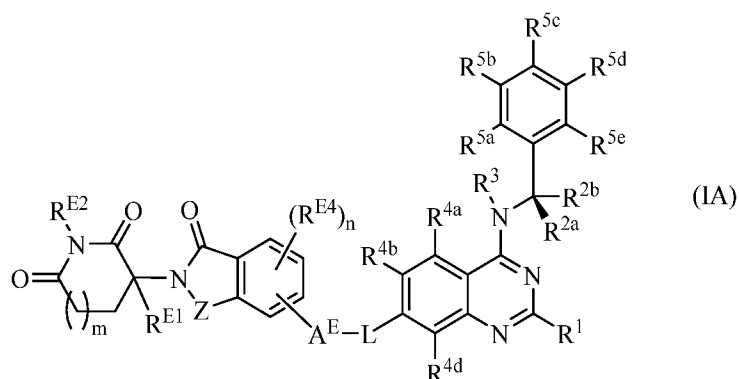


or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00182] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-

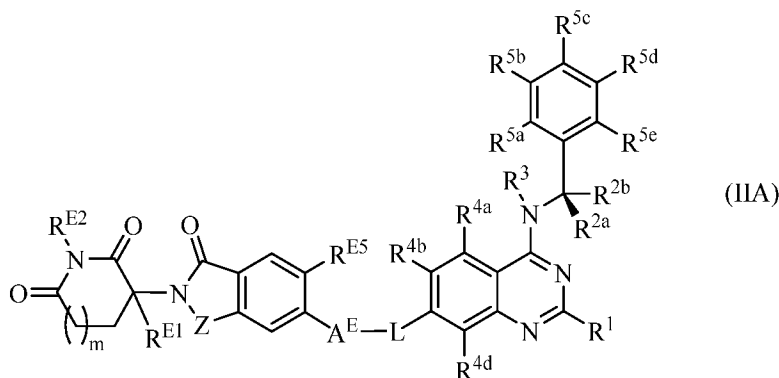
a) to (XXIII-j), and (XXIV-a) to (XXIV-e), R^E is a moiety having the structure of Formula **EC-30**, or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-e), R^E is a moiety having the structure of Formula **EC-31**, 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.

[00183] In one embodiment, provided herein is a compound of Formula (IA):



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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , R^{E4} , A^E , L , Z , m , and n are each as defined herein.

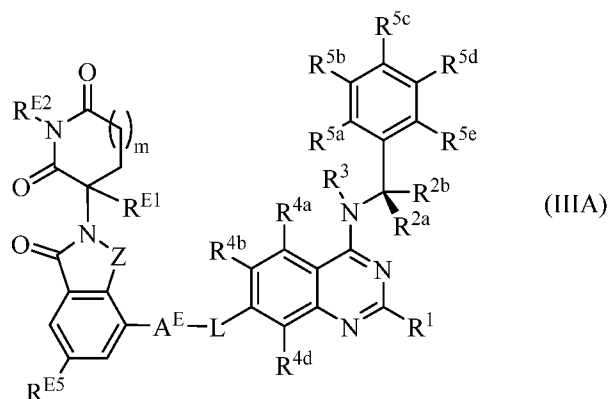
[00184] In another embodiment, provided herein is a compound of Formula (IIA):



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

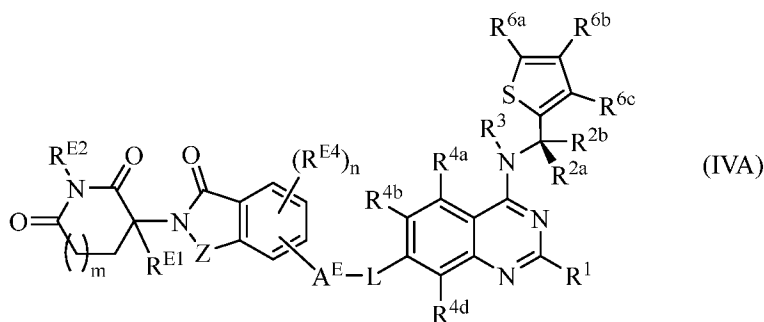
a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , R^{E5} , A^E , L , Z , and m are each as defined herein.

[00185] In yet another embodiment, provided herein is a compound of Formula (IIIA):



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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , R^{E5} , A^E , L , Z , and m are each as defined herein.

[00186] In one embodiment, provided herein is a compound of Formula (IVA):

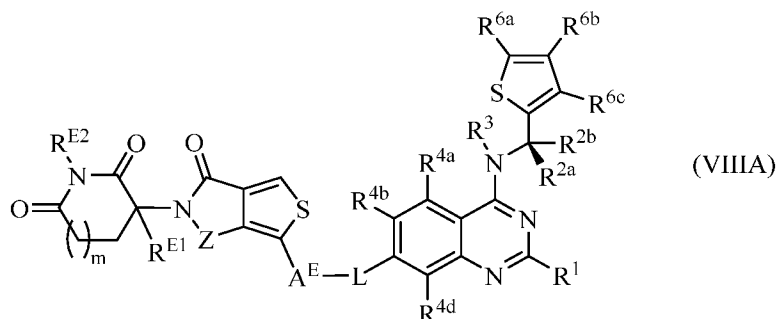


or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^{E1} , R^{E2} , R^{E4} , A^E , L , Z , m , and n are each as defined herein.

[00187] In another embodiment, provided herein is a compound of Formula (VA):

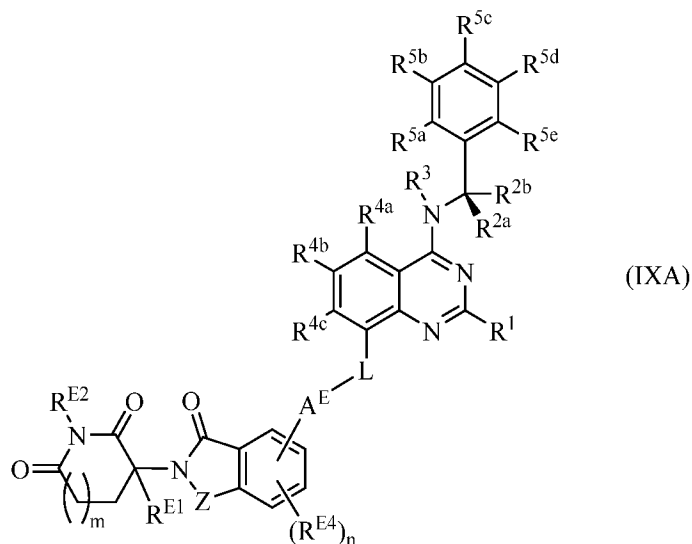
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , A^E , L , Z , and m are each as defined herein.

[00190] In another embodiment, provided herein is a compound of Formula (VIII A):



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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^{E1} , R^{E2} , A^E , L , Z , and m are each as defined herein.

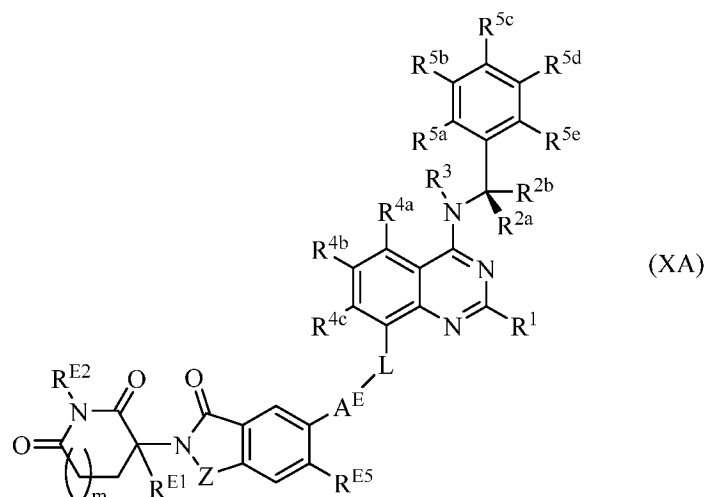
[00191] In one embodiment, provided herein is a compound of Formula (IX A):



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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4c} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , A^E , L , Z , and m are each as defined herein.

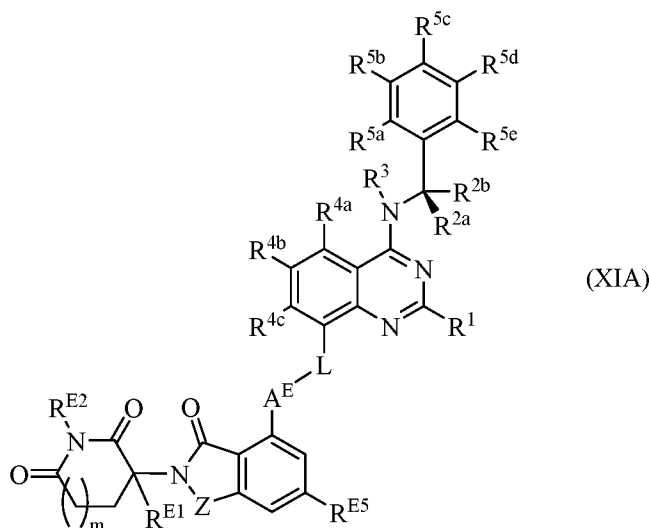
R^{4a} , R^{4b} , R^{4c} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , R^{E4} , A^E , L , Z , m , and n are each as defined herein.

[00192] In another embodiment, provided herein is a compound of Formula (XA):



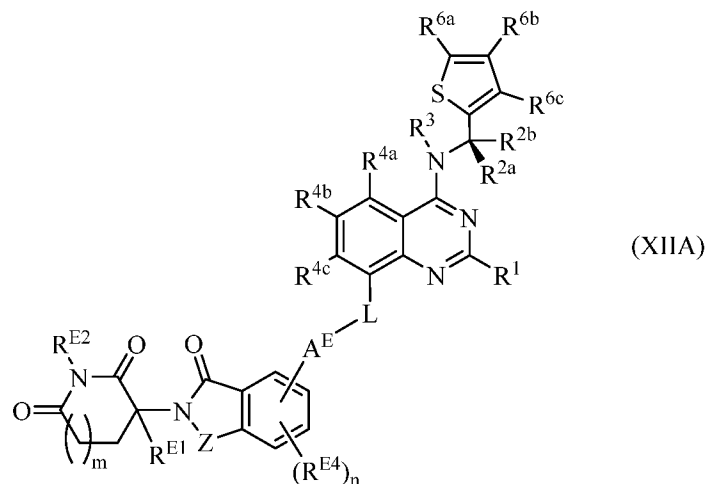
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4c} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , R^{E5} , A^E , L , Z , and m are each as defined herein.

[00193] In yet another embodiment, provided herein is a compound of Formula (XIA):



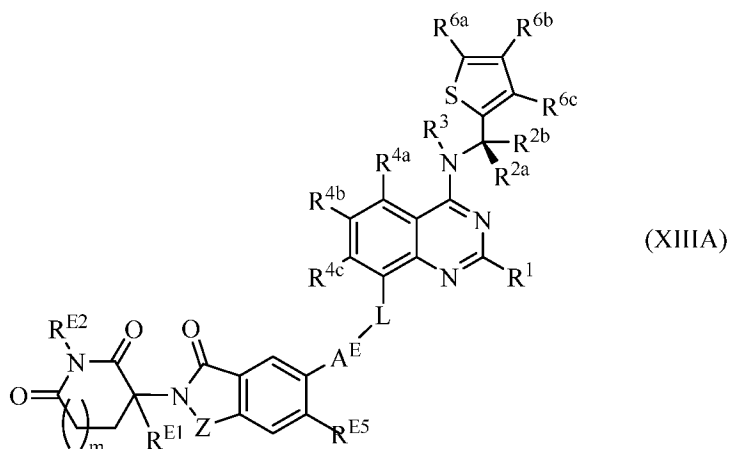
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4c} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , R^{E5} , A^E , L , Z , and m are each as defined herein.

[00194] In one embodiment, provided herein is a compound of Formula (XIIA):



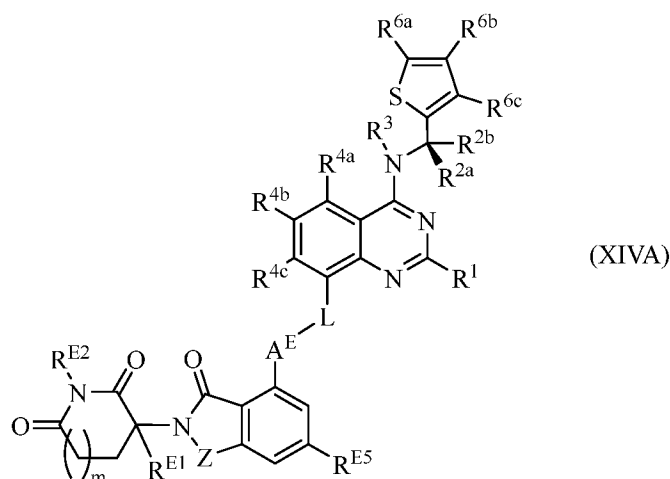
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R¹, R³, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{4c}, R^{6a}, R^{6b}, R^{6c}, R^{E1}, R^{E2}, R^{E4}, A^E, L, Z, m, and n are each as defined herein.

[00195] In another embodiment, provided herein is a compound of Formula (XIIIA):



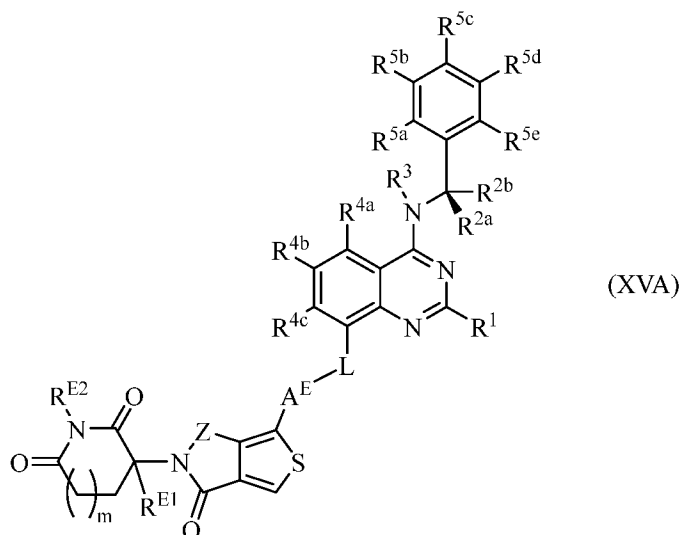
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R¹, R³, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{4c}, R^{6a}, R^{6b}, R^{6c}, R^{E1}, R^{E2}, R^{E5}, A^E, L, Z, and m are each as defined herein.

[00196] In yet another embodiment, provided herein is a compound of Formula (XIVA):



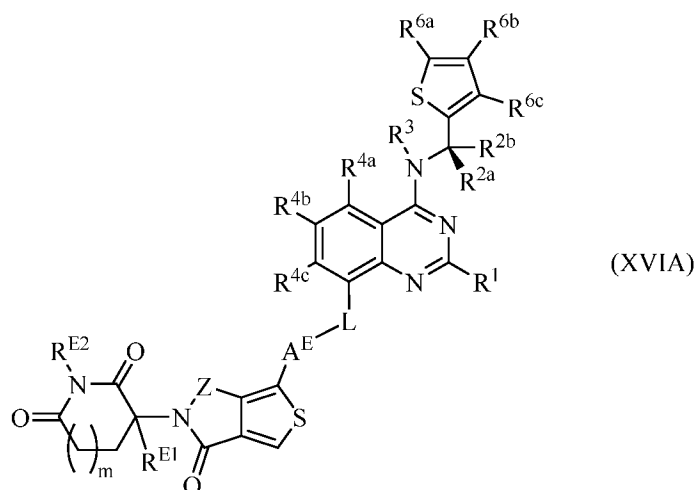
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4c} , R^{6a} , R^{6b} , R^{6c} , R^{E1} , R^{E2} , R^{E5} , A^E , L, Z, and m are each as defined herein.

[00197] In one embodiment, provided herein is a compound of Formula (XVA):



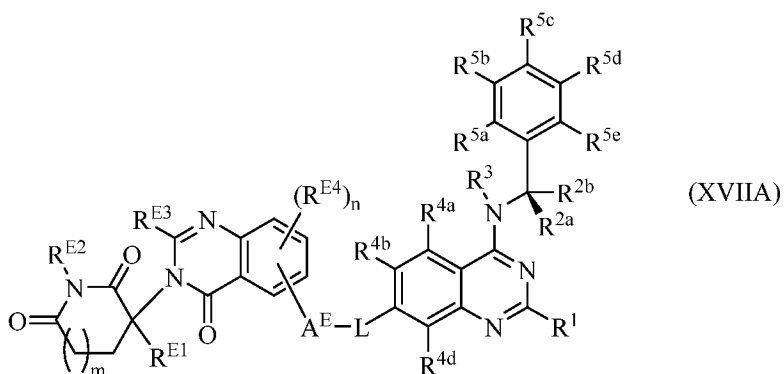
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4c} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , A^E , L, Z, and m are each as defined herein.

[00198] In another embodiment, provided herein is a compound of Formula (XVIA):



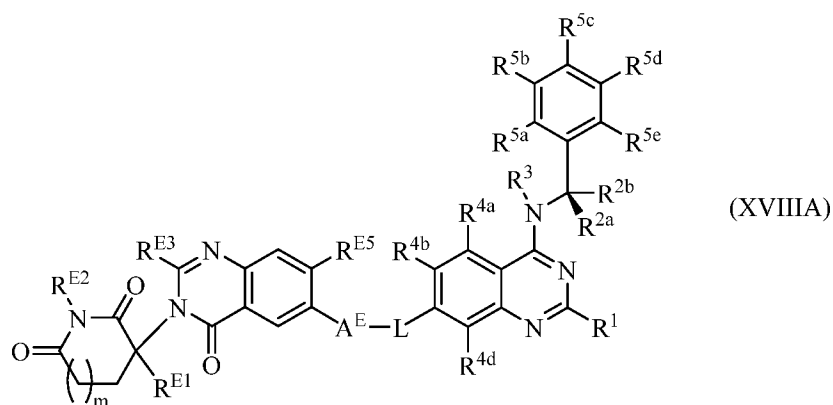
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4c} , R^{6a} , R^{6b} , R^{6c} , R^{E1} , R^{E2} , A^E , L , Z , and m are each as defined herein.

[00199] In one embodiment, provided herein is a compound of Formula (XVIA):



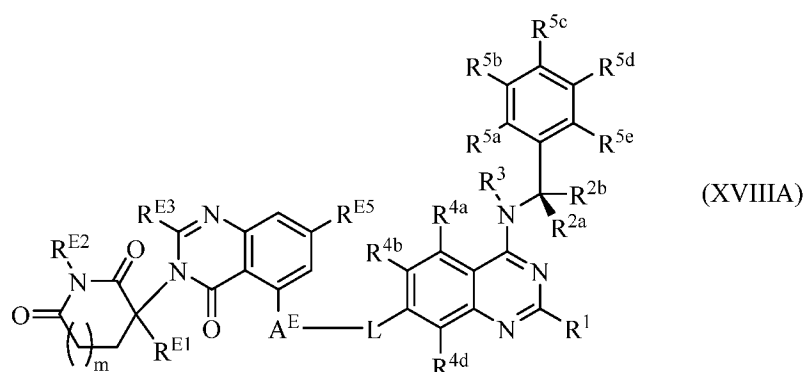
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , R^{E3} , R^{E4} , A^E , L , m , and n are each as defined herein.

[00200] In another embodiment, provided herein is a compound of Formula (XVIA):



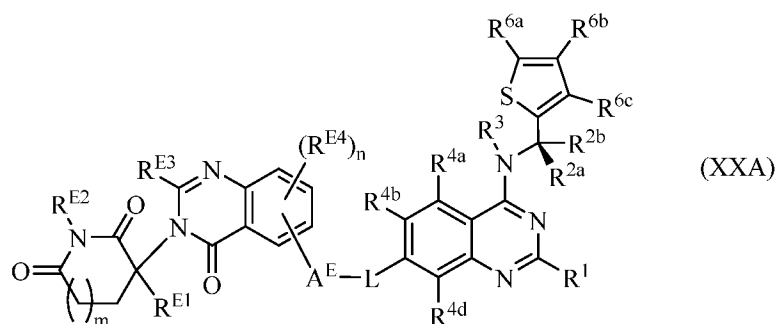
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , R^{E3} , R^{E5} , A^E , L , and m are each as defined herein.

[00201] In yet another embodiment, provided herein is a compound of Formula (XIXA):



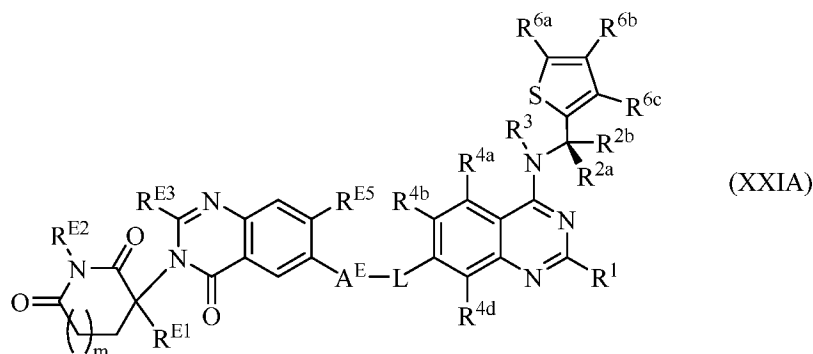
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{E1} , R^{E2} , R^{E3} , R^{E5} , A^E , L , and m are each as defined herein.

[00202] In one embodiment, provided herein is a compound of Formula (XXA):



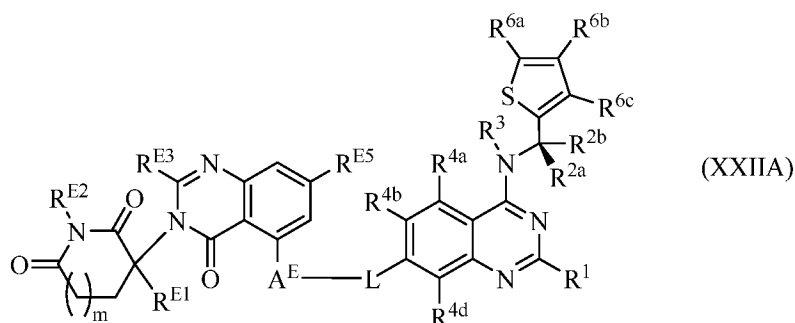
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R¹, R³, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{4d}, R^{6a}, R^{6b}, R^{6c}, R^{E1}, R^{E2}, R^{E3}, R^{E4}, A^E, L, m, and n are each as defined herein.

[00203] In another embodiment, provided herein is a compound of Formula (XXIA):



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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^{E1} , R^{E2} , R^{E3} , R^{E5} , A^E , L , and m are each as defined herein.

[00204] In yet another embodiment, provided herein is a compound of Formula (XXIIA):

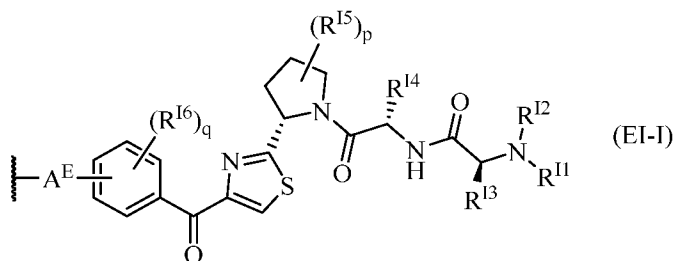


or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more

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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^{E1} , R^{E2} , R^{E5} , A^E , L , Z , and m are each as defined herein.

[00205] In certain embodiments, R^E is a moiety of an IAP E3 ligand.

[00206] In certain embodiments, R^E is a moiety having the structure of Formula (EI-I):



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

R^{I1} and R^{I2} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl;

R^{I3} and R^{I4} are each independently C_{1-6} alkyl, C_{3-10} cycloalkyl, or heterocyclyl;

each R^{I5} and R^{I6} is independently (i) deuterium, cyano, halo, nitro, or oxo; (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) $-C(O)R^{Ia}$, $-C(O)OR^{Ia}$, $-C(O)NR^{Ib}R^{Ic}$, $-C(O)SR^{Ia}$, $-C(NR^{Ia})NR^{Ib}R^{Ic}$, $-C(S)R^{Ia}$, $-C(S)OR^{Ia}$, $-C(S)NR^{Ib}R^{Ic}$, $-OR^{Ia}$, $-OC(O)R^{Ia}$, $-OC(O)OR^{Ia}$, $-OC(O)NR^{Ib}R^{Ic}$, $-OC(O)SR^{Ia}$, $-OC(NR^{Ia})NR^{Ib}R^{Ic}$, $-OC(S)R^{Ia}$, $-OC(S)OR^{Ia}$, $-OC(S)NR^{Ib}R^{Ic}$, $-OS(O)R^{Ia}$, $-OS(O)_2R^{Ia}$, $-OS(O)NR^{Ib}R^{Ic}$, $-OS(O)_2NR^{Ib}R^{Ic}$, $-NR^{Ib}R^{Ic}$, $-NR^{Ia}C(O)R^{Id}$, $-NR^{Ia}C(O)OR^{Id}$, $-NR^{Ia}C(O)NR^{Ib}R^{Ic}$, $-NR^{Ia}C(O)SR^{Id}$, $-NR^{Ia}C(NR^{Id})NR^{Ib}R^{Ic}$, $-NR^{Ia}C(S)R^{Id}$, $-NR^{Ia}C(S)OR^{Id}$, $-NR^{Ia}C(S)NR^{Ib}R^{Ic}$, $-NR^{Ia}S(O)R^{Id}$, $-NR^{Ia}S(O)_2R^{Id}$, $-NR^{Ia}S(O)NR^{Ib}R^{Ic}$, $-NR^{Ia}S(O)_2NR^{Ib}R^{Ic}$, $-SR^{Ia}$, $-S(O)R^{Ia}$, $-S(O)_2R^{Ia}$, $-S(O)NR^{Ib}R^{Ic}$, or $-S(O)_2NR^{Ib}R^{Ic}$;

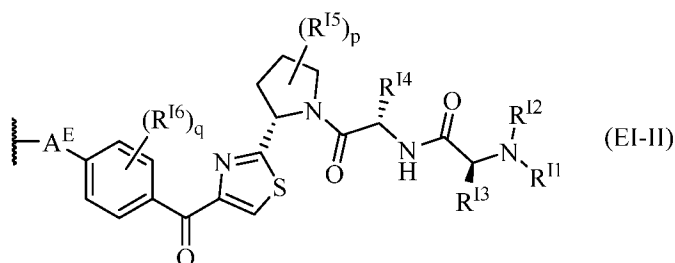
p is an integer of 0, 1, 2, 4, or 5;

q is an integer of 0, 1, 2, or 4; and

each R^{Ia} , R^{Ib} , R^{Ic} , R^{Id} , and A^E is as defined herein;

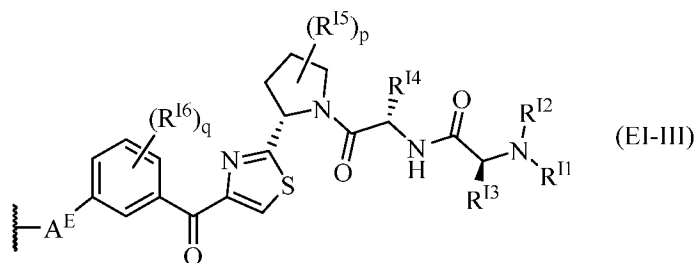
wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q .

[00207] In certain embodiments, R^E is a moiety having the structure of Formula (EI-II):



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , A^E , p , and q are each as defined herein.

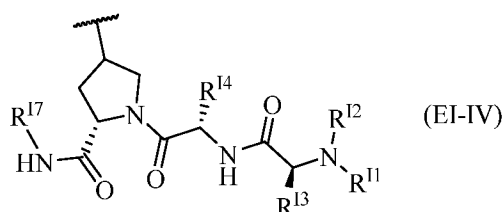
[00208] In certain embodiments, R^E is a moiety having the structure of Formula (EI-III):



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , A^E , p , and q are each as defined herein.

[00209] In one embodiment, in Formula (EI-I), (EI-II), or (EI-III), R^{11} is hydrogen; R^{12} is C_{1-6} alkyl; R^{13} is C_{1-6} alkyl; R^{14} is C_{1-6} alkyl or C_{3-10} cycloalkyl; R^{15} is $-OR^{1a}$; R^{16} is halo; and p and q are each independently an integer of 0 or 1. In another embodiment, in Formula (EI-I), (EI-II), or (EI-III), R^{11} is hydrogen; R^{12} is C_{1-6} alkyl; R^{13} is C_{1-6} alkyl; R^{14} is C_{3-10} cycloalkyl; R^{15} is $-OR^{1a}$; R^{16} is halo; and p and q are each independently an integer of 0 or 1. In yet another embodiment, in Formula (EI-I), (EI-II), or (EI-III), R^{11} is hydrogen; R^{12} and R^{13} are each methyl; R^{14} is cyclohexyl; R^{15} is hydroxyl; R^{16} is fluoro; and p and q are each independently an integer of 0 or 1.

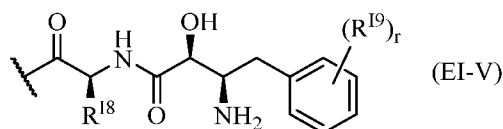
[00210] In certain embodiments, R^E is a moiety having the structure of Formula (EI-IV):



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein R^{17} is 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^{11} , R^{12} , R^{13} , and R^{14} are each as defined herein.

[00211] In one embodiment, in Formula (EI-IV), R^{11} is hydrogen; R^{12} is C_{1-6} alkyl; R^{13} is C_{1-6} alkyl; R^{14} is C_{1-6} alkyl or C_{3-10} cycloalkyl; and R^{17} is C_{3-10} cycloalkyl or C_{6-14} aryl. In another embodiment, in Formula (EI-IV), R^{11} is hydrogen; R^{12} is C_{1-6} alkyl; R^{13} is C_{1-6} alkyl; R^{14} is C_{3-10} cycloalkyl; and R^{17} is C_{3-10} cycloalkyl or C_{6-14} aryl. In yet another embodiment, in Formula (EI-IV), R^{11} is hydrogen; R^{12} is methyl; R^{13} is methyl; R^{14} is cyclohexyl; and R^{17} is 1,2,3,4-tetrahydronaphthalenyl. In still another embodiment, in Formula (EI-IV), R^{11} is hydrogen; R^{12} is methyl; R^{13} is methyl; R^{14} is cyclohexyl; and R^{17} is 1,2,3,4-tetrahydronaphthalen-1-yl.

[00212] In certain embodiments, R^E is a moiety having the structure of Formula (EI-V):



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

R^{18} is C_{1-6} alkyl, C_{3-10} cycloalkyl, or heterocyclyl;

each R^{19} is independently (i) deuterium, cyano, halo, nitro, or oxo; (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) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$,

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

r is an integer of 0, 1, 2, 4, or 5; and

each R^{1a} , R^{1b} , R^{1c} , and R^{1d} is as defined herein;

wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q.

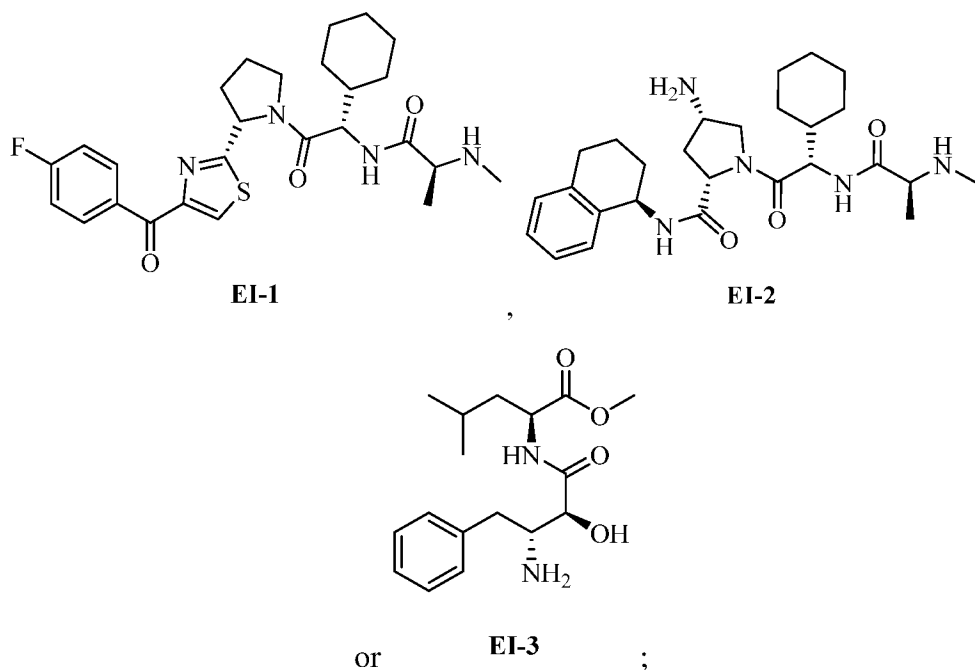
[00213] In one embodiment, in Formula (EI-V), R^{18} is C_{1-6} alkyl or C_{3-10} cycloalkyl; and r is an integer of 0 or 1. In another embodiment, in Formula (EI-V), R^{18} is C_{1-6} alkyl and r is an integer of 0. In yet another embodiment, in Formula (EI-V), R^{18} is isobutyl and r is an integer of 0.

[00214] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula (EI-I), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula (EI-II), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula (EI-III), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula (EI-IV), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula (EI-V), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00215] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EI-I), or a diastereomer, a mixture of two or more diastereomers, a

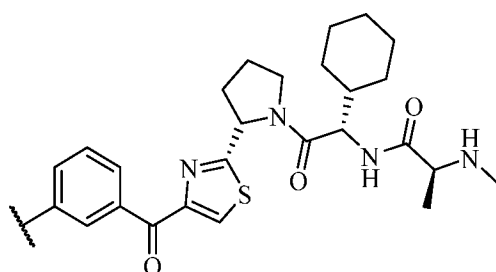
tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EI-II), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EI-III), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EI-IV), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EI-V), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00216] In certain embodiments, R^E is a moiety of an IAP E3 ligand having the structure of:



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00217] In certain embodiments, R^E is a moiety having the structure of:

**EI-4**

or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

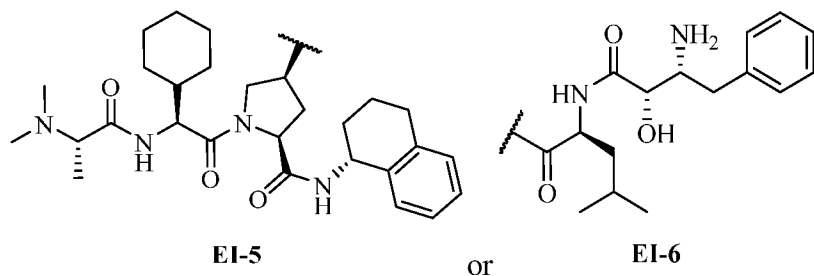
[00218] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EI-1**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EI-2**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EI-3**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EI-4**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00219] In one embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety of compound **EI-1**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety of compound **EI-2**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety of compound **EI-3**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another

embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety of compound **EI-4**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00220] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EI-1**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EI-2**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EI-3**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EI-4**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00221] In certain embodiments, R^E is a moiety having the structure of:



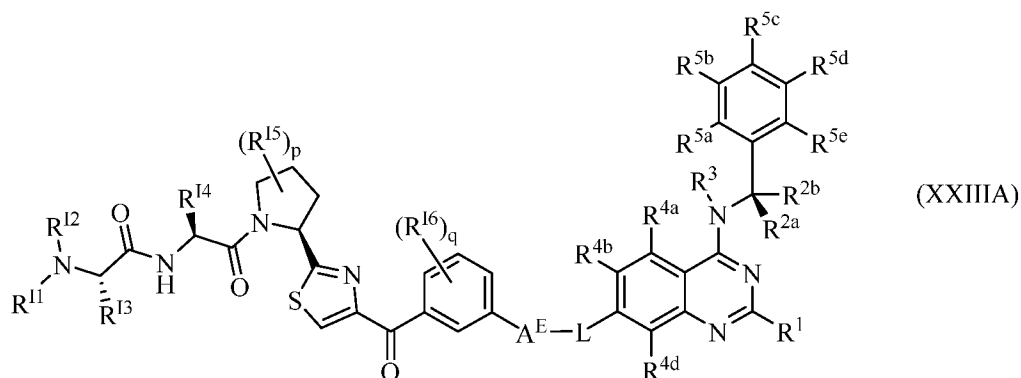
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00222] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), (XXIV-a) to (XXIV-c), and (XXIV-d), R^E is a moiety having the structure of Formula **EI-5**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), (XXIV-a) to (XXIV-c), and (XXIV-d), R^E is a moiety having the structure of Formula **EI-6**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic

variant thereof.

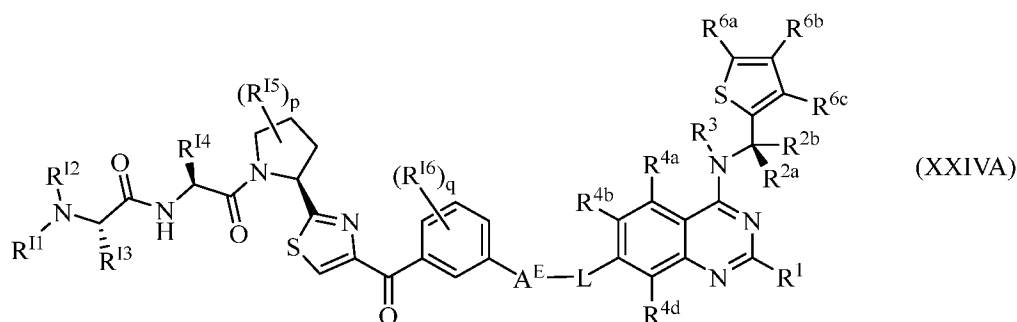
[00223] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EI-5**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EI-6**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00224] In one embodiment, provided herein is a compound of Formula (XXIIIa):



or 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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , A^E , L , p , and q are each as defined herein.

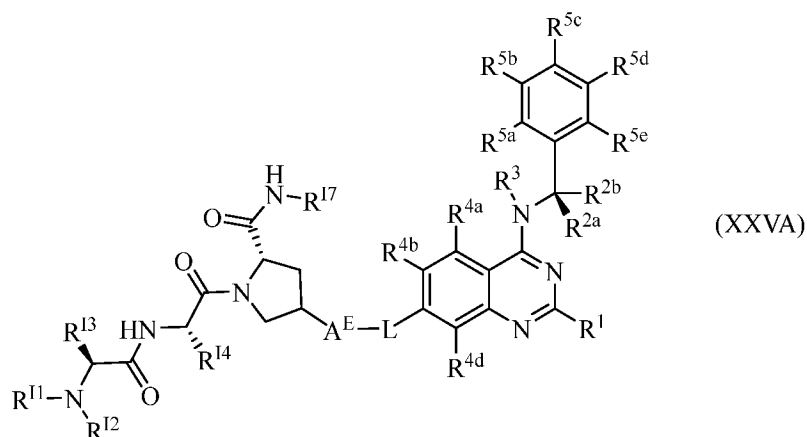
[00225] In another embodiment, provided herein is a compound of Formula (XXIVa):



or 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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} ,

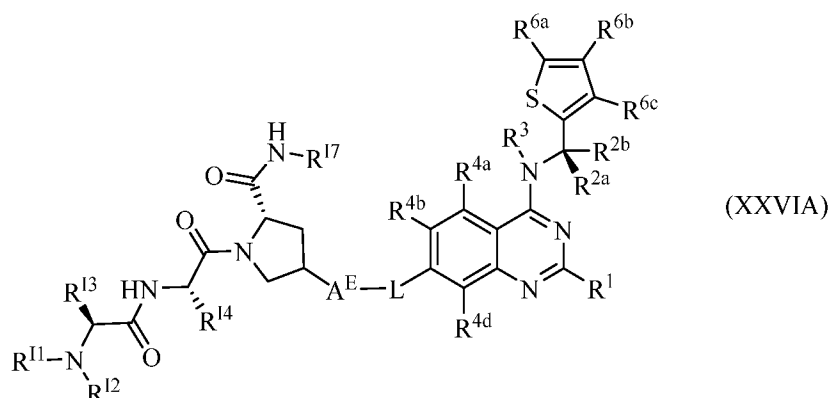
A^E , L, p, and q are each as defined herein.

[00226] In one embodiment, provided herein is a compound of Formula (XXVA):



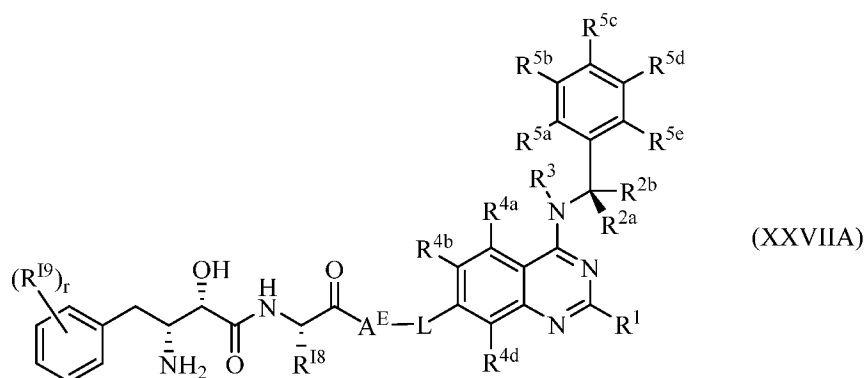
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{11} , R^{12} , R^{13} , R^{14} , R^{17} , A^E , and L are each as defined herein.

[00227] In another embodiment, provided herein is a compound of Formula (XXVIA):



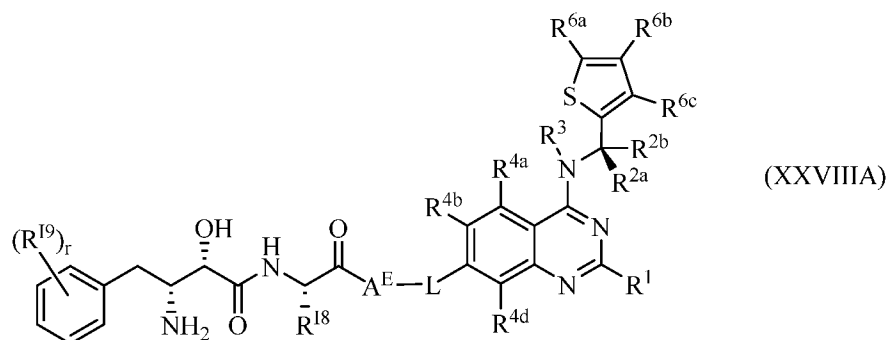
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^{11} , R^{12} , R^{13} , R^{14} , R^{17} , A^E , and L are each as defined herein.

[00228] In one embodiment, provided herein is a compound of Formula (XXVIIA):



or 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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{18} , R^{19} , A^E , L , and r are each as defined herein.

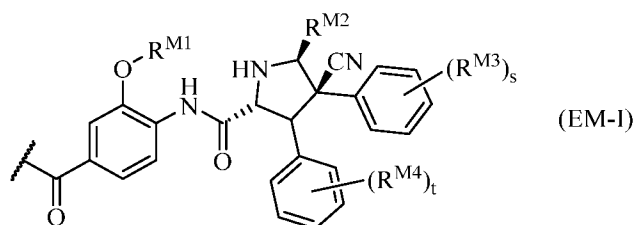
[00229] In another embodiment, provided herein is a compound of Formula (XXVIII):



or 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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^{18} , R^{19} , A^E , L , and r are each as defined herein.

[00230] In certain embodiments, R^E is a moiety of an MDM2 E3 ligand.

[00231] In certain embodiments, R^E is a moiety having the structure of Formula (EM-I):



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

R^{M1} and R^{M2} are each independently C_{1-6} alkyl or C_{3-10} cycloalkyl;

each R^{M3} and R^{M4} is independently (i) deuterium, cyano, halo, nitro, or oxo; (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) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$;

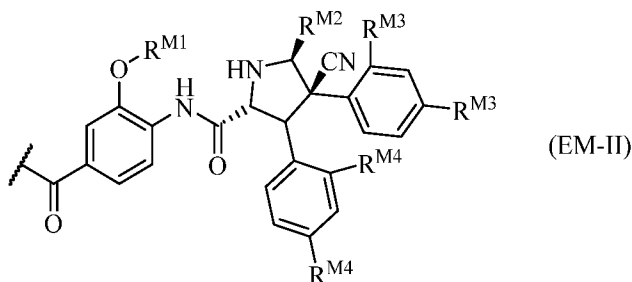
s and t are each independently an integer of 0, 1, 2, 3, 4, or 5; and

each R^{1a} , R^{1b} , R^{1c} , and R^{1d} is as defined herein;

wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q.

[00232] In one embodiment, in Formula (EM-I), R^{M1} and R^{M2} are each independently C_{1-6} alkyl; each R^{M3} and R^{M4} is independently deuterium or halo; and s and t are each independently an integer of 0, 1, or 2. In another embodiment, in Formula (EM-I), R^{M1} and R^{M2} are each independently methyl or 2,2-dimethylpropyl; each R^{M3} and R^{M4} is independently fluoro or chloro; and s and t are each independently an integer of 2.

[00233] In certain embodiments, R^E is a moiety having the structure of Formula (EM-II):

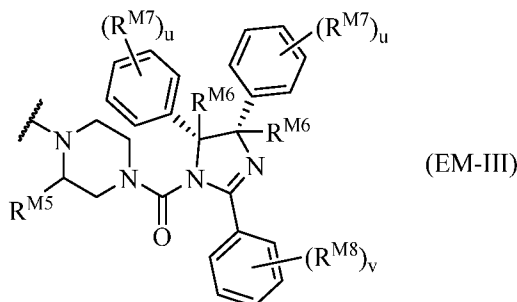


or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein R^{M1} , R^{M2} , R^{M3} , and R^{M4} are each as defined

herein.

[00234] In one embodiment, in Formula (EM-II), R^{M1} and R^{M2} are each independently C_{1-6} alkyl; and each R^{M3} and R^{M4} is independently deuterium or halo. In another embodiment, in Formula (EM-II), R^{M1} and R^{M2} are each independently methyl or 2,2-dimethylpropyl; and each R^{M3} and R^{M4} is independently fluoro or chloro.

[00235] In certain embodiments, R^E is a moiety having the structure of Formula (EM-III):



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

R^{M5} is hydrogen or oxo;

each R^{M6} is independently hydrogen, deuterium, or C_{1-6} alkyl; and

each R^{M7} and R^{M8} is independently (i) deuterium, cyano, halo, nitro, or oxo; (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) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$;

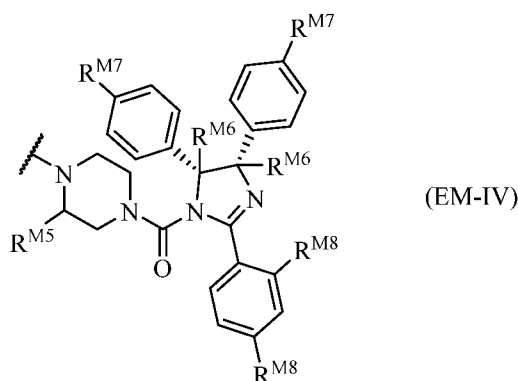
each u and v is independently an integer of 0, 1, 2, 3, 4, or 5; and

each R^{1a} , R^{1b} , R^{1c} , and R^{1d} is as defined herein;

wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q.

[00236] In one embodiment, in Formula (EM-III), R^{M5} is hydrogen or oxo; each R^{M6} is independently hydrogen, deuterium, or C_{1-6} alkyl; each R^{M7} is independently halo; each R^{M8} is independently C_{1-6} alkyl or $-OC_{1-6}$ alkyl; and each u and v is independently an integer of 0, 1, 2. In another embodiment, in Formula (EM-III), R^{M5} is hydrogen or oxo; each R^{M6} is independently hydrogen or methyl; each R^{M7} is chloro; each R^{M8} is independently *tert*-butyl, methoxy, ethoxy, or isopropoxy; u is an integer of 0 or 1; and v is an integer of 1 or 2. In yet another embodiment, in Formula (EM-III), R^{M5} is hydrogen or oxo; each R^{M6} is independently hydrogen or methyl; each R^{M7} is chloro; each R^{M8} is independently *tert*-butyl, methoxy, ethoxy, or isopropoxy; u is an integer of 1; and v is an integer of 2.

[00237] In certain embodiments, R^E is a moiety having the structure of Formula (EM-IV):



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein each R^{M5} , R^{M6} , R^{M7} , and R^{M8} is as defined herein.

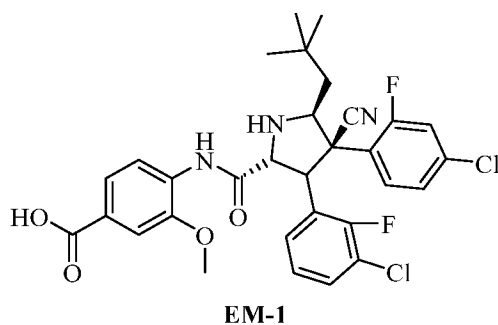
[00238] In one embodiment, in Formula (EM-IV), R^{M5} is hydrogen or oxo; each R^{M6} is independently hydrogen, deuterium, or C_{1-6} alkyl; each R^{M7} is independently halo; and each R^{M8} is independently C_{1-6} alkyl or $-OC_{1-6}$ alkyl. In another embodiment, in Formula (EM-IV), R^{M5} is hydrogen or oxo; each R^{M6} is independently hydrogen or methyl; each R^{M7} is chloro; and each R^{M8} is independently *tert*-butyl, methoxy, ethoxy, or isopropoxy.

[00239] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula (EM-I), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any

one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula (EM-II), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula (EM-III), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula (EM-IV), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00240] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EM-I), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EM-II), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EM-III), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EM-IV), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

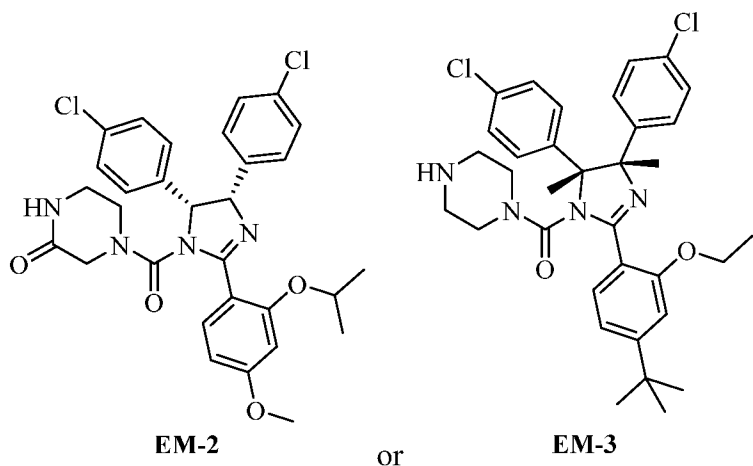
[00241] In certain embodiments, R^E is a moiety of an MDM2 E3 ligand having the structure of:



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00242] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EM-1**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety of compound **EM-1**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EM-1**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00243] In certain embodiments, R^E is a moiety of an MDM2 E3 ligand having the structure of:



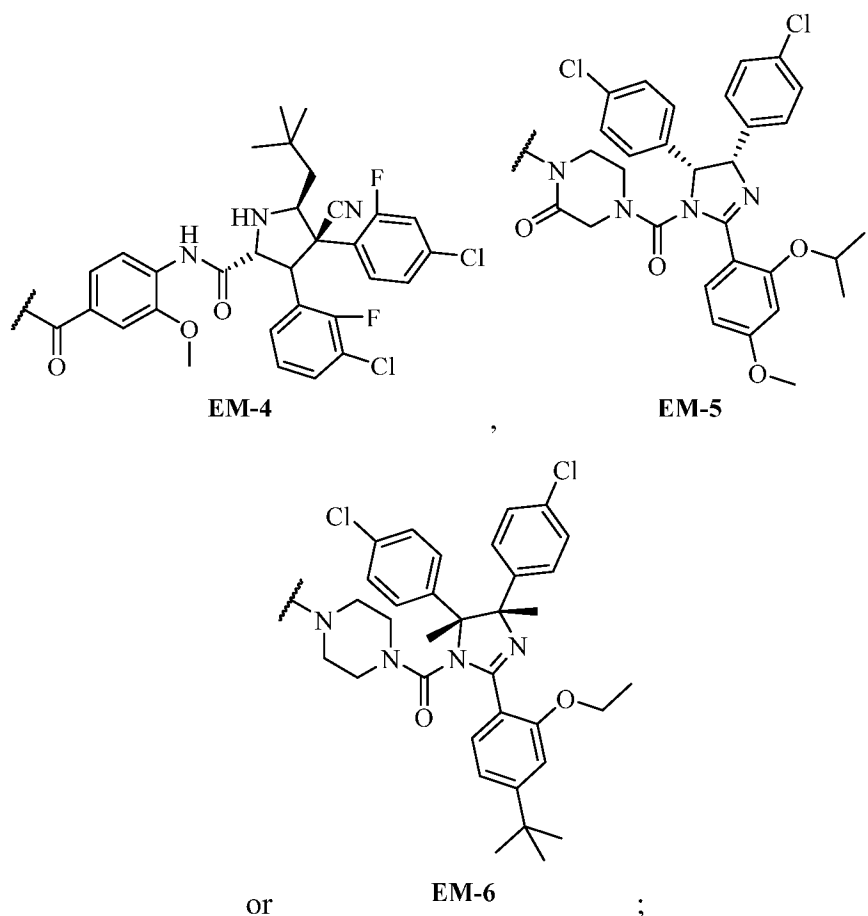
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00244] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety of compound **EM-2**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety of compound **EM-3**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a

mixture of two or more tautomers, or an isotopic variant thereof.

[00245] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EM-2**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EM-3**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00246] In certain embodiments, R^E is a moiety having the structure of:



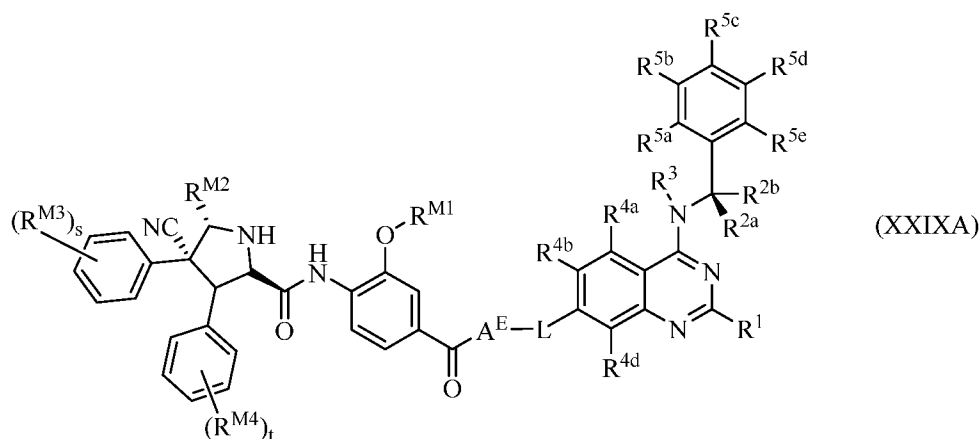
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00247] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula **EM-4**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or

more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula **EM-5**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-j), and (XXIV-a) to (XXIV-d), R^E is a moiety having the structure of Formula **EM-6**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

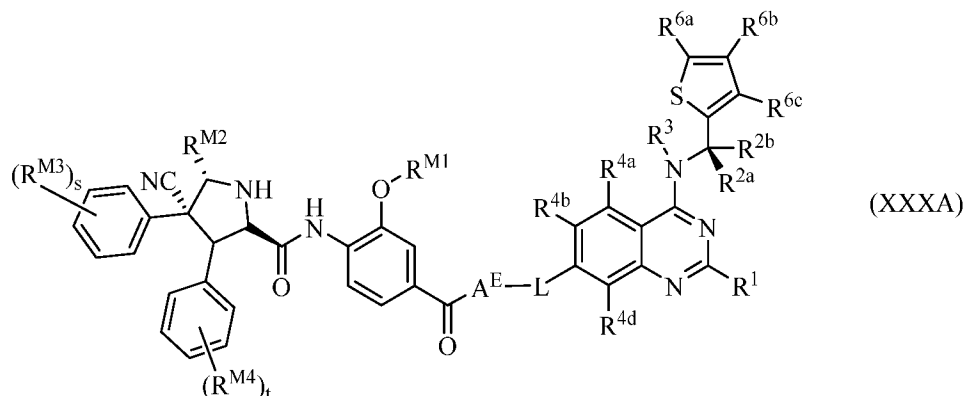
[00248] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EM-4**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EM-5**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EM-6**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00249] In one embodiment, provided herein is a compound of Formula (XXIXA):



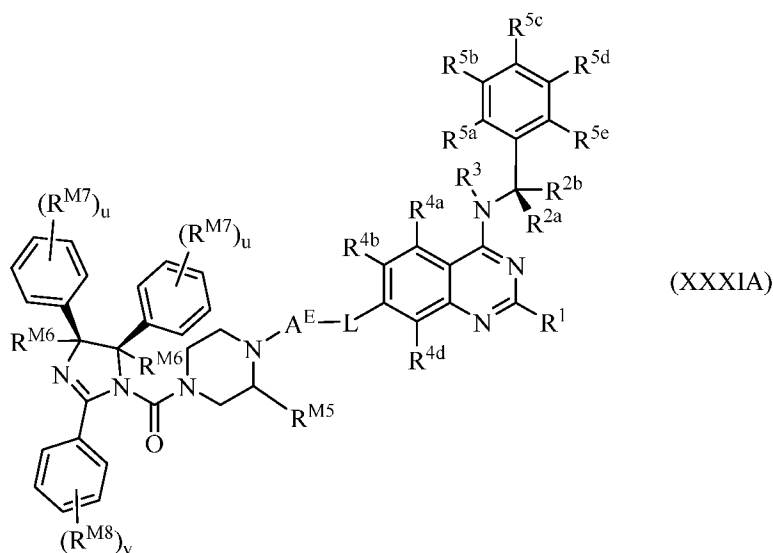
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{M1} , R^{M2} , R^{M3} , R^{M4} , A^E , L , s , and t are each as defined herein.

[00250] In another embodiment, provided herein is a compound of Formula (XXXA):



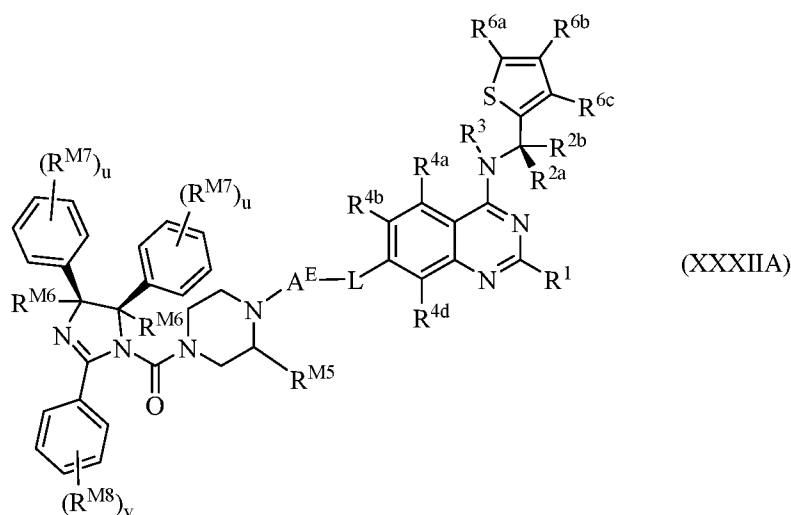
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^{M1} , R^{M2} , R^{M3} , R^{M4} , A^E , L , s , and t are each as defined herein.

[00251] In one embodiment, provided herein is a compound of Formula (XXXIA):



or 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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{M5} , R^{M6} , R^{M7} , R^{M8} , A^E , L , u , and v are each as defined herein.

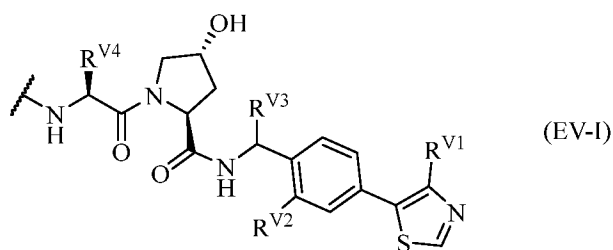
[00252] In another embodiment, provided herein is a compound of Formula (XXXIIA):



or 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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^{M5} , R^{M6} , R^{M7} , R^{M8} , A^E , L , u , and v are each as defined herein.

[00253] In certain embodiments, R^E is a moiety of a VHL E3 ligand.

[00254] In certain embodiments, R^E has the structure of Formula (EV-I):



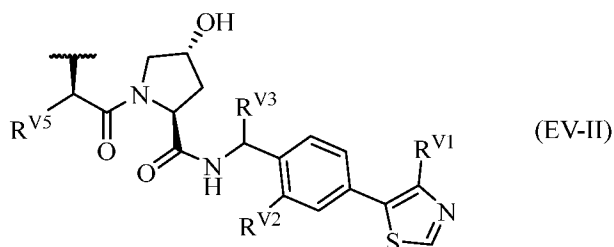
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein:

R^{V1} , R^{V3} , and R^{V4} are each independently hydrogen, deuterium, C_{1-6} alkyl, or C_{3-10} cycloalkyl; and

R^{V2} is hydrogen, deuterium, halo, hydroxyl, $-OC_{1-6}$ alkyl, or $-OC_{3-10}$ cycloalkyl;

wherein each alkyl and cycloalkyl is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q .

[00255] In certain embodiments, R^E has the structure of Formula (EV-II):

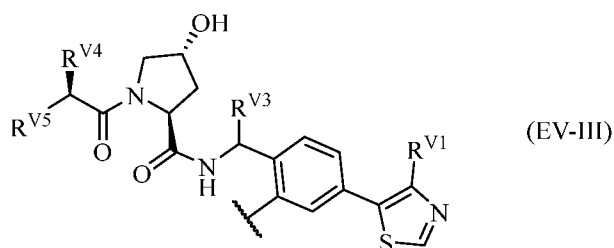


or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein:

R^{V5} is $-NHC(O)C_{1-6}$ alkyl, $-NHC(O)C_{3-10}$ cycloalkyl, or heterocyclyl, wherein the alkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; and

R^{V1} , R^{V2} , and R^{V3} are each as defined herein.

[00256] In certain embodiments, R^E has the structure of Formula (EV-III):



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein R^{V1} , R^{V3} , R^{V4} , and R^{V5} are each as defined herein.

[00257] In certain embodiments, in any one of Formulae (EV-I) to (EV-III),

R^{V1} is methyl;

R^{V2} , if present, is hydrogen;

R^{V3} is hydrogen;

R^{V4} , if present, is propyl, butyl, or cyclopropyl; and

R^{V5} , if present, is acetamido, cyclopropamido, or isoindolinyl;

wherein the propyl, butyl, cyclopropyl, acetamido, cyclopropamido, and isoindolinyl are each optionally substituted with cyano, fluoro, or trifluoromethyl.

[00258] In certain embodiments, in any one of Formulae (EV-I) to (EV-III),

R^{V1} is methyl;

R^{V2} , if present, is hydrogen;

R^{V3} is hydrogen;

R^{V4} , if present, is isopropyl, *tert*-butyl, cyclopropyl, 1-fluorocyclopropyl, or 1-trifluoromethylcyclopropyl; and

R^{V5} , if present, is acetamido, cyclopropamido, 1-cyanocyclopropamido, 1-fluorocyclopropamido, or 1-oxoisindolin-2-yl.

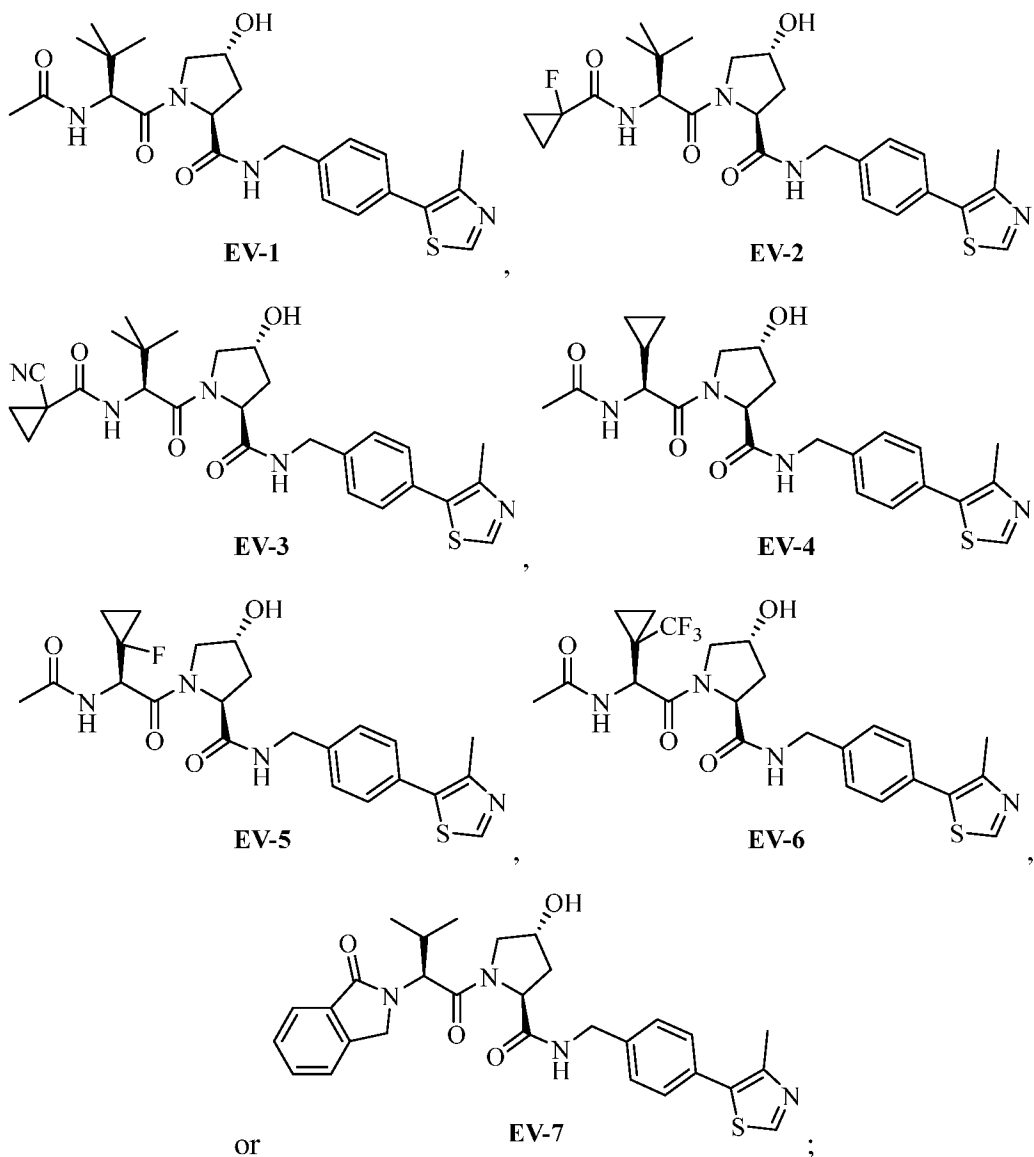
[00259] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EV-I), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EV-II), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula (EV-III), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00260] In one embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EV-I), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EV-II), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula (EV-III), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00261] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EV-I), or a diastereomer, a mixture of two or more diastereomers, a

tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EV-II), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula (EV-III), or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00262] In certain embodiments, R^E is a moiety of a VHL E3 ligand having the structure of:



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00263] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EV-1**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EV-2**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EV-3**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EV-4**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EV-5**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EV-6**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety of compound **EV-7**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

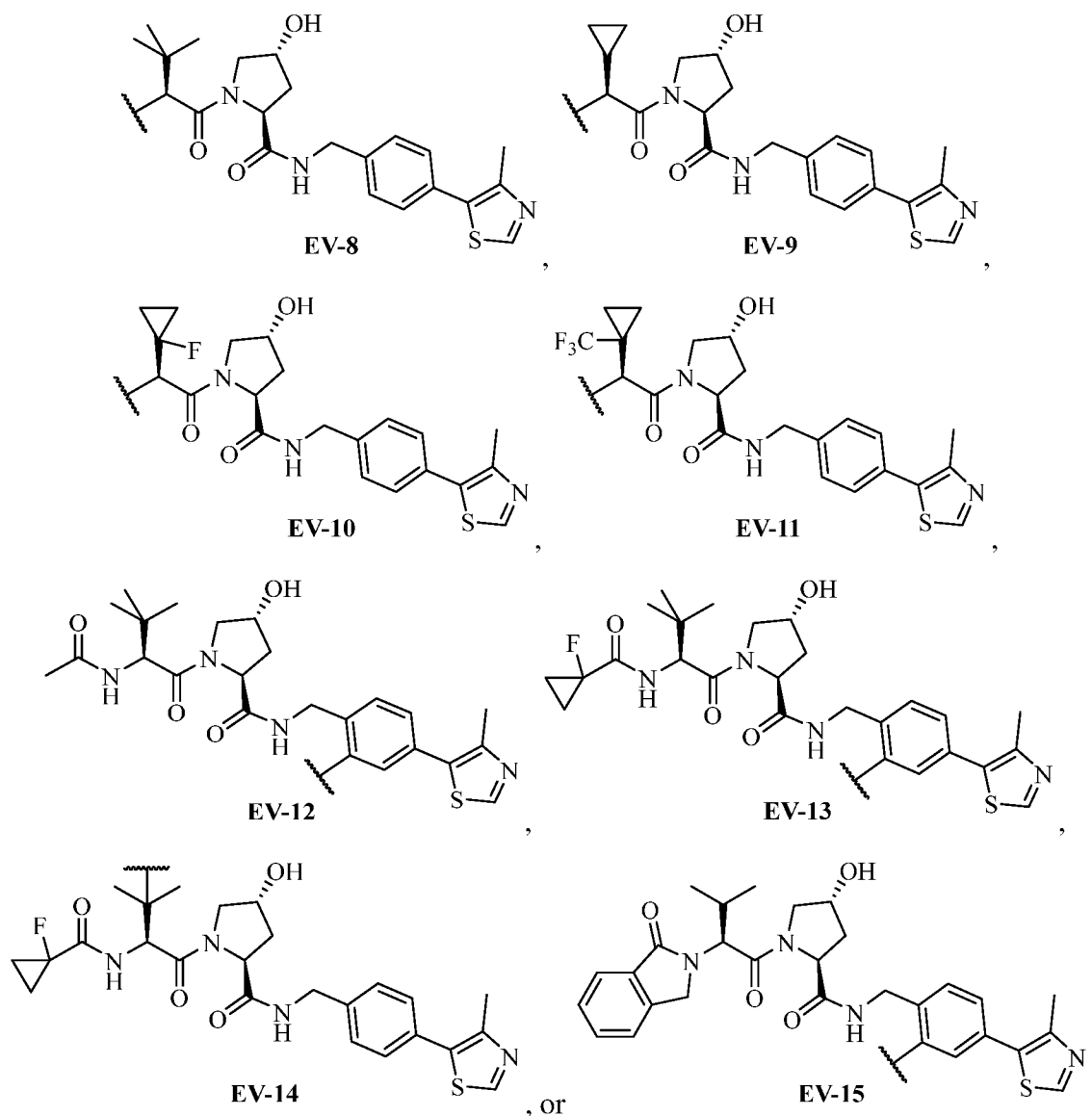
[00264] In one embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety of compound **EV-1**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-

d), R^E is a moiety of compound **EV-2**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety of compound **EV-3**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety of compound **EV-4**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety of compound **EV-5**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety of compound **EV-6**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety of compound **EV-7**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00265] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EV-1**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EV-2**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EV-3**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EV-4**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EV-5**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EV-**

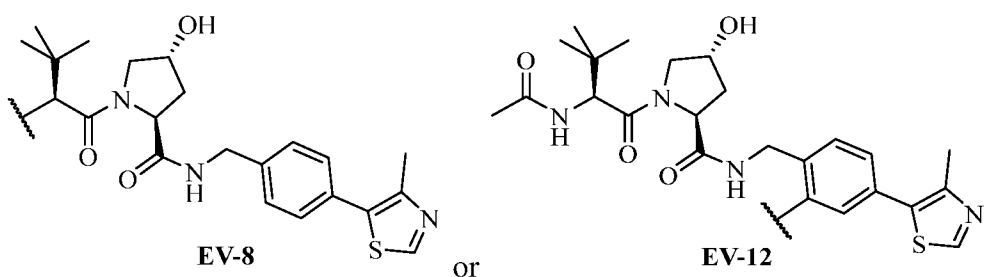
6, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety of compound **EV-7**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00266] In certain embodiments, R^E is a moiety having the structure of:



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00267] In certain embodiments, R^E is a moiety having the structure of:



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

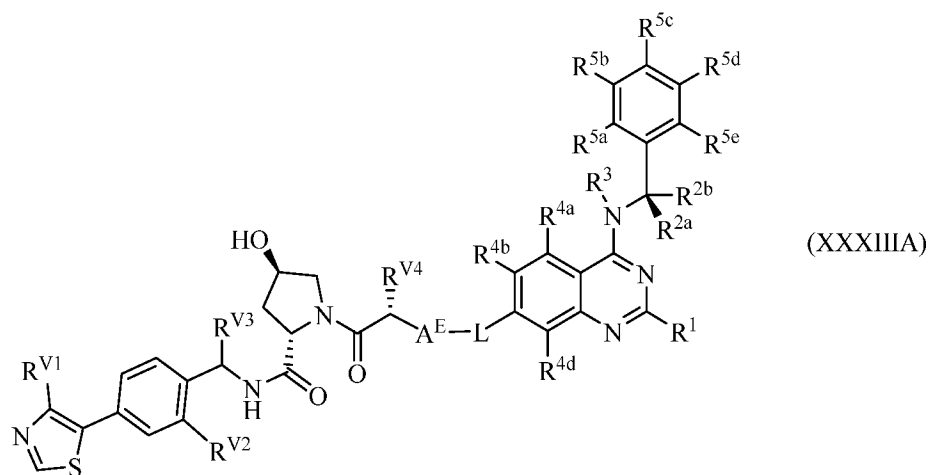
[00268] In one embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EV-8**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EV-9**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EV-10**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EV-11**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EV-12**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EV-13**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EV-14**, or

a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of any one of Formulae (I) to (XXII), (XXIII-a) to (XXIII-c), and (XXIV-a) to (XXIV-c), R^E is a moiety having the structure of Formula **EV-15**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00269] In one embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EV-8**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EV-9**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EV-10**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EV-11**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EV-12**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EV-13**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EV-14**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of any one of Formulae (XXIII-d) to (XXIII-j) and (XXIV-d), R^E is a moiety having the structure of Formula **EV-15**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

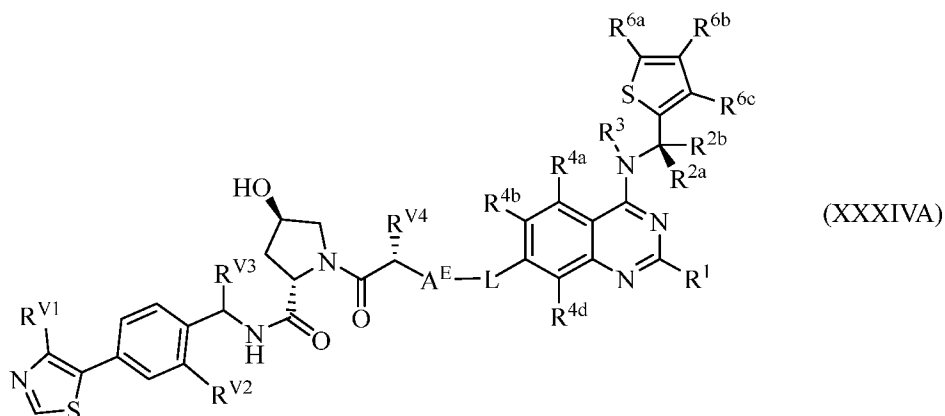
[00270] In one embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EV-8**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EV-9**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EV-10**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EV-11**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EV-12**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EV-13**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In yet another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EV-14**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof. In still another embodiment, in a compound of Formula (XXIV-e), R^E is a moiety having the structure of Formula **EV-15**, or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

[00271] In one embodiment, provided herein is a compound of Formula (XXXIIIa):



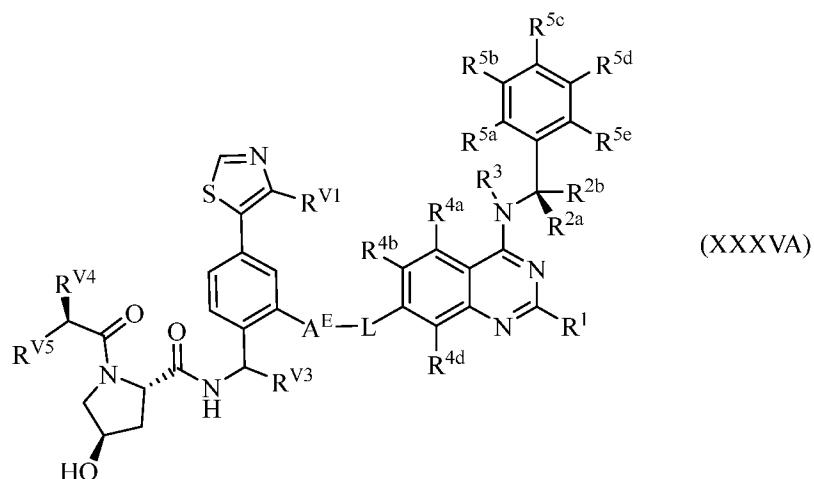
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{V1} , R^{V2} , R^{V3} , R^{V4} , A^E , and L are each as defined herein.

[00272] In another embodiment, provided herein is a compound of Formula (XXXIV A):



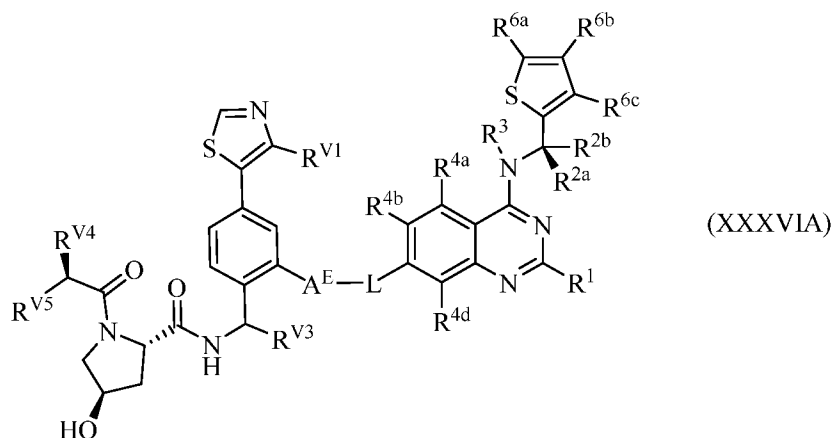
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R^1 , R^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^{V1} , R^{V2} , R^{V3} , R^{V4} , A^E , and L are each as defined herein.

[00273] In one embodiment, provided herein is a compound of Formula (XXXV A):



or 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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{V1} , R^{V3} , R^{V4} , R^{V5} , A^E , and L are each as defined herein.

[00274] In another embodiment, provided herein is a compound of Formula (XXXVIA):



or 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^3 , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{4d} , R^{6a} , R^{6b} , R^{6c} , R^{V1} , R^{V3} , R^{V4} , R^{V5} , A^E , and L are each as defined herein.

[00275] In certain embodiments, L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20} alkenylene, C_{2-20} heteroalkenylene, C_{2-20} alkynylene, C_{2-20} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene, each of which is optionally substituted with one or more substituents Q . In certain embodiments, L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20}

alkenylene, C₂₋₂₀ heteroalkenylene, C₂₋₂₀ alkynylene, or C₂₋₂₀ heteroalkynylene, each of which is optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ alkylene or C₁₋₂₀ heteroalkylene, each of which is optionally substituted with one or more substituents Q.

[00276] In certain embodiments, L is C₁₋₂₀ alkylene, optionally substituted with one, two, or three substituents Q. In certain embodiments, L is C₄₋₁₆ alkylene, optionally substituted with one, two, or three substituents Q. In certain embodiments, L is C₄₋₁₂ alkylene, optionally substituted with one, two, or three substituents Q. In certain embodiments, L is C₁₋₂₀ alkylene, optionally substituted with one or two oxo. In certain embodiments, L is C₄₋₁₆ alkylene, optionally substituted with one or two oxo. In certain embodiments, L is C₄₋₁₂ alkylene, optionally substituted with one or two oxo. In certain embodiments, L is $-(CH_2)_x-$, optionally substituted with one or two oxo; wherein x is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16. In certain embodiments, L is $-(CH_2)_x-$, optionally substituted with one or two oxo; wherein x is an integer of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12. In certain embodiments, L is $-(CH_2)_x-$, optionally substituted with one or two oxo; wherein x is an integer of 5, 6, 7, 8, or 9.

[00277] In certain embodiments, L is C₁₋₂₀ heteroalkylene, optionally substituted with one, two, or three substituents Q. In certain embodiments, L is C₄₋₁₆ heteroalkylene, optionally substituted with one, two, or three substituents Q. In certain embodiments, L is C₄₋₁₂ heteroalkylene, optionally substituted with one, two, or three substituents Q. In certain embodiments, L is C₁₋₂₀ heteroalkylene, optionally substituted with one, two, or three oxo. In certain embodiments, L is C₄₋₁₆ heteroalkylene, optionally substituted with one, two, or three oxo. In certain embodiments, L is C₄₋₁₂ heteroalkylene, optionally substituted with one, two, or three oxo.

[00278] In certain embodiments, L is C₂₋₂₀ heteroalkylene comprising an ethyleneoxy ($-CH_2CH_2O-$) group, optionally substituted with one or more substituents Q. In certain embodiments, L is C₂₋₁₄ heteroalkylene comprising an ethyleneoxy group, optionally substituted with one or more substituents Q. In certain embodiments, L is C₂₋₁₀ heteroalkylene comprising an ethyleneoxy group, optionally substituted with one or more substituents Q. In certain embodiments, L is C₃₋₂₀ heteroalkylene comprising a propyleneoxy ($-CH_2CH_2CH_2O-$) group,

optionally substituted with one or more substituents Q. In certain embodiments, L is C₃₋₁₄ heteroalkylene comprising a propyleneoxy group, optionally substituted with one or more substituents Q. In certain embodiments, L is C₃₋₁₀ heteroalkylene comprising a propyleneoxy group, optionally substituted with one or more substituents Q.

[00279] In certain embodiments, L is C₁₋₂₀ alkylene, C₁₋₂₀ heteroalkylene, C₂₋₂₀ alkenylene, C₂₋₂₀ heteroalkenylene, C₂₋₂₀ alkynylene, or C₂₋₂₀ heteroalkynylene, wherein one or more methylene groups are each independently replaced by a divalent group, and each divalent group is independently C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, heteroalkylene, alkenylene, heteroalkenylene, alkynylene, heteroalkynylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ alkylene or C₁₋₂₀ heteroalkylene, wherein one or more methylene groups are each independently replaced by a divalent group, and each divalent group is independently C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, heteroalkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents Q.

[00280] In certain embodiments, L is C₁₋₂₀ alkylene, wherein one or more methylene groups are each independently replaced by a divalent group, and each divalent group is independently C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ alkylene, wherein one or more methylene groups are each independently replaced by C₃₋₁₀ cycloalkylene; and wherein the alkylene and cycloalkylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ alkylene, wherein one or more methylene groups are each independently replaced by C₆₋₁₄ arylene; and wherein the alkylene and arylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ alkylene, wherein one or more methylene groups are each independently replaced by heterocyclylene; and wherein the alkylene

and heterocyclylene are each optionally substituted with one or more substituents Q.

[00281] In certain embodiments, L is C₁₋₂₀ alkylene, wherein one, two, or three methylene groups are each independently replaced by a divalent group; wherein each divalent group is independently cyclohexanediyl, phendiyl, 1,2,3-triazoldiyl, 2,5-dioxopyrrolidindiyl, piperazindiyl, or piperidindiyl. In certain embodiments, L is C₁₋₂₀ alkylene, wherein one, two, or three methylene groups are each independently replaced by a divalent group; wherein each divalent group is independently cyclohexane-1,4-diyl, phen-1,3-diyl, phen-1,4-diyl, 1,2,3-triazol-1,4-diyl, 2,5-dioxopyrrolidin-1,3-diyl, piperazin-1,4-diyl, or piperidin-1,4-diyl.

[00282] In certain embodiments, L is C₁₋₂₀ alkylene, wherein one or two methylene groups are each independently replaced by a divalent group; wherein each divalent group is independently C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ alkylene, wherein one or two methylene groups are each independently replaced by a divalent group; wherein each divalent group is independently cyclohexanediyl, phendiyl, 1,2,3-triazoldiyl, 2,5-dioxopyrrolidindiyl, piperazindiyl, or piperidindiyl. In certain embodiments, L is C₁₋₂₀ alkylene, wherein one or two methylene groups are each independently replaced by a divalent group; wherein each divalent group is independently cyclohexane-1,4-diyl, phen-1,3-diyl, phen-1,4-diyl, 1,2,3-triazol-1,4-diyl, 2,5-dioxopyrrolidin-1,3-diyl, piperazin-1,4-diyl, or piperidin-1,4-diyl.

[00283] In certain embodiments, L is C₁₋₂₀ alkylene, wherein a methylene group is replaced by a divalent group; wherein the divalent group is C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ alkylene, wherein a methylene group is replaced by a divalent group; wherein the divalent group is cyclohexanediyl, phendiyl, 1,2,3-triazoldiyl, 2,5-dioxopyrrolidindiyl, piperazindiyl, or piperidindiyl. In certain embodiments, L is C₁₋₂₀ alkylene, wherein a methylene group is replaced by a divalent group; wherein each divalent group is independently cyclohexane-1,4-diyl, phen-1,3-diyl, phen-1,4-diyl, 1,2,3-triazol-1,4-diyl, 2,5-dioxopyrrolidin-1,3-diyl, piperazin-1,4-diyl, or piperidin-1,4-diyl.

[00284] In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein one or more methylene groups are each independently replaced by a divalent group, and each divalent group is independently C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and wherein the heteroalkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein one or more methylene groups are each independently replaced by C₃₋₁₀ cycloalkylene; and wherein the heteroalkylene and cycloalkylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein one or more methylene groups are each independently replaced by C₆₋₁₄ arylene; and wherein the heteroalkylene and arylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein one or more methylene groups are each independently replaced by heteroarylene; and wherein the heteroalkylene and heteroarylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein one or more methylene groups are each independently replaced by heterocyclylene; and wherein the heteroalkylene and heterocyclylene are each optionally substituted with one or more substituents Q.

[00285] In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein one, two, or three methylene groups are each independently replaced by a divalent group; wherein each divalent group is independently cyclohexanediyl, phendiyl, 1,2,3-triazoldiyl, 2,5-dioxopyrrolidindiyl, piperazindiyl, or piperidindiyl. In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein one, two, or three methylene groups are each independently replaced by a divalent group; wherein each divalent group is independently cyclohexane-1,4-diyl, phen-1,3-diyl, phen-1,4-diyl, 1,2,3-triazol-1,4-diyl, 2,5-dioxopyrrolidin-1,3-diyl, piperazin-1,4-diyl, or piperidin-1,4-diyl.

[00286] In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein one or two methylene groups are each independently replaced by a divalent group; wherein each divalent group is independently C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and wherein the heteroalkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein one or two methylene groups are each independently replaced by a divalent group; wherein each divalent group is independently cyclohexanediyl, phendiyl, 1,2,3-

triazoldiyl, 2,5-dioxopyrrolidindiyl, piperazindiyl, or piperidindiyl. In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein one or two methylene groups are each independently replaced by a divalent group; wherein each divalent group is independently cyclohexane-1,4-diyl, phen-1,3-diyl, phen-1,4-diyl, 1,2,3-triazol-1,4-diyl, 2,5-dioxopyrrolidin-1,3-diyl, piperazin-1,4-diyl, or piperidin-1,4-diyl.

[00287] In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein a methylene group is replaced by a divalent group; wherein the divalent group is C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and wherein the heteroalkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein a methylene group is replaced by a divalent group; wherein the divalent group is cyclohexanediyl, phendiyl, 1,2,3-triazoldiyl, 2,5-dioxopyrrolidindiyl, piperazindiyl, or piperidindiyl. In certain embodiments, L is C₁₋₂₀ heteroalkylene, wherein a methylene group is replaced by a divalent group; wherein each divalent group is independently cyclohexane-1,4-diyl, phen-1,3-diyl, phen-1,4-diyl, 1,2,3-triazol-1,4-diyl, 2,5-dioxopyrrolidin-1,3-diyl, piperazin-1,4-diyl, or piperidin-1,4-diyl.

[00288] In certain embodiments, L is C₁₋₁₅ alkylene-C₃₋₁₀ cycloalkylene, C₁₋₁₅ heteroalkylene-C₃₋₁₀ cycloalkylene, C₁₋₁₅ alkylene-C₆₋₁₄ arylene, C₁₋₁₅ heteroalkylene-C₆₋₁₄ arylene, C₁₋₁₅ alkylene-heteroarylene, C₁₋₁₅ heteroalkylene-heteroarylene, C₁₋₁₅ alkylene-heterocyclylene, C₁₋₁₅ heteroalkylene-heterocyclylene, or heteroarylene-heterocyclylene, where each alkylene, heteroalkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene is optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₁₅ alkylene-C₃₋₁₀ cycloalkylene, where the alkylene and cycloalkylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₁₅ heteroalkylene-C₃₋₁₀ cycloalkylene, where the heteroalkylene and cycloalkylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₁₅ alkylene-C₆₋₁₄ arylene, where the alkylene and arylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₁₅ heteroalkylene-C₆₋₁₄ arylene, where the heteroalkylene and arylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₁₅ alkylene-heteroarylene, where the alkylene and heteroarylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₁₅ heteroalkylene-

heteroarylene, where the heteroalkylene and heteroarylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₁₅ alkylene-heterocyclylene, where the alkylene and heterocyclylene are each optionally substituted with one or more one, two, three, or four, substituents Q. In certain embodiments, L is C₁₋₁₅ heteroalkylene-heterocyclylene, where the heteroalkylene and heterocyclylene are each optionally substituted with one or more substituents Q. In certain embodiments, L is C₁₋₁₅ heteroarylene-heterocyclylene, where the heteroarylene and heterocyclylene are each optionally substituted with one or more substituents Q.

[00289] In certain embodiments, L is a linker having the structure of L¹-L²-L³, wherein:
L¹ is a bond, C₁₋₁₀ alkylene, C₁₋₁₀ heteroalkylene, or heterocyclylene;
L² is C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and
L³ is C₁₋₁₀ alkylene, C₁₋₁₀ heteroalkylene, heteroarylene, or heterocyclylene;
wherein each alkylene, heteroalkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene is optionally substituted with one or more substituents Q.

[00290] In certain embodiments, L² is C₃₋₁₀ cycloalkylene, optionally substituted with one or more substituents Q. In certain embodiments, L² is monocyclic C₃₋₁₀ cycloalkylene, optionally substituted with one or more substituents Q. In certain embodiments, L² is cyclopentanedyl or cyclohexanedyl, each optionally substituted with one or more substituents Q. In certain embodiments, L² is cyclopentane-1,3-diyl or cyclohexane-1,4-diyl, each optionally substituted with one or more substituents Q.

[00291] In certain embodiments, L² is C₆₋₁₄ arylene, optionally substituted with one or more substituents Q. In certain embodiments, L² is phendiyl, optionally substituted with one or more substituents Q. In certain embodiments, L² is phen-1,3-diyl, optionally substituted with one or more substituents Q. In certain embodiments, L² is phen-1,4-diyl, optionally substituted with one or more substituents Q.

[00292] In certain embodiments, L² is heteroarylene, optionally substituted with one or more substituents Q. In certain embodiments, L² is monocyclic heteroarylene, optionally substituted with one or more substituents Q. In certain embodiments, L² is 5- or 6-membered heteroarylene, each optionally substituted with one or more substituents Q. In certain

embodiments, L^2 is triazoldiyl, optionally substituted with one or more substituents Q. In certain embodiments, L^2 is 1,2,3-triazol-1,4-diyl, optionally substituted with one or more substituents Q.

[00293] In certain embodiments, L^2 is heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, L^2 is monocyclic heterocyclylene, optionally substituted with one or more substituents Q. In certain embodiments, L^2 is 5- or 6-membered heterocyclylene, each optionally substituted with one or more substituents Q. In certain embodiments, L^2 is piperazindiyl or piperidindiyl, each optionally substituted with one or more substituents Q. In certain embodiments, L^2 is piperazin-1,4-diyl, piperidin-1,3-diyl, or piperidin-1,4-diyl, each optionally substituted with one or more substituents Q.

[00294] In certain embodiments, L is a linker having the structure of $-Z^L-(R^L-Z^L)_z-$, wherein:

each R^L is independently C_{1-10} alkylene, C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene;

each Z^L is independently a bond, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{1b}-$, $-C(O)S-$, $-C(NR^{1a})NR^{1b}-$, $-C(S)-$, $-C(S)O-$, $-C(S)NR^{1b}-$, $-O-$, $-OC(O)O-$, $-OC(O)NR^{1b}-$, $-OC(O)S-$, $-OC(NR^{1a})NR^{1b}-$, $-OC(S)-$, $-OC(S)O-$, $-OC(S)NR^{1b}-$, $-OS(O)-$, $-OS(O)_2-$, $-OS(O)NR^{1b}-$, $-OS(O)_2NR^{1b}-$, $-NR^{1b}-$, $-NR^{1a}C(O)NR^{1b}-$, $-NR^{1a}C(O)S-$, $-NR^{1a}C(NR^{1d})NR^{1b}-$, $-NR^{1a}C(S)NR^{1b}-$, $-NR^{1a}S(O)NR^{1b}-$, $-NR^{1a}S(O)_2NR^{1b}-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{1b}-$, or $-S(O)_2NR^{1b}-$; where 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;

wherein each alkylene, alkenylene, alkynylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene is optionally substituted with one or more substituents Q.

[00295] In certain embodiments, each R^L is independently C_{1-10} alkylene, C_{2-10} alkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene, each optionally substituted with one or more substituents Q; each Z^L is independently a bond, $-C(O)-$, $-C(O)NR^{1b}-$, $-C(NR^{1a})NR^{1b}-$, $-O-$, $-OC(O)NR^{1b}-$, $-NR^{1b}-$, $-NR^{1a}C(O)NR^{1b}-$, $-NR^{1a}C(NR^{1d})NR^{1b}-$, $-NR^{1a}S(O)NR^{1b}-$, $-NR^{1a}S(O)_2NR^{1b}-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{1b}-$, or $-S(O)_2NR^{1b}-$; and z is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; where each R^{1a} , R^{1b} , and R^{1d} is as defined herein.

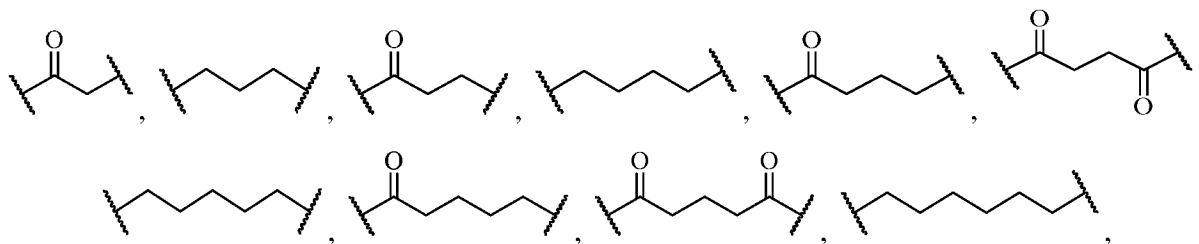
[00296] In certain embodiments, each R^L is independently C_{1-10} alkylene, C_{2-10} alkynylene,

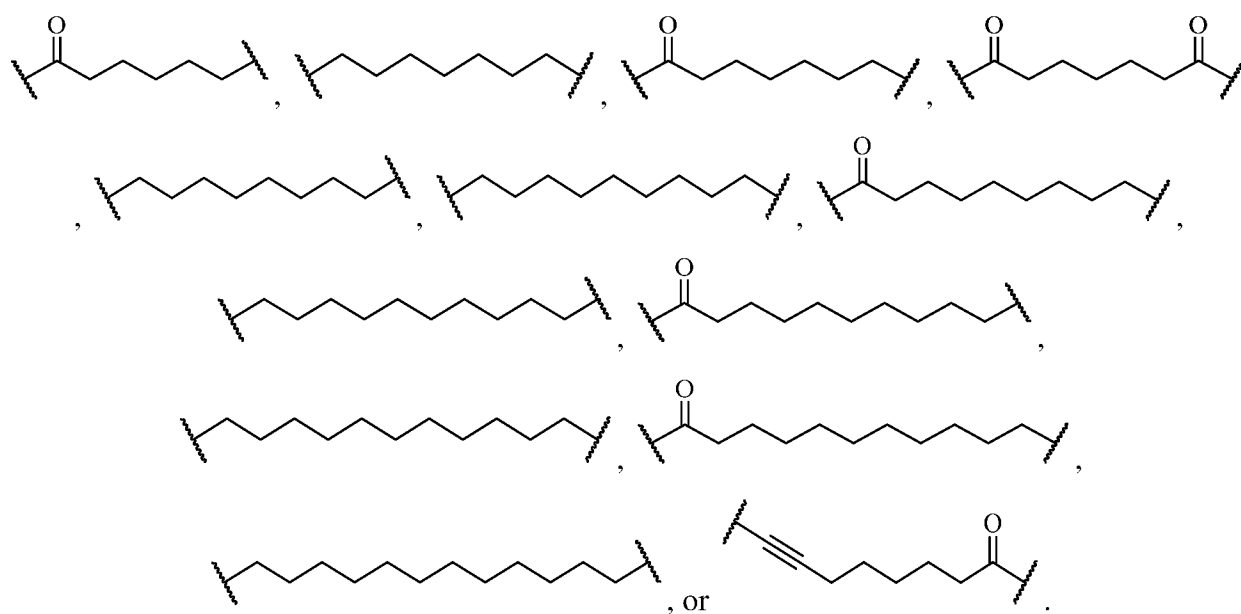
C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene, each optionally substituted with one or more substituents Q; each Z^L is independently a bond, -C(O)-, -C(O)NR^{1b}-, -O-, -OC(O)NR^{1b}-, -NR^{1b}-, -NR^{1a}C(O)NR^{1b}-, or -NR^{1a}C(NR^{1d})NR^{1b}-; and z is an integer of 1, 2, 3, 4, 5, 6, 7, or 8; where each R^{1a}, R^{1b}, and R^{1d} is as defined herein.

[00297] In certain embodiments, each R^L is independently methanediyl, ethanediyl, propanediyl, butanediyl, pentanediyl, hexanediyl, heptanediyl, octanediyl, ethynediyl, cyclopentanediyl, cyclohexanediyl, bicyclo[2.2.2]octanediyl, phendiyl, pyrazoldiyl, imidazoldiyl, tetrazoldiyl, pyrimidindiyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazindiyl, 1,3-dioxandiyl, piperazindiyl, piperidindiyl, or 3,9-diazaspiro[5.5]undecanediyl, each optionally substituted with one or more substituents Q; each Z^L is independently a bond, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)NH-, -O-, -NH-, -N(CH₃)-, or -NHC(O)NH-; and z is an integer of 1, 2, 3, 4, 5, 6, 7, or 8.

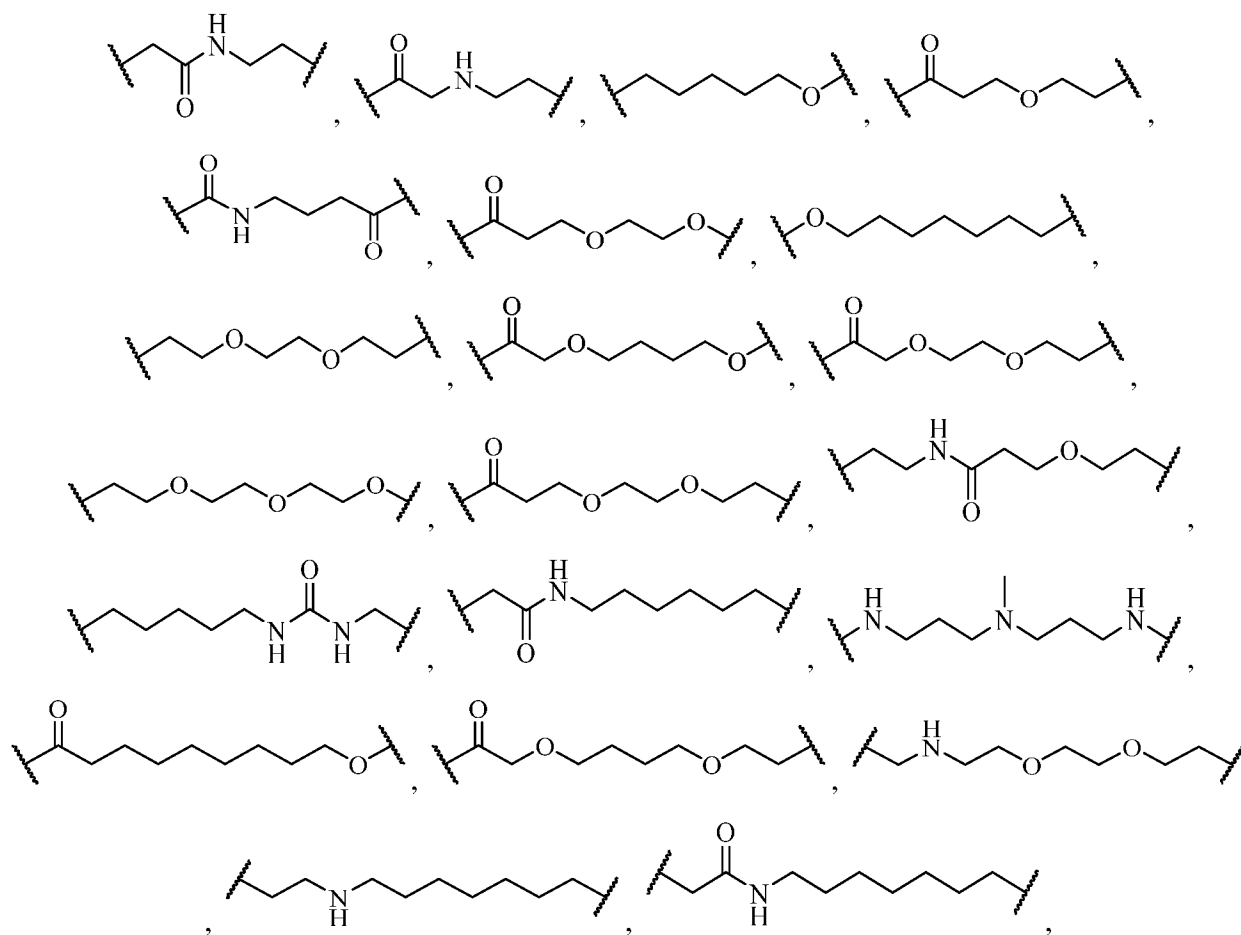
[00298] In certain embodiments, each R^L is independently methanediyl, ethane-1,2-diyl, propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl, hexane-1,6-diyl, heptane-1,7-diyl, octane-1,8-diyl, ethyne-1,2-diyl, cyclopentane-1,3-diyl, cyclohexane-1,3-diyl, cyclohexane-1,4-diyl, bicyclo[2.2.2]octane-1,4-diyl, 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, 1,3-dioxan-2,5-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; each Z^L is independently a bond, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)NH-, -O-, -NH-, -N(CH₃)-, or -NHC(O)NH-; and z is an integer of 1, 2, 3, 4, 5, 6, 7, or 8.

[00299] In certain embodiments, L is:

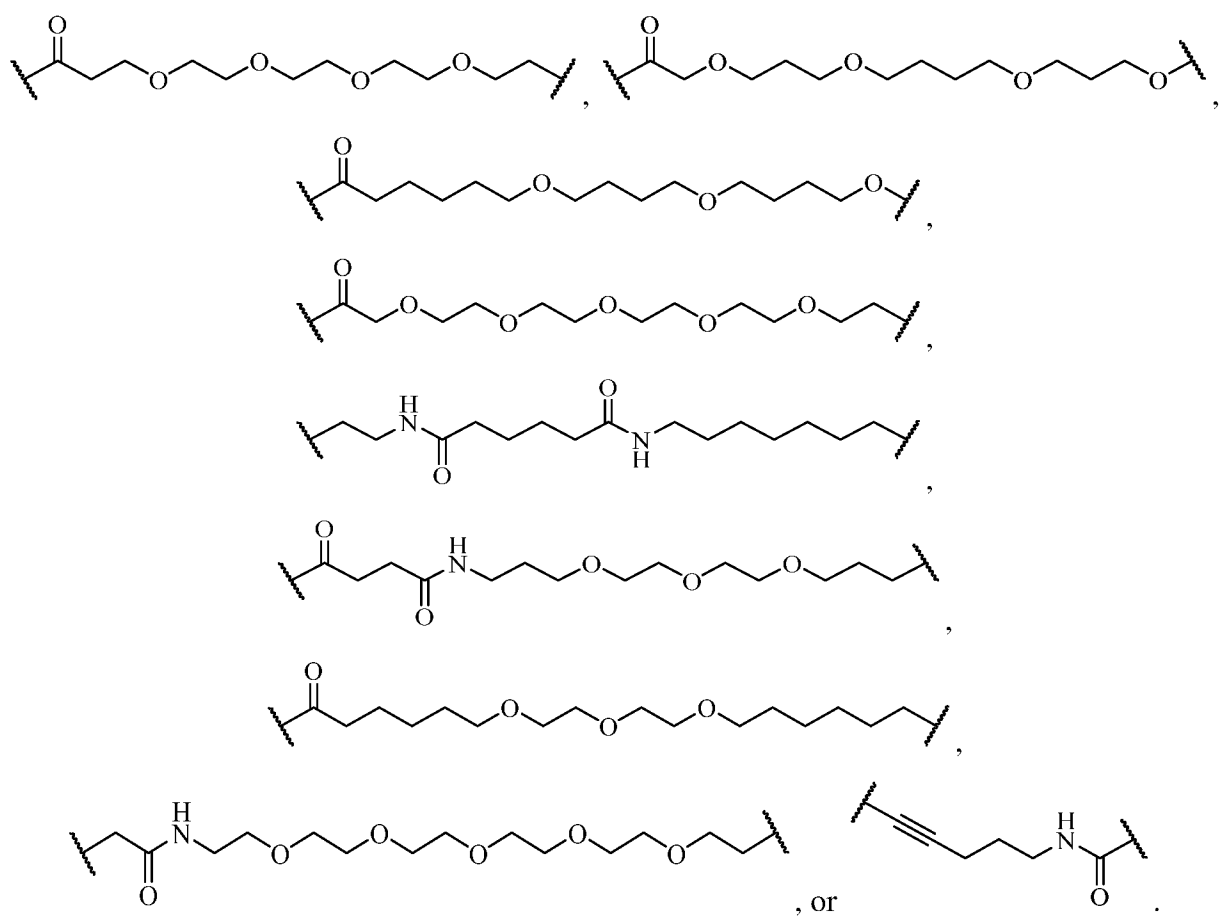




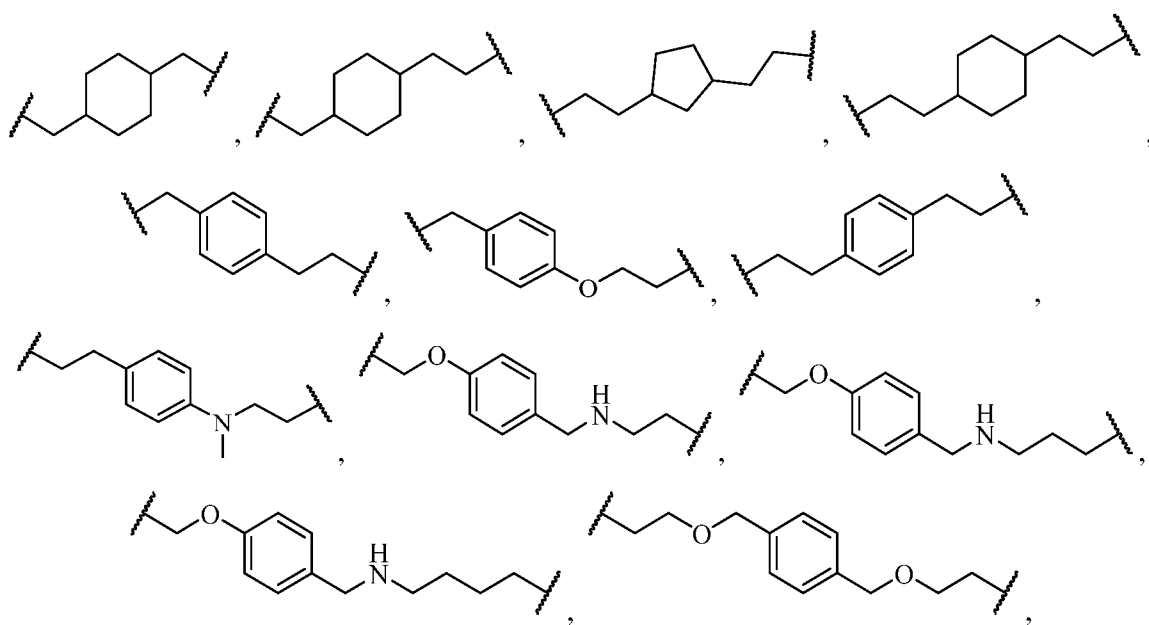
[00300] In certain embodiments, L is:

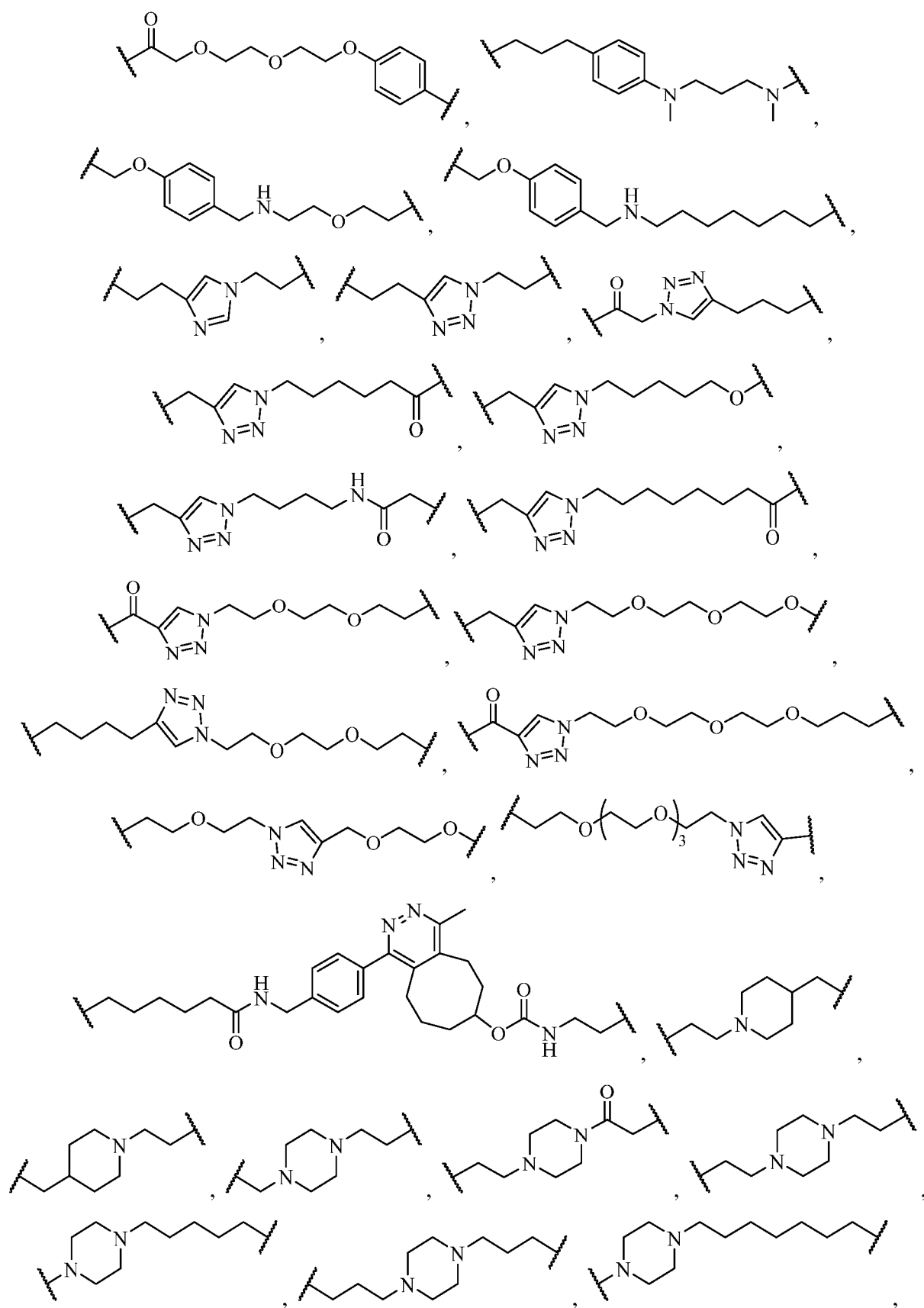


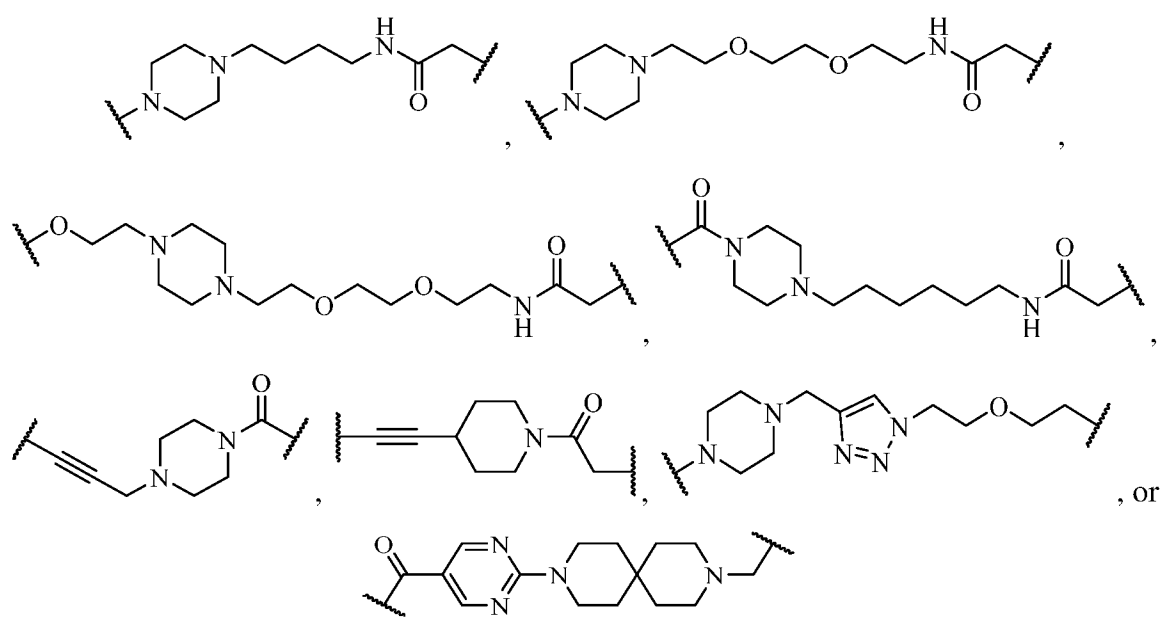




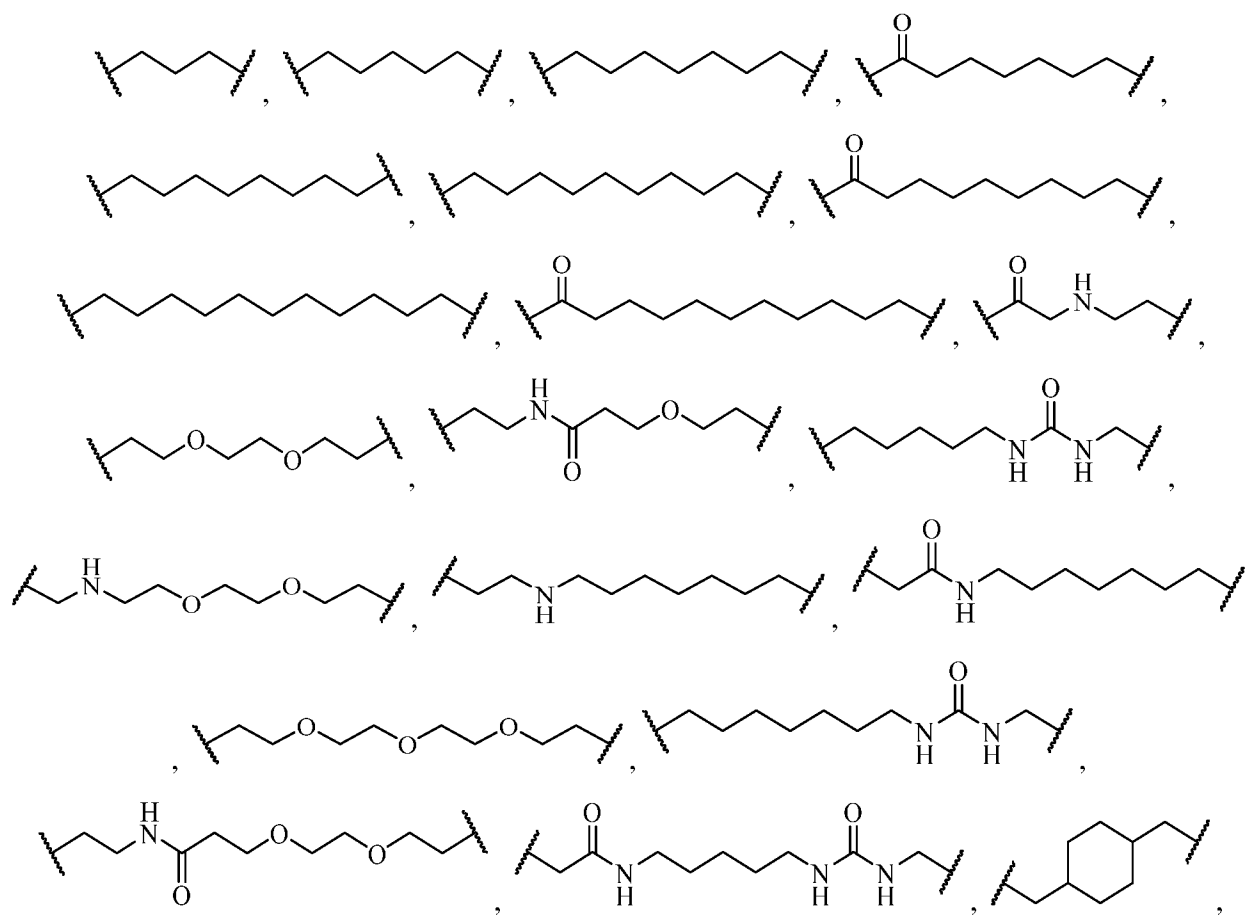
[00301] In certain embodiments, L is:

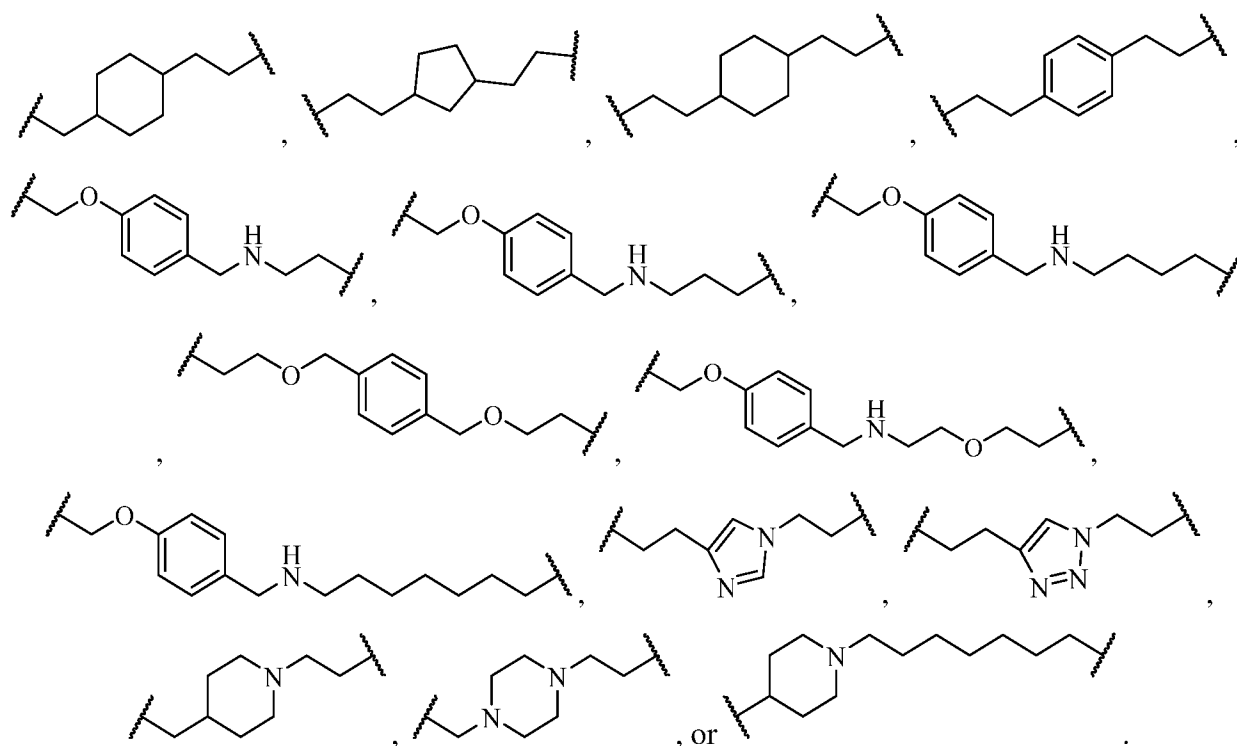




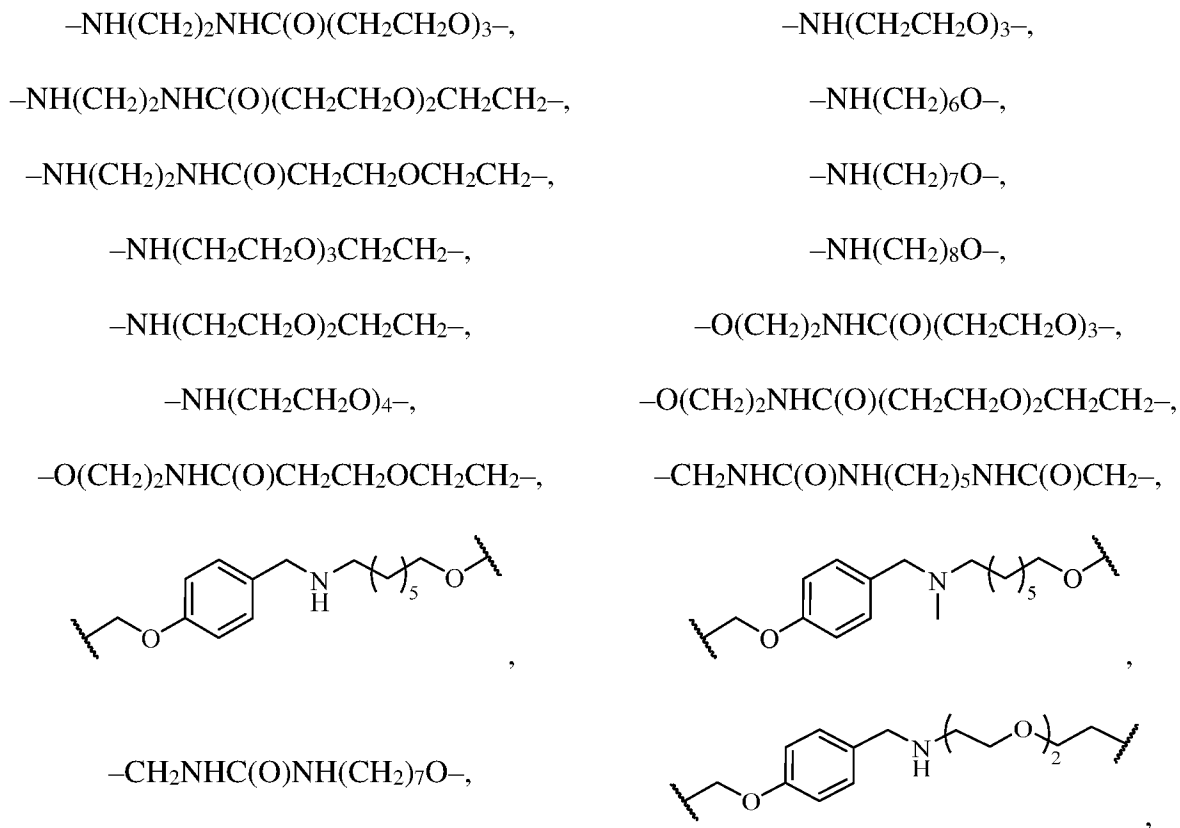


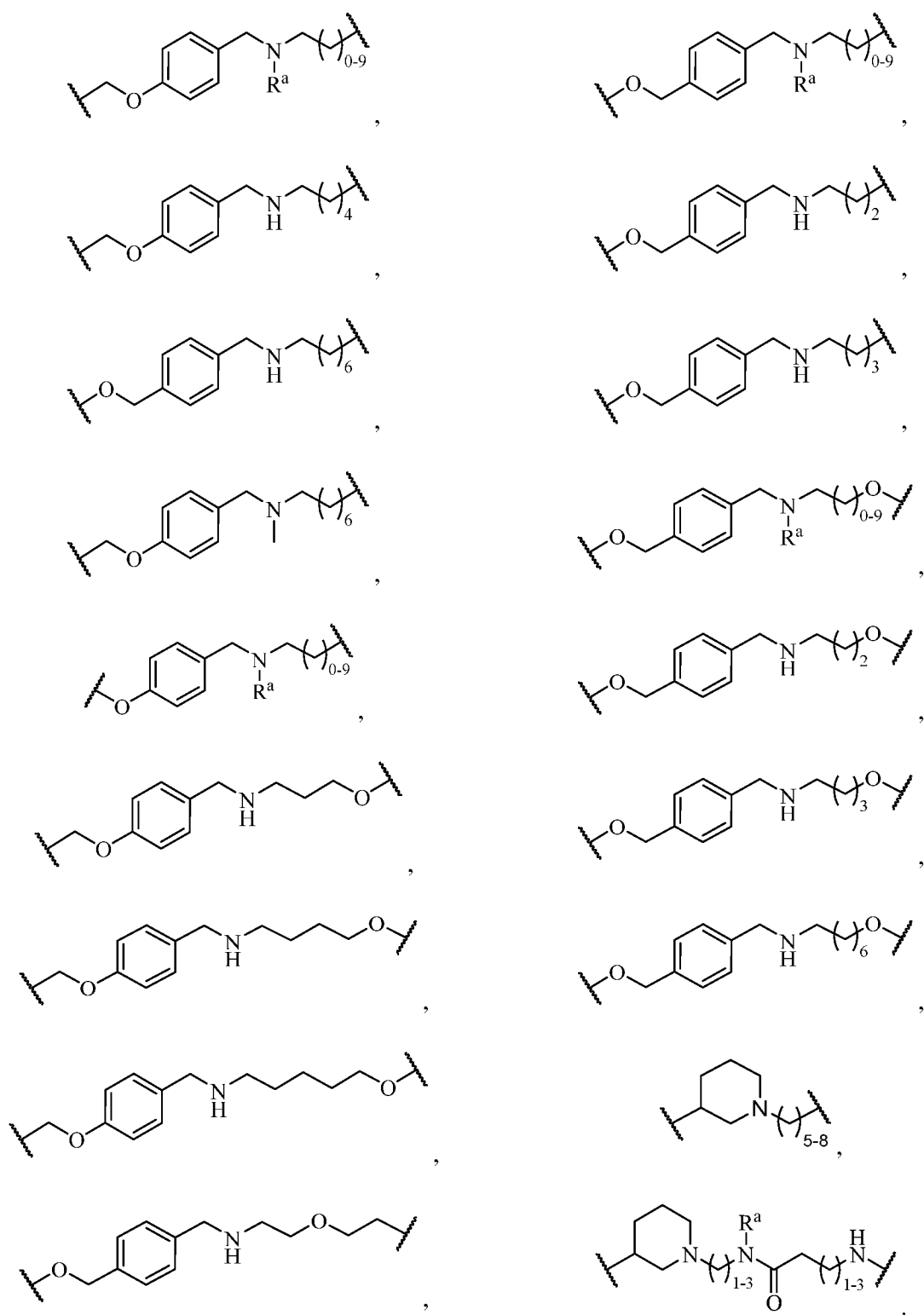
[00302] In certain embodiments, L is

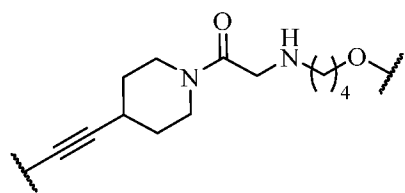
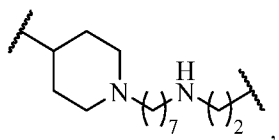
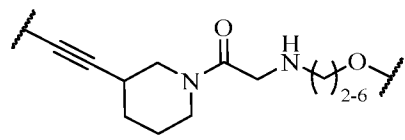
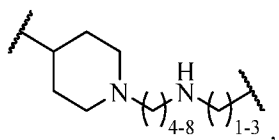
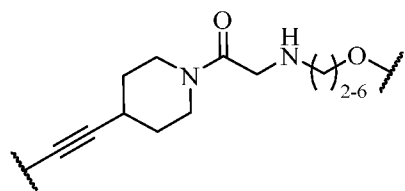
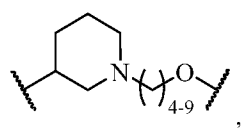
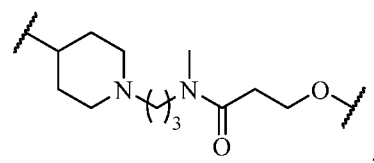
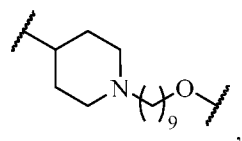
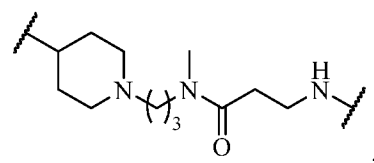
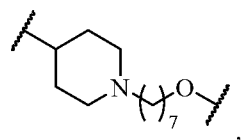
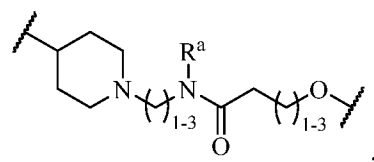
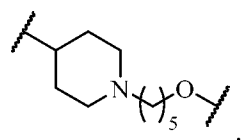
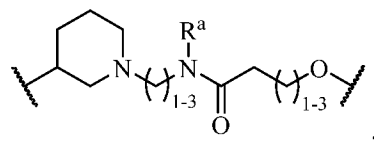
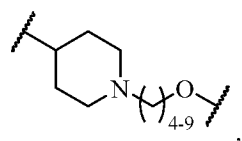
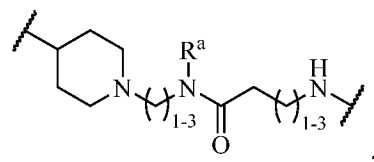
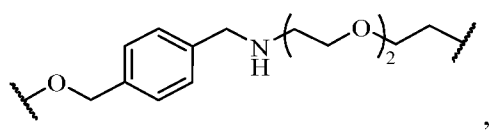


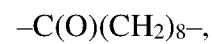
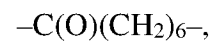
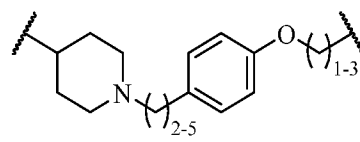
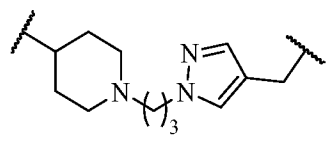
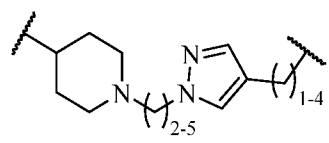
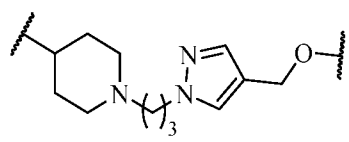
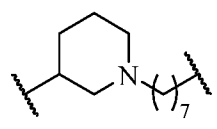
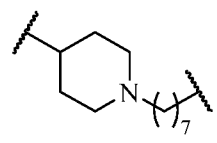
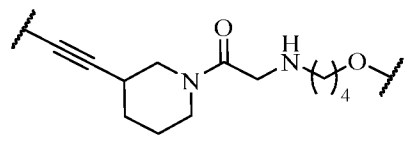
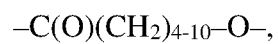
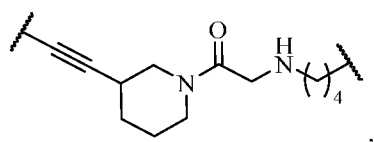
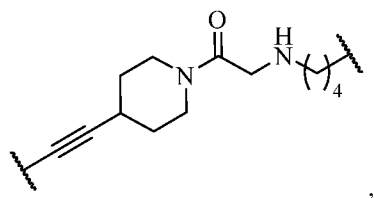
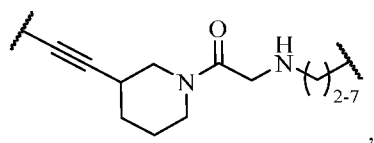
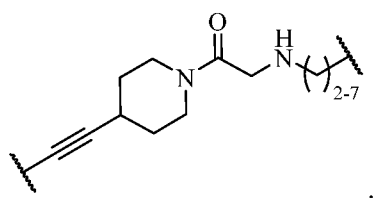
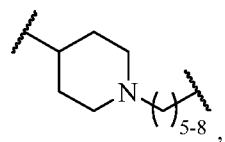
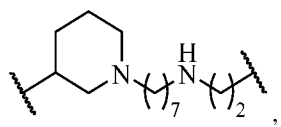
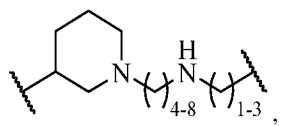


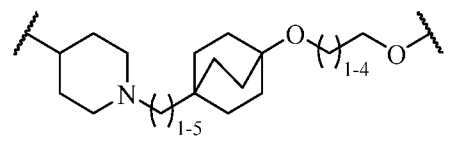
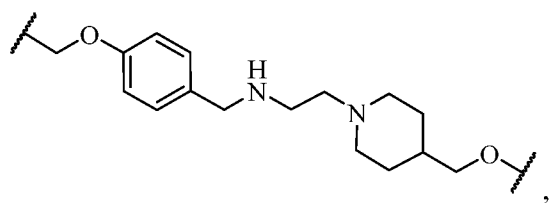
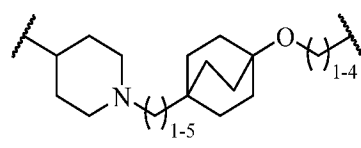
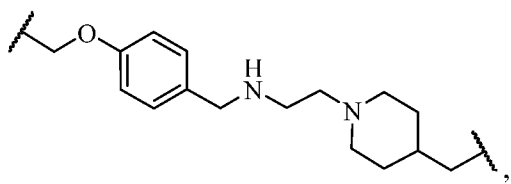
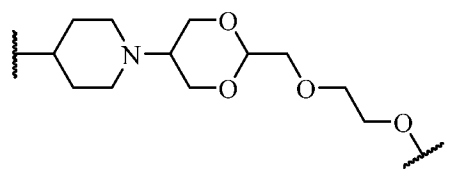
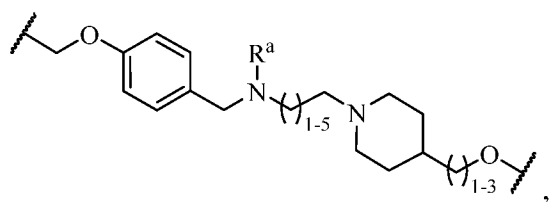
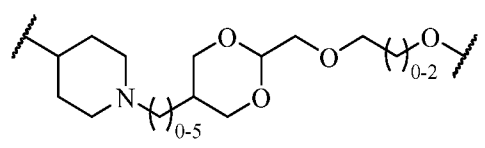
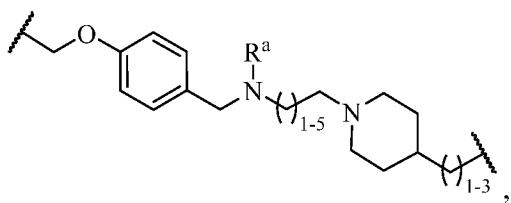
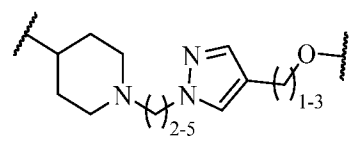
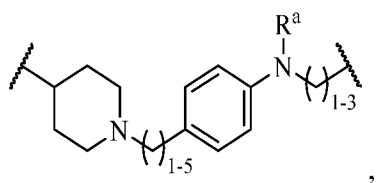
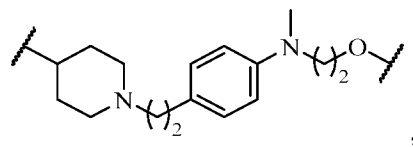
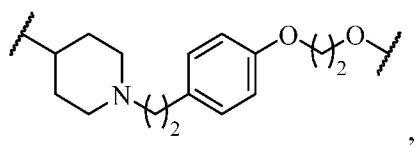
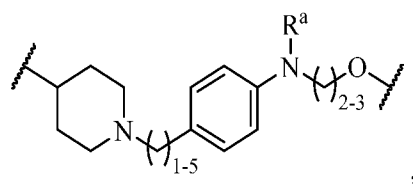
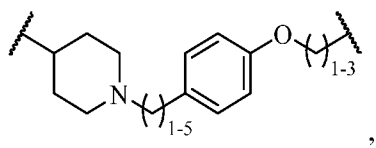
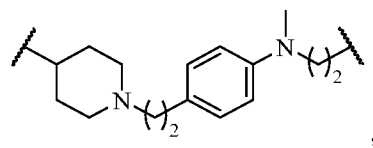
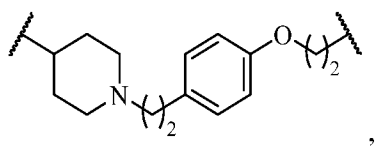
[00303] In certain embodiments, L is:

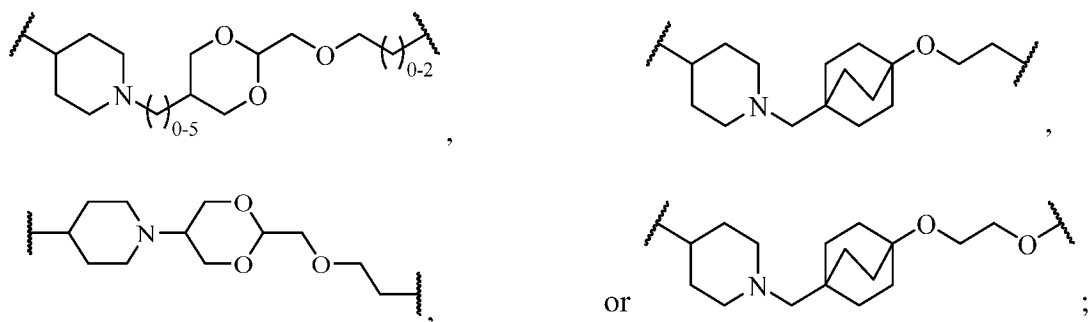






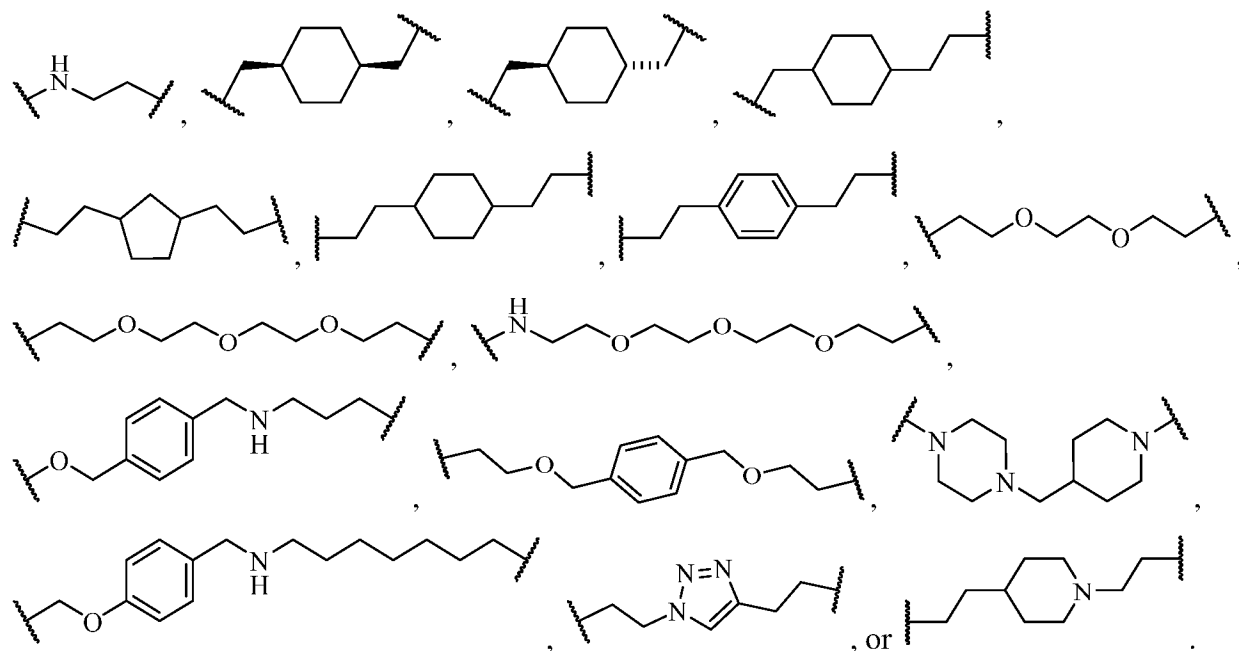




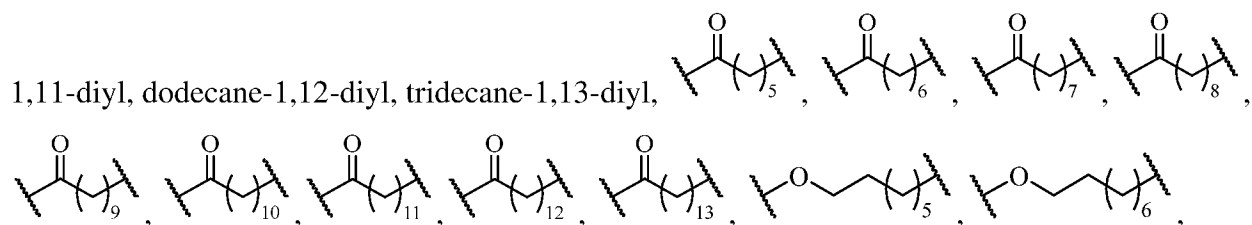


wherein each R^a is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents Q.

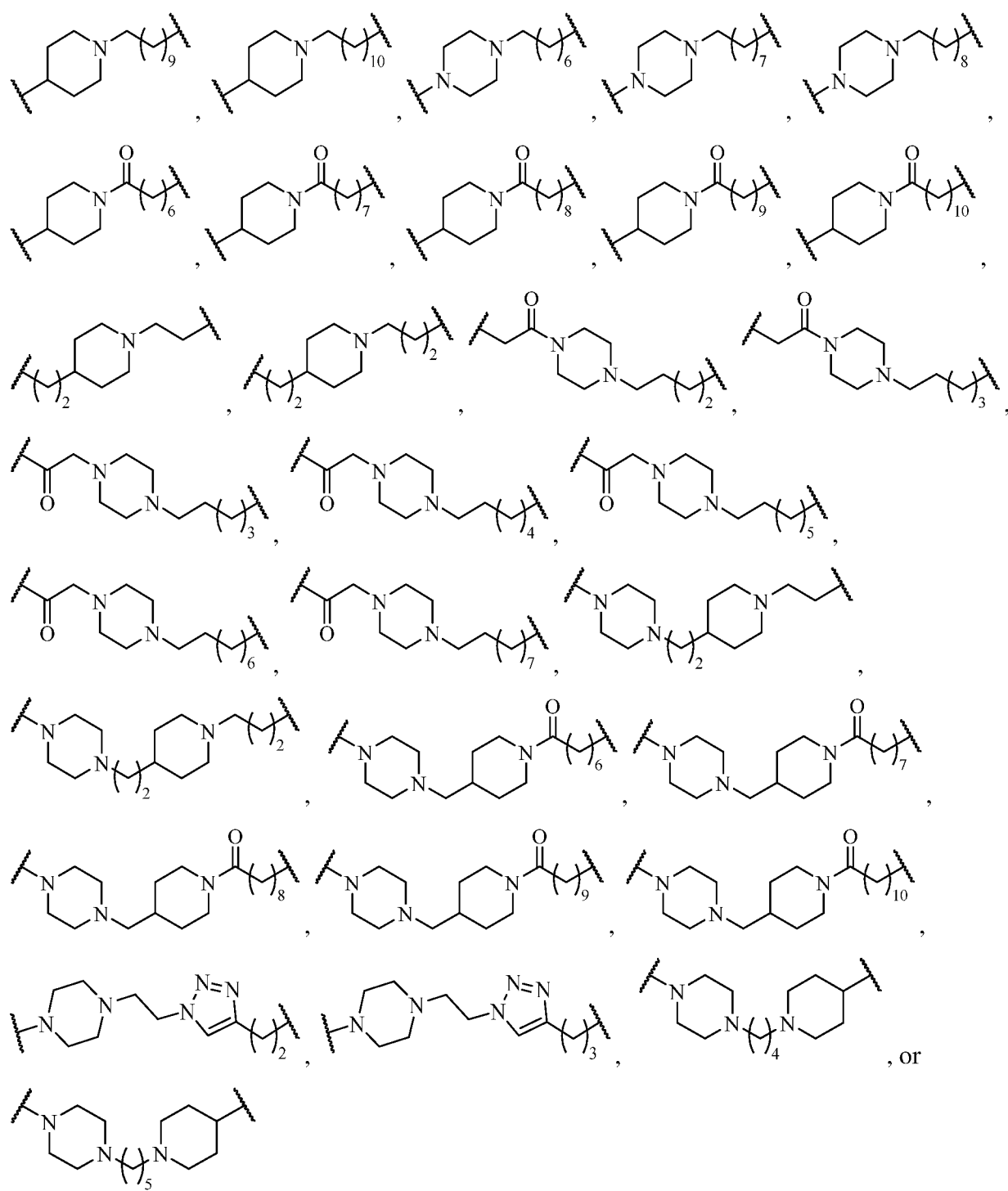
[00304] In certain embodiments, L is pentan-1,5-diyl, hexan-1,6-diyl, heptan-1,7-diyl, octan-1,8-diyl, nonan-1,9-diyl, decan-1,10-diyl, undecan-1,11-diyl, piperazin-1,4-diyl,



[00305] In certain embodiments, L is propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl, hexane-1,6-diyl, heptane-1,7-diyl, octane-1,8-diyl, nonan-1,9-diyl, decane-1,10-diyl, undecane-







[00306] In one embodiment, provided herein is a compound of:

3-(4-(1-(7-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione
A1;

3-(4-(1-(7-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A2**;

3-(4-(1-(7-((6-methoxy-2-methyl-4-(((R)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A3**;

4-((2-(2-(2-(2-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione **A4**;

2-(2,6-dioxopiperidin-3-yl)-4-((2-(2-(2-(2-((6-methoxy-2-methyl-4-(((R)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)amino)isoindoline-1,3-dione **A5**;

9-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-oxy)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)methyl)nonanamide **A6**;

8-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-oxy)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)methyl)octanamide **A7**;

8-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-oxy)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)octanamide **A8**;

9-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-oxy)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)nonanamide **A9**;

3-(4-(1-(3-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)propyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A10**;

3-(4-(1-(5-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A11**;

3-(4-(1-(9-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A12**;

3-(4-(2-(4-(4-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A13**;

3-(4-(2-(4-(5-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A14**;

3-(6-fluoro-4-(1-(7-((6-methoxy-2-methyl-4-(((R)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A15**;

3-(6-fluoro-4-(1-(7-((6-methoxy-2-methyl-4-(((S)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A16**;

3-(4-(1-(5-(4-(4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)piperidin-1-yl)pentyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A17**;

3-(4-(1-(4-(4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)piperidin-1-yl)butyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A18**;

3-(4-(1-(7-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-7-methoxy-2-methyl-quinazolin-6-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A19**;

3-(4-(1-(7-(4-(((R)-1-(3-bromophenyl)ethyl)amino)-6,7-dimethoxy-2-methyl-quinazolin-8-yl)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A20**;

3-(5-(1-(5-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)pentyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A21**;

3-(5-(1-(7-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A22**;

3-(5-(1-(9-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)nonyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A23**;

3-(5-(1-(11-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)undecyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione

A24;

3-(6-fluoro-5-(1-(7-((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A25**;

3-(6-fluoro-5-(1-(7-((6-methoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A26**;

3-(5-(1-(7-((4-(((*R*)-1-(3-(1,1-difluoro-2-hydroxyethyl)phenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A27**;

3-(5-(1-(7-((4-(((*R*)-1-(3-amino-5-(trifluoromethyl)phenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A28**;

3-(5-(2-(4-(4-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A29**;

3-(5-((2-(4-(4-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A30**;

3-(5-(2-(4-(5-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A31**;

3-(5-((2-(4-(5-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A32**;

5-(4-((1-(7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisindoline-1,3-dione **A33**;

5-(4-((1-(9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisindoline-1,3-dione **A34**;

5-(4-((1-(11-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecanoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione **A35**;

4-((2-(2-(2-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione **A36**;

6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)-methyl)hexanamide **A37**;

8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)-methyl)octanamide **A38**;

10-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)-methyl)decanamide **A39**;

12-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)-methyl)dodecanamide **A40**;

3-(1-((4-(((7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)amino)methyl)phenoxy)methyl)-4-oxo-4*H*-thieno[3,4-*c*]pyrrol-5(6*H*)-yl)piperidine-2,6-dione **A41**;

3-(5-(3-(4-(6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)piperazin-1-yl)propyl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A42**;

3-(5-(3-(4-(6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)piperazin-1-yl)prop-1-yn-1-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A43**;

3-(5-(9-(3-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)propyl)-3,9-diazaspiro[5.5]undecan-3-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A44**;

3-(5-((9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methyl-

quinazolin-7-yl)oxy)nonyl)amino)-2-methyl-4-oxoquinazolin-3(4*H*)-yl)piperidine-2,6-dione **A45**;

3-(5-((11-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecyl)amino)-2-methyl-4-oxoquinazolin-3(4*H*)-yl)piperidine-2,6-dione **A46**;

3-(5-((7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)amino)-2-methyl-4-oxoquinazolin-3(4*H*)-yl)piperidine-2,6-dione **A47**;

3-(5-(1-(7-((4-(((*S*)-1-(3-(1,1-difluoro-2-hydroxyethyl)phenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A48**;

16-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methyl)-hexadecanamide **A49**;

3-(5-(1-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A50**;

3-(4-(1-(10-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A51**;

3-(6-fluoro-4-(1-(7-((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)-1-methylpiperidine-2,6-dione **A52**;

3-(6-fluoro-4-(1-(7-((6-methoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)-1-methylpiperidine-2,6-dione **A53**;

3-(4-(1-(7-(6,7-dimethoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-8-yl)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A54**;

3-(4-((2-(4-(5-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisindolin-2-

yl)piperidine-2,6-dione **A55**;

3-(4-(1-(7-(6,7-dimethoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)methyl)-phenyl)thiophen-2-yl)ethyl)amino)quinazolin-8-yl)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A56**;

3-(4-((2-(4-(4-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A57**; or

3-(4-(1-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A58**;

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.

[00307] In another embodiment, provided herein is a compound of:

(*S*)-*N*-(((*S*)-2-((*S*)-2-(4-(3-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B1**;

(*S*)-*N*-(((*S*)-2-((*S*)-2-(4-(3-(((8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B2**;

(*S*)-*N*-(((*S*)-2-((*S*)-2-(4-(3-(((10-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B3**;

(*S*)-*N*-(((*S*)-2-((*S*)-2-(4-(3-(((12-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)dodecyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B4**;

(2*S*,4*S*)-4-(7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanamido)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)-acetyl)-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide **B5**;

(*S*)-2-((2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanamido)-*N*-(6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)-4-methyl-

pentanamide **B6**;

(*S*)-2-((2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanamido)-*N*-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)-4-methyl-

pentanamide **B7**;

(*S*)-2-((2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanamido)-*N*-(10-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)-4-methyl-

pentanamide **B8**;

(*S*)-2-((2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanamido)-*N*-(12-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)dodecyl)-4-methyl-

pentanamide **B9**;

(2*S*,4*S*)-4-(13-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)tridecanamido)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)-acetyl)-*N*-(*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide **B10**; or

(2*S*,4*S*)-4-(11-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecanamido)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)-acetyl)-*N*-(*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide **B11**;

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.

[00308] In yet another embodiment, provided herein is a compound of:

2-(4-((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)-2-oxopiperazin-1-yl)-*N*-(6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)acetamide **C1**;

2-(4-((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)-2-oxopiperazin-1-yl)-*N*-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)acetamide **C2**;

2-(4-((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)-2-oxopiperazin-1-yl)-*N*-(10-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)acetamide **C3**;

2-(4-((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-*N*-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)-

amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)acetamide **C4**;

2-(4-(((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-*N*-(10-(((4-(((*R*)-1-(3-bromophenyl)ethyl)-amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)acetamide **C5**; or

2-(4-(((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-*N*-(12-(((4-(((*R*)-1-(3-bromophenyl)ethyl)-amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)dodecyl)acetamide **C6**;

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.

[00309] In still another embodiment, provided herein is a compound of:

(2*S*,4*R*)-1-((*S*)-2-(7-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D1**;

(2*S*,4*R*)-1-((*S*)-2-(9-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D2**;

(2*S*,4*R*)-1-((*S*)-2-(11-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D3**;

(2*S*,4*R*)-1-((*S*)-2-(13-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)tridecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D4**;

(2*S*,4*R*)-4-hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*R*)-1-(thiophen-2-yl)-ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D5**;

(2*S*,4*R*)-4-hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*S*)-1-(thiophen-2-yl)-ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D6**;

(2*S*,4*R*)-1-((*S*)-2-(9-(((4-(((*R*)-1-(4-bromothiophen-2-yl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methyl-

thiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D7**;

(2*S*,4*R*)-1-((*S*)-2-(9-((4-(((*S*)-1-(4-bromothiophen-2-yl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D8**;

(2*S*,4*R*)-4-hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D9**;

(2*S*,4*R*)-4-hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D10**;

(2*S*,4*R*)-1-((*S*)-2-acetamido-3,3-dimethylbutanoyl)-*N*-(2-((7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D11**;

(2*S*,4*R*)-1-((*S*)-2-acetamido-3,3-dimethylbutanoyl)-*N*-(2-((9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D12**;

(2*S*,4*R*)-1-((*S*)-2-acetamido-3,3-dimethylbutanoyl)-*N*-(2-((11-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D13**; or

(2*S*,4*R*)-1-((*S*)-2-acetamido-3,3-dimethylbutanoyl)-*N*-(2-((13-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)tridecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D14**;

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.

[00310] In certain embodiments, a compound provided herein is deuterium-enriched. In certain embodiments, a compound provided herein is carbon-13 enriched. In certain embodiments, a compound provided herein is carbon-14 enriched. In certain embodiments, a compound provided herein contains one or more less prevalent isotopes for other elements, including, but not limited to, ¹⁵N for nitrogen; ¹⁷O or ¹⁸O for oxygen, and ³⁴S, ³⁵S, or ³⁶S for sulfur.

[00311] In certain embodiments, a compound provided herein has an isotopic enrichment factor of no less than about 5, no less than about 10, no less than about 20, no less than about 50, no less than about 100, no less than about 200, no less than about 500, no less than about 1,000, no less than about 2,000, no less than about 5,000, or no less than about 10,000. In any events, however, an isotopic enrichment factor for a specified isotope is no greater than the maximum isotopic enrichment factor for the specified isotope, which is the isotopic enrichment factor when a compound at a given position is 100% enriched with the specified isotope. Thus, the maximum isotopic enrichment factor is different for different isotopes. The maximum isotopic enrichment factor is 6,410 for deuterium and 90 for carbon-13.

[00312] In certain embodiments, a compound provided herein has a deuterium enrichment factor of no less than about 64 (about 1% deuterium enrichment), no less than about 130 (about 2% deuterium enrichment), no less than about 320 (about 5% deuterium enrichment), no less than about 640 (about 10% deuterium enrichment), no less than about 1,300 (about 20% deuterium enrichment), no less than about 3,200 (about 50% deuterium enrichment), no less than about 4,800 (about 75% deuterium enrichment), no less than about 5,130 (about 80% deuterium enrichment), no less than about 5,450 (about 85% deuterium enrichment), no less than about 5,770 (about 90% deuterium enrichment), no less than about 6,090 (about 95% deuterium enrichment), no less than about 6,220 (about 97% deuterium enrichment), no less than about 6,280 (about 98% deuterium enrichment), no less than about 6,350 (about 99% deuterium enrichment), or no less than about 6,380 (about 99.5% deuterium enrichment). The deuterium enrichment can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy. In certain embodiments, at least one of the atoms of a compound provided herein, as specified as deuterium-enriched, has deuterium enrichment of no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, or no less than about 98%.

[00313] 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.

[00314] 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.

[00315] 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.

[00316] 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.

[00317] 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.

[00318] 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, or 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-(diethylamino)-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.

[00319] 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

[00320] In one embodiment, provided herein is a pharmaceutical composition, comprising a compound provided herein, *e.g.*, a compound of Formula (I), or 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.

[00321] 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.

[00322] 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.

[00323] 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.

[00324] 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

[00325] 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.

[00326] 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 arabogalactan, 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.

[00327] 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.

[00328] 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 algins. 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.

[00329] 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.

[00330] 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 carbomethylcellulose, 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.

[00331] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[00332] 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.

[00333] 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.

[00334] 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).

[00335] 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.

[00336] 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.

[00337] 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.

[00338] 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.

[00339] Coloring and flavoring agents can be used in all of the dosage forms described herein.

[00340] 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

[00341] The pharmaceutical composition provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[00342] 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.*

[00343] 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.

[00344] 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.

[00345] 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[®]).

[00346] 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.

[00347] 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.

[00348] 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.

[00349] 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.

[00350] Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, 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.

[00351] 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, polydimethyl siloxanes, 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

[00352] 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.

[00353] 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.

[00354] 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.

[00355] The pharmaceutical composition can also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis, or microneedle or needle-free injection, such as POWDERJECT™ and BIOJECT™.

[00356] 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.

[00357] 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.

[00358] 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.

[00359] 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*.

[00360] 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.

[00361] 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.

[00362] 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.

[00363] 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.

[00364] 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.

[00365] 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.

[00366] 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

[00367] 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 polymorphorism of the active ingredient(s).

1. Matrix Controlled Release Devices

[00368] 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.

[00369] In certain embodiments, the pharmaceutical composition provided herein in a modified release dosage form is formulated using an erodible matrix device, which is water-swellaable, erodible, or soluble polymers, including, but not limited to, synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00370] 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; celluloses, such as ethyl cellulose (EC),

methylethyl cellulose (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.

[00371] 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.

[00372] 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.

[00373] 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

[00374] 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).

[00375] 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, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00376] 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.

[00377] 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 MANNOGEMTM 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.

[00378] 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.

[00379] 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.

[00380] 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.

[00381] 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.

[00382] 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.

[00383] 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.

[00384] 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.

[00385] 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.

[00386] 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

[00387] 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 Pelletization Technology*; Ghebre-Sellassie Eds.; Drugs and the Pharmaceutical Sciences 37; CRC Press: 1989.

[00388] 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

[00389] 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

[00390] In one embodiment, provided herein is a method of treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition mediated by a son of sevenless homolog 1 (SOS1) 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.

[00391] In certain embodiments, the disorder, disease, or condition mediated by an SOS1 is a proliferative disease.

[00392] In another embodiment, provided herein is a method of treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition mediated by a Ras 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.

[00393] In certain embodiments, the disorder, disease, or condition mediated by a Ras is a proliferative disease. In certain embodiments, the Ras is a KRas. In certain embodiments, the Ras is a HRas. In certain embodiments, the Ras is an NRas.

[00394] In yet another embodiment, provided herein is a method of 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.

[00395] In certain embodiments, the proliferative disease is cancer. In certain embodiments, the cancer is a solid tumor. In certain embodiments, the cancer is colon cancer, colorectal cancer, lung cancer, or pancreatic cancer. In certain embodiments, the cancer is colon cancer. In certain embodiments, the cancer is colorectal cancer. In certain embodiments, the cancer is lung cancer. In certain embodiments, the cancer is non-small cell lung cancer (NSCLC). In certain embodiments, the cancer is pancreatic cancer. In certain embodiments, the cancer is an unresectable solid tumor. In certain embodiments, the cancer is a hematologic malignancy.

[00396] 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.

[00397] 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.

[00398] In certain embodiments, the cancer bears a KRAS mutation. In certain embodiments, the cancer bears a KRAS mutation at the G12 or G13 position. In certain embodiments, the cancer bears a KRAS mutation of G12C, G12D, G12V, G12A, G12S, or G12R. In certain embodiments, the cancer bears a KRAS mutation of G12C. In certain embodiments, the cancer bears a KRAS mutation of G12D. In certain embodiments, the cancer bears a KRAS mutation of G12V. In certain embodiments, the cancer bears a KRAS mutation of

G12A. In certain embodiments, the cancer bears a KRAS mutation of G12S. In certain embodiments, the cancer bears a KRAS mutation of G12R. In certain embodiments, the cancer bears a KRAS mutation at the G13 position. In certain embodiments, the cancer bears a KRAS mutation of G13D.

[00399] In certain embodiments, the cancer is a solid tumor with a KRas mutation. In certain embodiments, the cancer is a solid tumor with a KRas mutation at the G12 or G13 position. In certain embodiments, the cancer is a solid tumor with a KRas mutation of G12C, G12D, G12V, G12A, G12S, or G12R. In certain embodiments, the cancer is a solid tumor with a KRas mutation of G12C. In certain embodiments, the cancer is a solid tumor with a KRas mutation of G12D. In certain embodiments, the cancer is a solid tumor with a KRas mutation of G12V. In certain embodiments, the cancer is a solid tumor with a KRas mutation of G12A. In certain embodiments, the cancer is a solid tumor with a KRas mutation of G12S. In certain embodiments, the cancer is a solid tumor with a KRas mutation of G12R. In certain embodiments, the cancer is a solid tumor with a KRas mutation at the G13 position. In certain embodiments, the cancer is a solid tumor with a KRas mutation of G13D.

[00400] In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a human.

[00401] In certain embodiments, the therapeutically effective amount of a compound provided herein is ranging 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 60 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 100 mg/kg/day. In 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 60 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.

[00402] 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.

[00403] 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.

[00404] 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.

[00405] 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.

[00406] 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.

[00407] 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.

[00408] 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.

[00409] 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.

[00410] 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.

[00411] In one embodiment, provided herein is a method of inhibiting the growth of a cell, comprising contacting the cell with 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.

[00412] 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.

[00413] In certain embodiments, the cell is a cell of colon cancer, colorectal cancer, lung cancer, or pancreatic cancer. In certain embodiments, the cell is a cell of non-small cell lung cancer (NSCLC).

[00414] In certain embodiments, the cell is a cancerous cell bearing a KRAS mutation. In certain embodiments, the cell is a cancerous cell bearing a KRAS mutation at the G12 or G13 position. In certain embodiments, the cell is a cancerous cell bearing a KRAS mutation of G12C, G12D, G12V, G12A, G12S, or G12R. In certain embodiments, the cell is a cancerous cell bearing a KRAS mutation of G12C. In certain embodiments, the cell is a cancerous cell bearing a KRAS mutation of G12D. In certain embodiments, the cell is a cancerous cell bearing

a KRAS mutation of G12V. In certain embodiments, the cell is a cancerous cell bearing a KRAS mutation of G12A. In certain embodiments, the cell is a cancerous cell bearing a KRAS mutation of G12S. In certain embodiments, the cell is a cancerous cell bearing a KRAS mutation of G12R. In certain embodiments, the cell is a cancerous cell bearing a KRAS mutation at the G13 position. In certain embodiments, the cell is a cancerous cell bearing a KRAS mutation of G13D.

[00415] In another embodiment, provided herein is a method of inducing degradation of an SOS1, comprising contacting the SOS1 with 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.

[00416] 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.

[00417] 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.

[00418] 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, needleless injectors drip bags, patches, and inhalers. The kits provided herein can also include condoms for administration of the active ingredients.

[00419] 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.

[00420] The disclosure will be further understood by the following non-limiting examples.

EXAMPLES

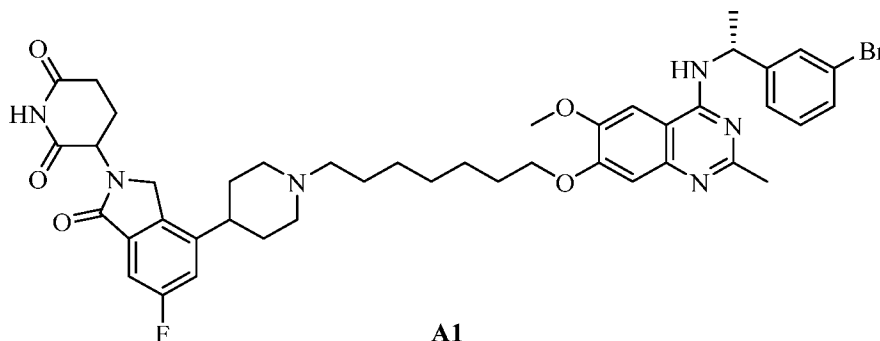
[00421] As used herein, the symbols and conventions used in these processes, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society, 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); h (hour or hours); min (minutes); AcOH (acetic acid); DCM (dichloromethane); DMF (dimethylformamide); DMSO (dimethyl sulfoxide); MeOH (methanol); EtOAc (ethyl acetate); PE (petroleum ether); THF (tetrahydrofuran); BOP (benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate); DBU (2,3,4,6,7,8,9,10-octahydropyrimidol[1,2-*a*]azepine); DIPEA (*N,N*-diisopropylethylamine); DMAP (4-dimethylaminopyridine); DPPA (diphenylphosphoryl azide); EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide); HOBt (hydroxybenzotriazole); NaOAc (sodium acetate); Pd(dppf)Cl₂ ((1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride); TEA or Et₃N (triethylamine); TFA (trifluoroacetic acid); Boc (*tert*-butoxycarbonyl); Cbz (benzyloxycarbonyl); MS (mass spectrometry); and NMR (nuclear magnetic resonance).

[00422] 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 3-(4-(1-(7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A1**



[00423] Compound **A1** was synthesized as shown in Scheme 1.

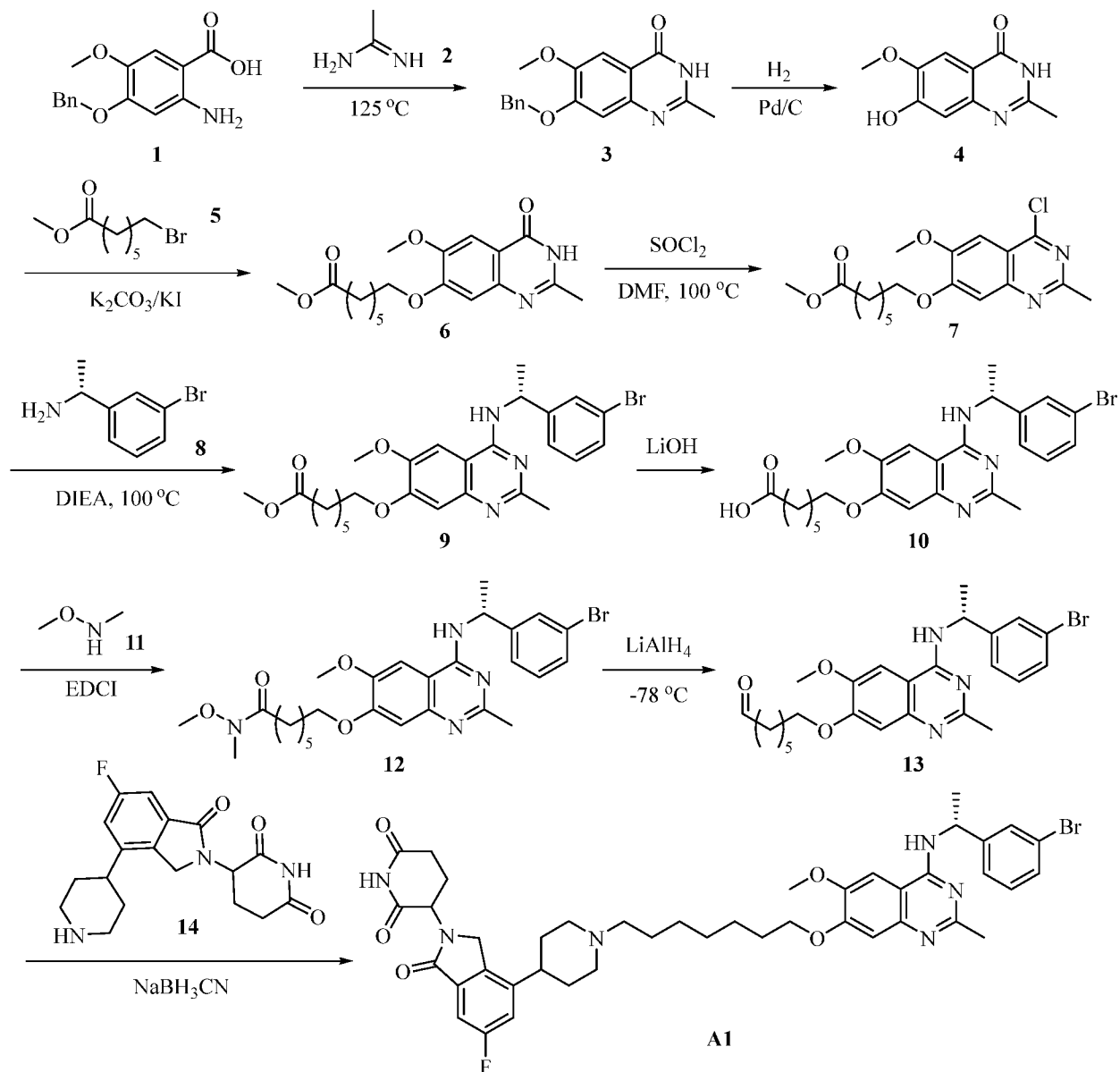
[00424] 7-(Benzyloxy)-6-methoxy-2-methylquinazolin-4(3*H*)-one **3**. To a solution of 2-amino-4-(benzyloxy)-5-methoxybenzoic acid **1** (5.00 g, 18.3 mmol) in 2-methoxyethanol (100 mL) were added acetamidine hydrochloride **2** (3.44 g, 36.6 mmol) and NaOAc (3.76 g, 45.8 mmol). After stirred for 8 h at 125 °C, the mixture was cooled to room temperature. The precipitate was collected, washed with water, and dried to give compound **3** (4.2 g) in 78% yield. MS (ESI) *m/z*: 297.1 [M+H]⁺.

[00425] 7-Hydroxy-6-methoxy-2-methylquinazolin-4(3*H*)-one **4**. To a solution of compound **3** (4.20 g, 14.2 mmol) in MeOH (100 mL) was added Pd/C (1.2 g). After stirred for 8 h under H₂, the mixture was filtered. The filtrate was concentrated and the residue was purified using silica gel eluting with MeOH in DCM from 0% to 10% to give compound **4** (2.28 g) in 60% yield. MS (ESI) *m/z*: 207.1 [M+H]⁺.

[00426] Methyl 7-((6-methoxy-2-methyl-4-oxo-3,4-dihydroquinazolin-7-yl)oxy)heptanoate **6**. To a solution of compound **4** (1.00 g, 4.85 mmol) and K₂CO₃ (1.34 g, 9.7 mmol) in DMF (20 mL) were added methyl 7-bromoheptanoate **5** (1.62 g, 7.28 mmol) and KI (0.080 g,

0.485 mmol). After stirred for 8 h at room temperature, the mixture was filtered and washed with MeOH. The filtrate was concentrated and the residue was purified using silica gel eluting with EtOAc in PE from 0% to 80% to give compound **6** (660 mg) in 39% yield. MS (ESI) m/z : 349.1 $[M+H]^+$.

Scheme 1



[00427] Methyl 7-((4-chloro-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanoate **7**. To a solution of compound **6** (560 mg, 1.61 mmol) in SOCl₂ (8 mL) was added DMF (0.5 mL). After stirred for 1 h at 100 °C, the mixture was cooled to room temperature and concentrated. The

residue was purified using silica gel eluting with MeOH in DCM from 0% to 10% to give compound **7** (560 mg) in 95% yield. MS (ESI) m/z : 367.1 $[M+H]^+$.

[00428] (*R*)-Methyl 7-((4-((1-(5-bromocyclohexa-1,5-dien-1-yl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanoate **9**. To a solution of compound **7** (560 mg, 1.53 mmol) in 1,4-dioxane (20 mL) were added DIPEA (395 mg, 3.06 mmol) and (*R*)-1-(3-bromophenyl)-ethanamine **8** (459 mg, 2.30 mmol). After stirred for 8 h at 100 °C, the mixture was cooled to room temperature and concentrated. The residue was purified using silica gel eluting with MeOH in DCM from 0% to 10% to give compound **9** (726 mg) in 89% yield. MS (ESI) m/z : 532.2 $[M+H]^+$.

[00429] (*R*)-7-((4-((1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanoic acid **10**. To a solution of compound **9** (626 mg, 1.18 mmol) in MeOH (16 mL) was added a solution of LiOH (100 mg, 2.37 mmol) in water (4 mL) at 0 °C. After stirred for 8 h at room temperature, the mixture was adjusted to a pH 5 using 1 N HCl and then extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated to give compound **10** (600 mg). MS (ESI) m/z : 516.1 $[M+H]^+$.

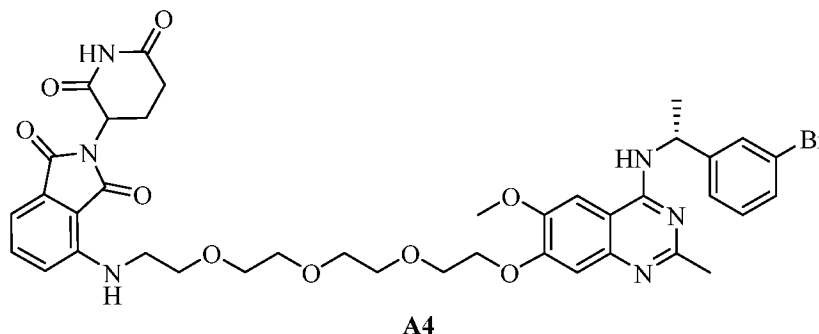
[00430] 7-((4-((3-Bromobenzyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-methoxy-*N*-methylheptanamide **12**. To a solution of *N,O*-dimethylhydroxylamine hydrochloride **11** (136 mg, 1.40 mmol) in DCM (10 mL) at 0 °C was added TEA (294 mg, 2.91 mmol) and EDCI·HCl (335 mg, 1.75 mmol), followed by addition of compound **10** (1.18 mmol). After stirred for 8 h, the mixture was concentrated. The residue was purified using silica gel eluting with EtOAc in PE from 0 to 80% to give compound **12** (300 mg) in 46% yield. MS (ESI) m/z : 559.1 $[M+H]^+$.

[00431] 7-((4-((3-Bromobenzyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanal **13**. To a solution of compound **12** (100 mg, 0.179 mmol) in THF (6 mL) was added LiAlH₄ (0.450 mL, 0.448 mmol, 1M in THF) at -78 °C under N₂. After stirred for 1 h at -78 °C, the reaction was quenched with NH₄Cl (5 mL) and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated to give compound **13** (80 mg). MS (ESI) m/z : 500.1 $[M+H]^+$.

[00432] 3-(4-(1-(7-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A1**. To a solution of 3-(6-fluoro-1-oxo-4-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione **14** (62 mg, 0.179 mmol) in DCM/MeOH (4 mL/1 mL) were added DIPEA (46 mg, 0.358 mmol) at 0 °C, compound **13** (80 mg, 0.179 mmol), NaBH₃CN (23 mg, 0.358 mmol), and acetic acid (1 drop). After stirred for 8 h at room temperature, the mixture was concentrated. The residue was purified using silica gel eluting with MeOH in DCM from 0% to 10% to afford compound **A1** (43 mg) in 29% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.99 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.63 (s, 1H), 7.45-7.38 (m, 3H), 7.34 (dd, *J* = 2.4, 7.2 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 5.60 (t, *J* = 7.2 Hz, 1H), 5.13 (dd, *J* = 5.6, 13.6 Hz, 1H), 4.52-4.31 (m, 2H), 4.07 (t, *J* = 6.4 Hz, 2H), 3.91 (s, 3H), 2.97-2.95 (m, 2H), 2.92-2.87 (m, 1H), 2.62-2.58 (m, 2H), 2.46-2.41 (m, 1H), 2.33 (s, 3H), 2.29 (t, *J* = 7.6 Hz, 2H), 2.03-1.99 (m, 1H), 1.79-1.73 (m, 6H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.47-1.29 (m, 10H); MS (ESI) *m/z*: 829.3 [M+H]⁺.

Example 2

Preparation of 4-((2-(2-(2-(2-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione **A4**

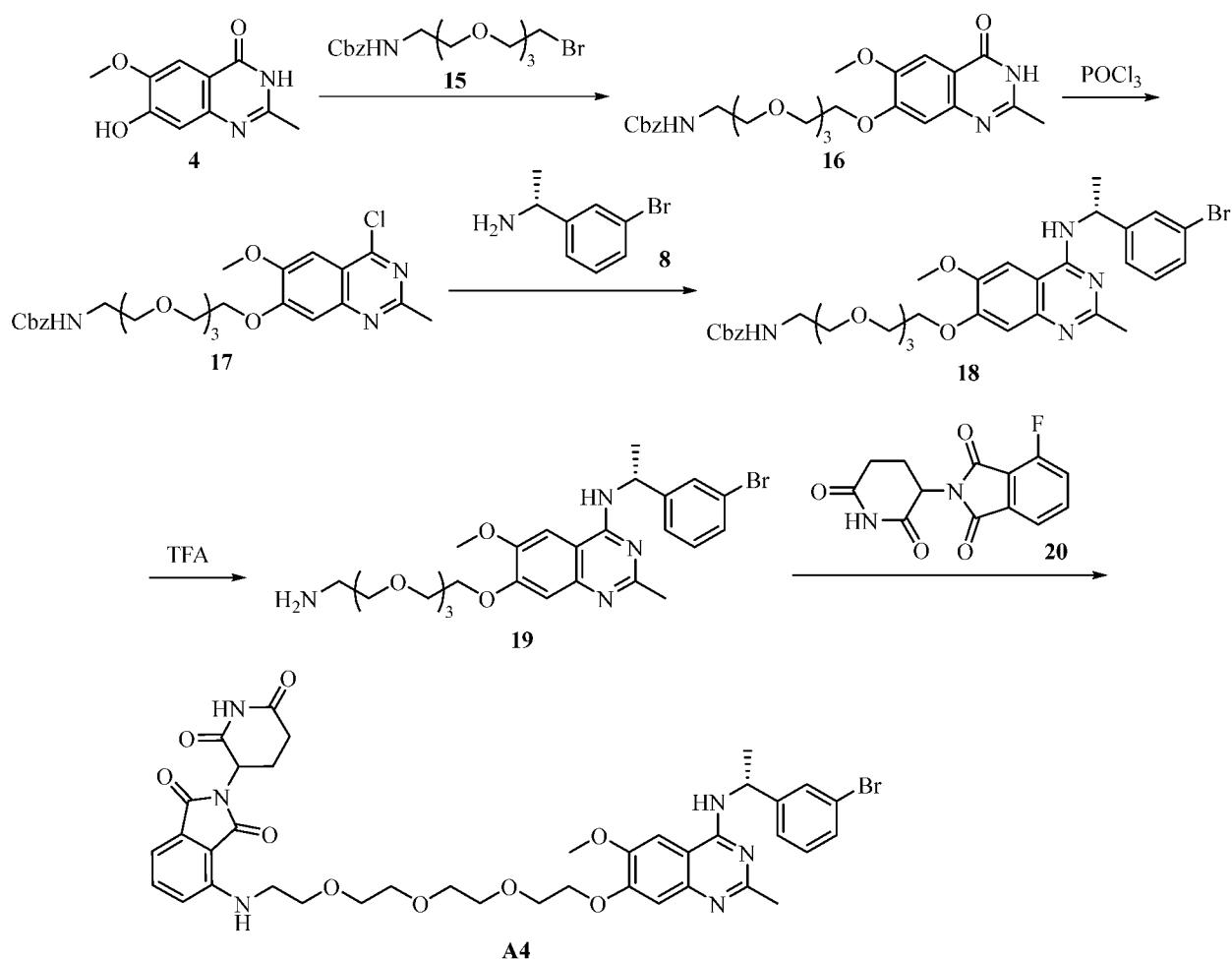


[00433] Compound **A4** was synthesized as shown in Scheme 2.

[00434] Benzyl (2-(2-(2-(2-((6-methoxy-2-methyl-4-oxo-3,4-dihydroquinazolin-7-yl)-oxy)ethoxy)ethoxy)ethoxy)ethyl)carbamate **16**. To a mixture of 7-hydroxy-6-methoxy-2-methylquinazolin-4(3*H*)-one **4** (1.33 g, 6.47 mmol) and K₂CO₃ (2.14 g, 15.54 mmol) in DMF (20 mL) were added benzyl (2-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)ethyl)carbamate **15** (3.03 g, 7.77 mmol) and KI (129 mg, 0.78 mmol). After stirred at room temperature for 8 h, the mixture

was filtered and washed with methanol. The combined filtrate was concentrated and the residue was purified by silica-gel column chromatography eluting with MeOH in DCM from 6% to 8%) to give compound **16** (2.3 g) in 58% yield. MS (ESI) m/z : 516.2 $[M+H]^+$.

Scheme 2



[00435] Benzyl (2-(2-(2-(2-((4-chloro-6-methoxy-2-methylquinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)carbamate **17**. To a solution of compound **16** (600 mg, 1.17 mmol) in toluene (10 mL) were added DIPEA (598 mg, 464 mmol) and POCl₃ (532 mg, 3.48 mmol). After stirred at 100 °C overnight, the mixture was concentrated to give compound **17** (619 mg) in 99% yield. MS (ESI) m/z : 534.1 $[M+H]^+$.

[00436] (*R*)-Benzyl (2-(2-(2-(2-((1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)carbamate **18**. To a solution of

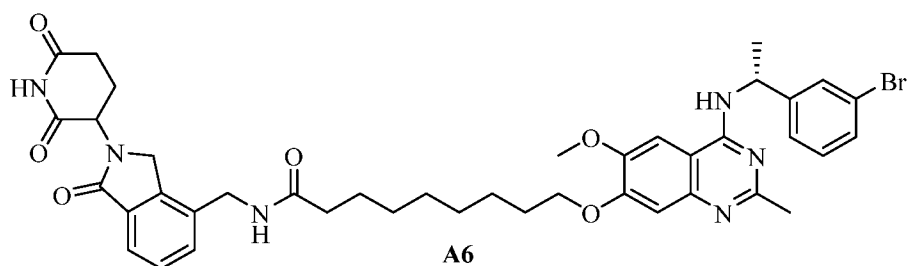
compound **17** (619 mg, 1.16 mmol) in 1,4-dioxane (20 mL) were added DIPEA (448 mg, 3.48 mmol) and (*R*)-1-(3-bromophenyl)ethanamine **8** (464 mg, 2.32 mmol). After the mixture was stirred at 100 °C for 8 h, additional DIPEA (448 mg, 3.48 mmol) and (*R*)-1-(3-bromophenyl)ethanamine **8** (464 mg, 2.32 mmol) were added room temperature. After stirred at 100 °C for additional 8 h, the mixture was concentrated and the residue was silica-gel column chromatography eluting with MeOH in DCM from 0% to 10% to give compound **18** (770 mg) in 95% yield. MS (ESI) *m/z*: 697.2, 699.2 [*M*+1, *M*+3]⁺.

[00437] (*R*)-7-(2-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)ethoxy)-*N*-(1-(3-bromophenyl)ethyl)-6-methoxy-2-methylquinazolin-4-amine **19**. A solution of compound **18** (380 mg, 0.55 mmol) in TFA (2 mL) was heated at 40 °C for 5 h. The solution was then concentrated and diluted with methanol. The mixture was adjusted to pH 7 with sodium bicarbonate, filtered, and concentrated. The residue was purified by prep-TLC (DCM/MeOH: 10/1) to give compound **19** (200 mg) in 65% yield. MS (ESI) *m/z*: 563.1, 565.1 [*M*+1, *M*+3]⁺.

[00438] 4-((2-(2-(2-(2-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione **A4**. To a solution of compound **19** (200 mg, 0.36 mmol) in 1-methyl-2-pyrrolidinone (4 mL) were added 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione **20** (149 mg, 0.54 mmol) and DIPEA (139 mg, 1.08 mmol). After stirred at 150 °C under microwave for 1 h, the mixture was diluted with H₂O (10 mL) and extracted with ethyl acetate (15 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by silica-gel column chromatography eluting with MeOH in DCM from 0% to 10% and then prep-TLC (DCM/MeOH: 15/1) to give compound **A4** in 22% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.11 (s, 1H), 8.76 (s, 1H), 7.89-7.83 (m, 1H), 7.71-7.65 (m, 1H), 7.56-7.52 (m, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.33-7.29 (m, 1H), 7.10-7.08 (m, 2H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.58 (t, *J* = 5.6 Hz, 1H), 5.70-5.63 (m, 1H), 5.05 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.20 (t, *J* = 4.0 Hz, 2H), 3.94 (s, 3H), 3.81-3.79 (m, 2H), 3.63-3.59 (m, 4H), 3.63-3.59 (m, 4H), 3.57-3.52 (m, 8H), 2.93-2.79 (m, 1H), 2.67-2.54 (m, 2H), 2.43 (s, 3H), 2.05-2.01 (m, 1H), 1.62 (d, *J* = 7.2 Hz, 3H); MS (ESI) *m/z*: 819.4, 821.4 [*M*+1, *M*+3]⁺.

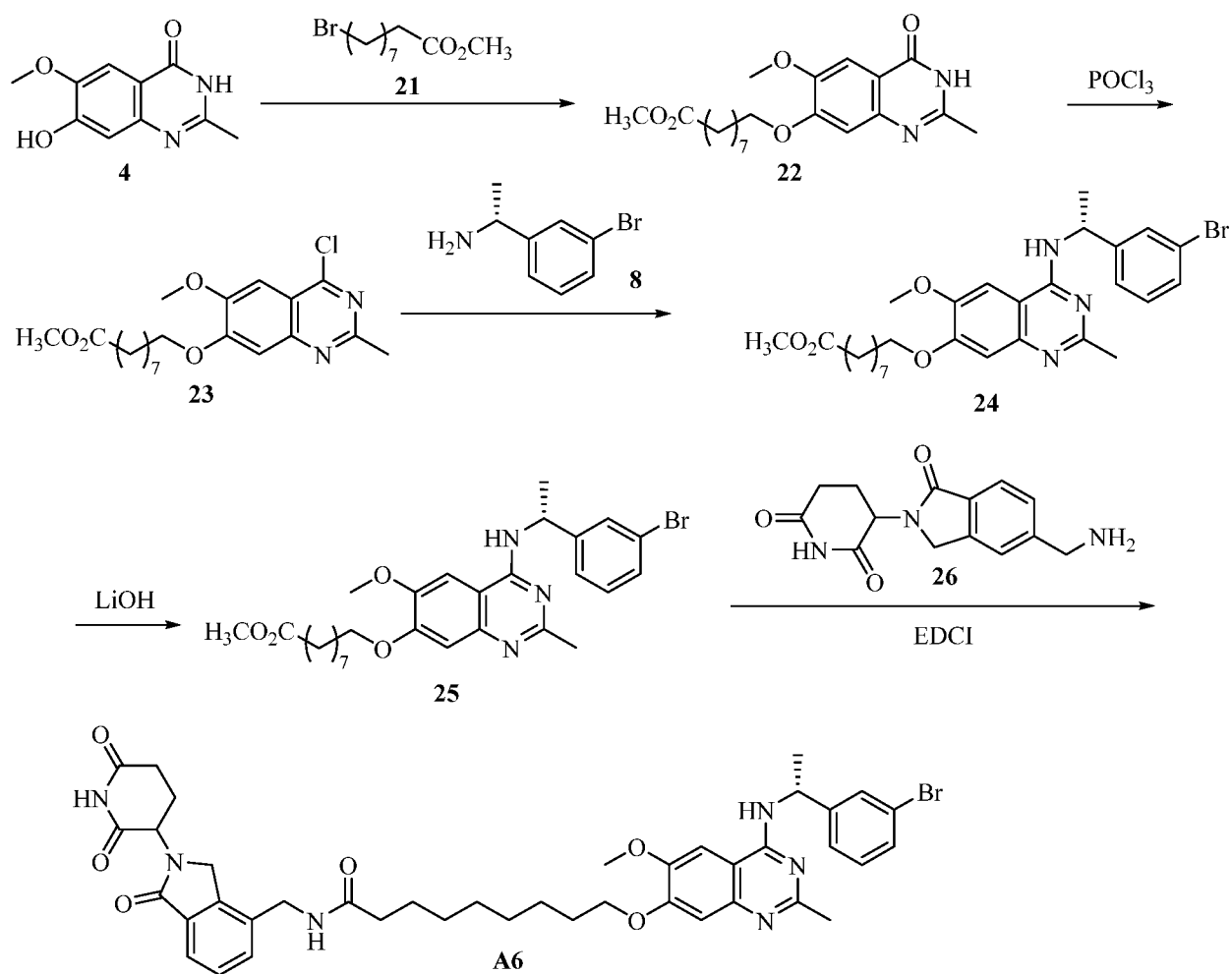
Example 3

Preparation of 9-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)methyl)nonanamide **A6**



[00439] Compound **A6** was synthesized as shown in Scheme 3.

Scheme 3



[00440] Methyl 9-((6-methoxy-2-methyl-4-oxo-3,4-dihydroquinazolin-7-yl)oxy)-nonanoate **22**. To a solution of 7-hydroxy-6-methoxy-2-methylquinazolin-4(3*H*)-one **4** (0.063 g, 0.325 mmol) in DMF (3 mL) at room temperature were added K₂CO₃ (0.108 g, 0.78 mmol) and methyl 9-bromononanoate **21** (98 mg, 0.390 mmol). After stirred at room temperature overnight, the mixture was extracted with EtOAc (15 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was triturated with hexanes and filtered to give compound **22** (0.106 g) in 90% yield.

[00441] Methyl 9-((4-chloro-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoate **23**. A solution of compound **22** in POCl₃ (2 mL) was stirred at 100° C overnight. The mixture was concentrated and then diluted with EtOAc. The mixture was then washed with water, dried over anhydrous Na₂SO₄, filtered, and concentrated to give compound **23** (0.111 g) in 96% yield. MS (ESI) *m/z*: 394.9 [M+H]⁺.

[00442] Methyl (*R*)-9-((4-((1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoate **24**. To a solution of compound **23** (0.111 g, 0.292 mmol) in dioxane (2 mL) at room temperature were added (*R*)-1-(3-bromophenyl)ethan-1-amine **8** (0.089, 0.439 mmol) and DIPEA (75.66 mg, 0.058 mmol). After stirred at 100 °C overnight, the reaction mixture was concentrated and then diluted with EtOAc. The mixture was washed with water, dried over anhydrous Na₂SO₄, filtered, and concentrated to give compound **24** (0.086 g) in 77% yield.

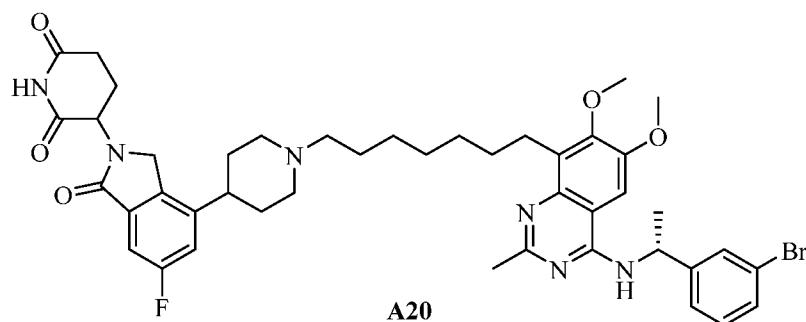
[00443] (*R*)-9-((4-((1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoic acid **25**. To a solution of compound **24** (0.086 g, 0.154 mmol) in THF and water (1.5mL/1.5 mL) at room temperature was added LiOH (0.008 g, 0.308 mmol). After stirred at room temperature overnight, the mixture was acidified with 1N HCl to pH 2. The resulting precipitate was collected by filtration to afford compound **25** (0.84 g) in 97% yield.

[00444] 8-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)octanamide **A6**. To a solution of compound **25** (0.0863 g, 0.158 mmol) in DMF (3 mL) at room temperature were added DIPEA (0.102 g, 0.7893 mmol), HOBt (25.7 mg, 0.190 mmol), EDCI (36.5 mg, 0.190 mmol.), and 3-(5-(aminomethyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **26** as a TFA salt

(52.2 mg, 0.1586 mmol). After stirred at room temperature overnight, the reaction mixture was concentrated under vacuum. The residue was purified by silica-gel column chromatography eluting with EtOAc in hexanes from 0% to 50% to give compound **A6** (15.7 mg) in 13% yield. MS (ESI) m/z : 799.7 $[M+1]^+$

Example 4

Preparation of 3-(4-(1-(7-(4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6,7-dimethoxy-2-methylquinazolin-8-yl)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A20**



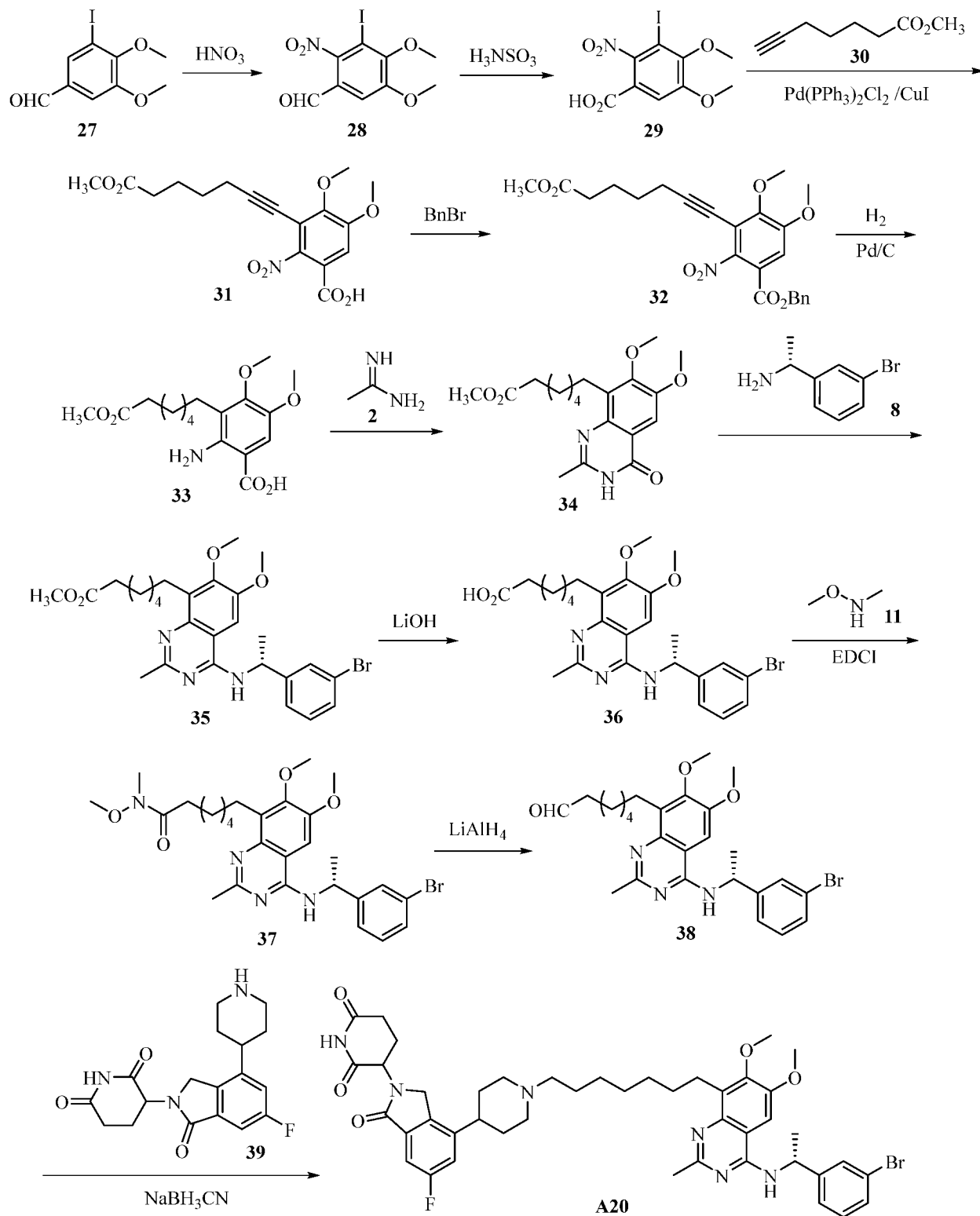
[00445] Compound **A20** was synthesized as shown in Scheme 4.

[00446] 3-Iodo-4,5-dimethoxy-2-nitrobenzoic acid **29**. To a solution of compound **28** (4.1 g, 12.2 mmol) in acetic acid (60 mL) was added sulfamic acid (3.54 g, 36.5 mmol) at 0 °C, followed by addition of a solution of sodium chlorite (3.28 g, 36.5 mmol) in water (56 mL) 15 min later. After stirred at room temperature overnight, the mixture was diluted with water (50 mL) and extracted with DCM (3 x 60 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by silica-gel chromatography eluting with MeOH in DCM from 0% to 10% to give compound **29** (2.4 g) in 53% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.07 (br, 1H), 7.46 (s, 1H), 3.95 (s, 3H), 3.83 (s, 3H).

[00447] 4,5-Dimethoxy-3-(7-methoxy-7-oxohept-1-yn-1-yl)-2-nitrobenzoic acid **31**. To a solution of compound **29** (2.2 g, 6.23 mmol), methyl hept-6-ynoate **30** (2.2 g, 15.6 mmol), and TEA (1.57 g, 15.6 mmol) in DMF (40 mL) were added Pd(PPh₃)₂Cl₂ (875 mg, 1.25 mmol) and CuI (237 mg, 1.25 mmol) under nitrogen at room temperature. After stirred at 50 °C overnight under nitrogen, the mixture was concentrated. The residue was purified by silica-gel

chromatography (DCM/MeOH: 30/1) to give compound **31** (2.1 g). MS (ESI) m/z : 364.3 $[M-H]^-$.

Scheme 4



[00448] Benzyl 4,5-dimethoxy-3-(7-methoxy-7-oxohept-1-yn-1-yl)-2-nitrobenzoate **32**. To a solution of compound **31** (2.1 g) in DMF (20 mL) were added benzyl bromide (1.3 g, 7.81 mmol) and sodium bicarbonate (1.1 g, 13.0 mmol) at room temperature. After stirred at room temperature overnight, the mixture was diluted with water (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by silica-gel chromatography eluting with EtOAc in PE from 0% to 20% to give compound **32** (720 mg) in 26% for 2 steps. ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.28 (m, 6H), 5.30 (s, 2H), 3.99 (s, 3H), 3.92 (s, 3H), 3.67 (s, 3H), 2.47 (t, J = 9.2 Hz, 2H), 2.37 (t, J = 9.6 Hz, 2H), 1.85-1.76 (m, 2H), 1.76-1.60 (m, 2H).

[00449] 2-Amino-4,5-dimethoxy-3-(7-methoxy-7-oxoheptyl)benzoic acid **33**. To a solution of compound **32** (380 mg, 0.835 mmol) in MeOH (15 mL) was added Pd/C (100 mg) under nitrogen. After stirred at room temperature under hydrogen overnight, the mixture was filtered and washed with MeOH (3 x 10 mL). The combined filtrate was concentrated and the residue was purified by prep-TLC (DCM/MeOH: 20/1) to give compound **33** (159 mg) in 48% yield. MS (ESI) m/z : 340.2[M+H]⁺.

[00450] Methyl 7-(6,7-dimethoxy-2-methyl-4-oxo-3,4-dihydroquinazolin-8-yl)heptanoate **34**. To a solution of compound **33** (159 mg, 0.469 mmol) and acetimidamide hydrochloride **2** (90 mg, 0.938 mmol) in ethylene glycol monomethyl ether (5 mL) was added sodium acetate (77 mg, 0.938 mmol) at room temperature. After stirred at 125 °C overnight, the mixture was concentrated and washed with water (3 x 10 mL) to afford compound **34** (152 mg). MS (ESI) m/z : 363.2[M+H]⁺.

[00451] (*R*)-Methyl 7-(4-((1-(3-bromophenyl)ethyl)amino)-6,7-dimethoxy-2-methylquinazolin-8-yl)heptanoate **35**. To a solution of compound **34** (152 mg crude) in DMF (3 mL) were added DBU (238 mg, 0.539 mmol), BOP (95 mg, 0.622 mmol) and (*R*)-1-(3-bromophenyl)ethanamine **8** (100 mg, 0.497 mmol) at room temperature. After the mixture was stirred at room temperature overnight, additional (*R*)-1-(3-bromophenyl)ethanamine **8** (100 mg, 0.497 mmol) was added. After stirred at 50 °C for additional 12 h, the mixture was cooled to room temperature, diluted with water (15 mL), and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The

residue was purified by silica-gel column chromatography (DCM/MeOH: 20/1) to give compound **35** (192 mg) in 85% yield. MS (ESI) m/z : 544.2 $[M+H]^+$.

[00452] *(R)*-7-(4-((1-(3-Bromophenyl)ethyl)amino)-6,7-dimethoxy-2-methylquinazolin-8-yl)heptanoic acid **36**. To a solution of compound **35** (192 mg, 0.354 mmol) in THF/MeOH/H₂O (4:1:1, 3 mL) was added LiOH·H₂O (30 mg, 0.707 mmol) at room temperature. After stirred at room temperature overnight, the mixture was diluted with water (5 mL) and concentrated, followed by addition of H₂O (5 mL). The mixture was adjusted to pH 6 with 1N HCl and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated to give compound **36** (190 mg). MS (ESI) m/z : 530.2 $[M+H]^+$.

[00453] *(R)*-7-(4-((1-(3-Bromophenyl)ethyl)amino)-6,7-dimethoxy-2-methylquinazolin-8-yl)-N-methoxy-N-methylheptanamide **37**. To a solution of compound **36** (190 mg, crude) in DCM (3 mL) at room temperature were added EDCI (104 mg, 0.539 mmol), TEA (104 mg, 0.539 mmol), *N,O*-dimethylhydroxylamine HCl (53 mg, 0.539 mmol), and DMAP (5 mg, 0.036 mmol). After stirred at room temperature overnight, the mixture was diluted with H₂O (10 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by prep-TLC (DCM/MeOH: 18/1) to give compound **37** (133 mg) in 66% yield for 2 steps. MS (ESI) m/z : 573.2 $[M+H]^+$.

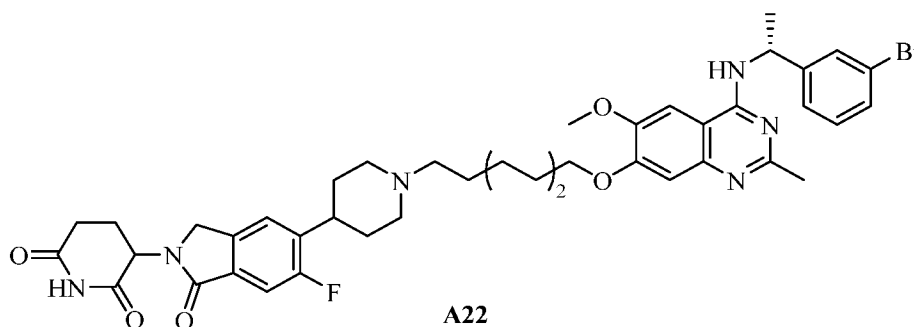
[00454] *(R)*-7-(4-((1-(3-Bromophenyl)ethyl)amino)-6,7-dimethoxy-2-methylquinazolin-8-yl)heptanal **38**. To a solution of compound **37** (67 mg, 0.117 mmol) in THF (6 mL) at -70 °C under N₂ was added LiAlH₄ (0.3 mL, 1 M in THF) dropwise. After stirred at -70 °C for 1 h, the reaction was quenched with sat. NH₄Cl (10 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated to give compound **38**, which was used directly in the next step without further purification. MS (ESI) m/z : 514.2 $[M+H]^+$.

[00455] 3-(4-(1-(7-(4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6,7-dimethoxy-2-methylquinazolin-8-yl)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A20**. To a solution of 3-(6-fluoro-1-oxo-4-(piperidin-4-yl)isindolin-2-yl)piperidine-2,6-dione **39** in DCM/MeOH (4:1, 2 mL) was added DIPEA (2 drops) at 0 °C to adjust pH 7, followed by

addition of compound **38** in DCM/MeOH (4:1, 2 mL), acetic acid (1 drop), and NaBH₃CN (29.5 mg, 0.468 mmol) at 0 °C. After stirred at room temperature overnight, the mixture was concentrated. The residue was purified by silica-gel column chromatography eluting with MeOH in DCM from 0% to 13% and further purified by prep-HPLC to give compound **A20** (12.7 mg) in 13% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.00 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.63-7.61 (m, 1H), 7.47-7.32 (m, 4H), 7.28 (t, *J* = 8.0 Hz, 1H), 5.65-5.55 (m, 1H), 5.13 (dd, *J* = 13.2 Hz, 5.2 Hz, 1H), 4.52-4.31 (m, 2H), 3.95 (s, 3H), 3.80 (s, 3H), 3.04-2.85 (m, 5H), 2.65-2.55 (m, 2H), 2.43 (dd, *J* = 13.2 Hz, 4.4 Hz, 1H), 2.37 (s, 3H), 2.35-2.27 (m, 2H), 2.05-1.95 (m, 3H), 1.73 (s, 4H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.50-1.47 (m, 2H), 1.47-1.38 (m, 2H), 1.35-1.26 (m, 6H); MS (ESI) *m/z*: 843.3 [M+H]⁺.

Example 5

Preparation of 3-(5-(1-(7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A22**

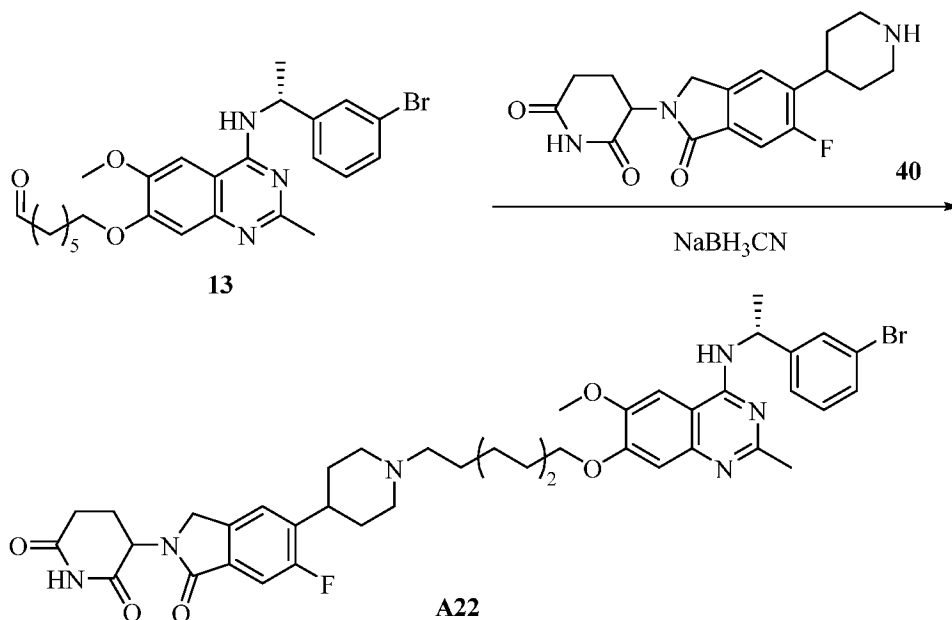


[00456] Compound **A22** was synthesized as shown in Scheme 5.

[00457] 3-(5-(1-(7-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A22**. To a solution of compound **13** (134 mg, 0.269 mmol) in DCM/MeOH (8 mL/2 mL) were added 3-(6-fluoro-1-oxo-5-(piperidin-4-yl)isindolin-2-yl)piperidine-2,6-dione **40** (83 mg, 0.24 mmol), NaBH₃CN (34 mg, 0.54 mmol), and acetic acid (1 drop). After stirred at room temperature for 8 h, the mixture was concentrated. The residue was purified by silica-gel column chromatography eluting with MeOH in DCM from 0% to 10% to give compound **A22** (100.3 mg) in 45% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.99 (s, 1H), 7.97 (d, *J* = 8.0 Hz,

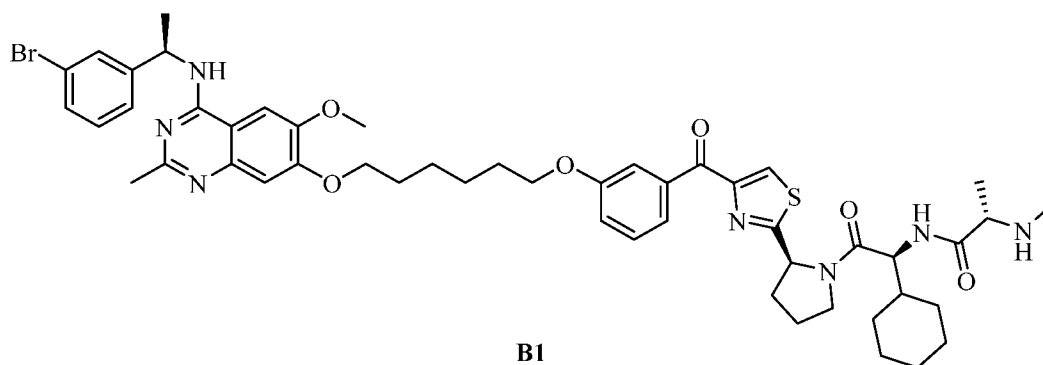
1H), 7.67 (s, 1H), 7.63-7.60 (m, 2H), 7.47-7.40 (m, 3H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.01 (s, 1H), 5.60 (t, $J = 7.6$ Hz, 1H), 5.10 (dd, $J = 13.2, 5.2$ Hz, 1H), 4.43-4.26 (m, 2H), 4.07 (t, $J = 6.4$ Hz, 2H), 3.91 (s, 3H), 2.99-2.97 (m, 2H), 2.91-2.86 (m, 1H), 2.67-2.57 (m, 1H), 2.39-2.37 (m, 1H), 2.33 (s, 3H), 2.30-2.28 (m, 2H), 2.03-1.99 (m, 1H), 1.79-1.73 (m, 6H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.46-1.44 (m, 4H), 1.38-1.30 (m, 4H), 1.25-1.22 (m, 3H); MS (ESI) m/z : 829.3, 831.3 [$M+1$, $M+3$] $^+$.

Scheme 5



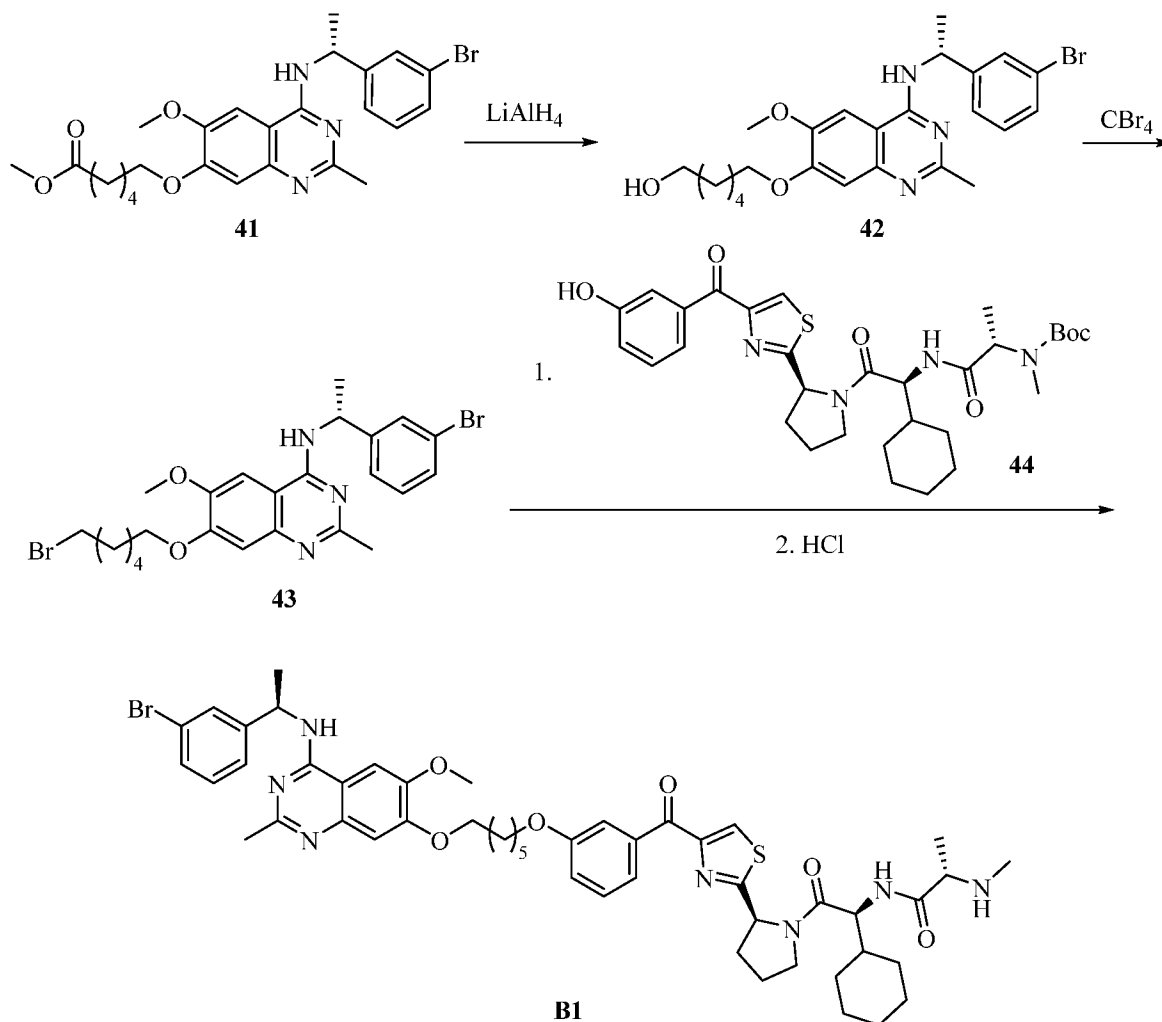
Example 6

Preparation of (*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B1**



[00458] Compound **B1** is synthesized as shown in Scheme 6.

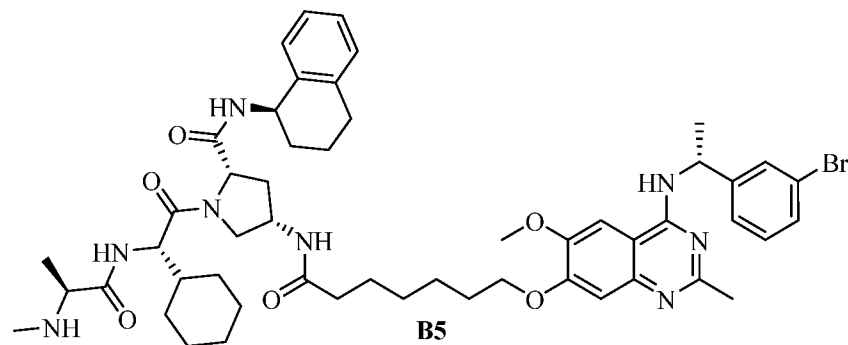
Scheme 6



Example 7

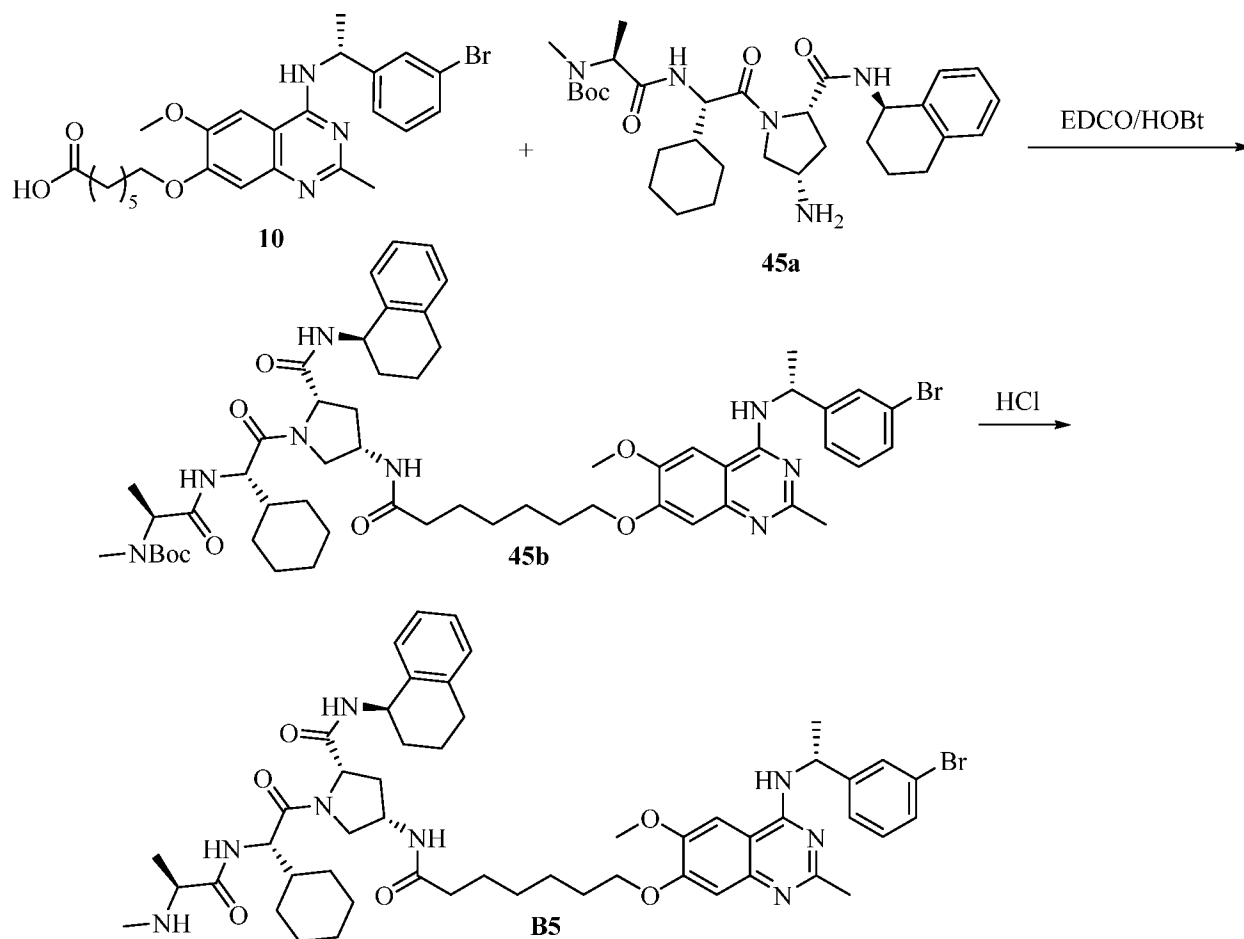
Preparation of (2*S*,4*S*)-4-(7-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanamido)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)-

acetyl)-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide **B5**



[00459] Compound **B5** was synthesized as shown in Scheme 7.

Scheme 7



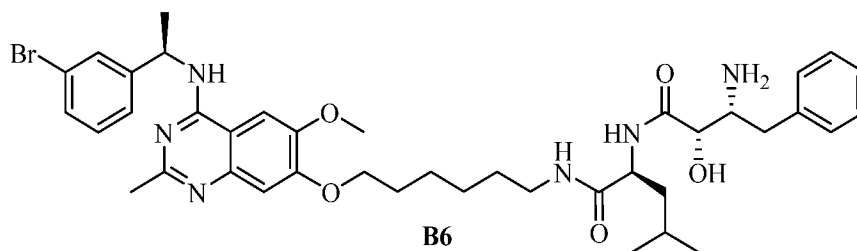
[00460] *Tert*-butyl ((*S*)-1-(((*S*)-2-((2*S*,4*S*)-4-(7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanamido)-2-(((*R*)-1,2,3,4-tetrahydronaphthalen-1-

yl)carbamoyl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate **45b**. To a solution of (*R*)-7-((4-((1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanoic acid **10** (190 mg, 0.369 mmol) in DMF (3 mL) were added DIPEA (143 mg, 1.118 mmol), *tert*-butyl ((*S*)-1-(((*S*)-2-((2*S*,4*S*)-4-amino-2-(((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate **45a** (216 mg, 0.369 mmol), HOBt (100 mg, 0.738 mmol), and EDCI (141 mg, 0.738 mmol). After stirred at room temperature overnight, the mixture was concentrated. The residue was purified by silica-gel chromatography eluting with MeOH in DCM from 0% to 10% to afford compound **45b** (104 mg) in 26% yield. MS (ESI) *m/z*: 1081.5 [M+1]⁺.

[00461] (2*S*,4*S*)-4-(7-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanamido)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)-acetyl)-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide **B5**. To a solution of compound **45b** (56 mg, 0.052 mmol) in DCM (2.4 mL) was added HCl in EtOAc (0.8 mL) at room temperature. After stirred at room temperature for 1 h, the mixture was concentrated and the residue was purified by silica-gel chromatography eluting with MeOH in DCM from 5% to 10% and further purified by prep-HPLC to afford compound **B5** (46 mg) in 91% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.59 (s, 1H), 10.05 (s, 1H), 9.19 (s, 1H), 8.89-8.77 (m, 2H), 8.43 (d, *J* = 8.8 Hz, 1H), 8.21-8.19 (m, 2H), 7.73 (s, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.35-7.25 (m, 3H), 7.16-7.06 (m, 3H), 5.79-5.73 (m, 1H), 4.94-4.89 (m, 1H), 4.40-4.25 (m, 3H), 4.13-4.08 (m, 3H), 3.98 (s, 3H), 3.84 (s, 1H), 2.73-2.67 (m, 2H), 2.58 (s, 3H), 2.41-2.32 (m, 1H), 2.09 (t, *J* = 6.8 Hz, 2H), 1.92 (d, *J* = 11.2 Hz, 1H), 1.84-1.76 (m, 5H), 1.74-1.64 (m, 8H), 1.62-1.41 (m, 6H), 1.38-1.29 (m, 5H), 1.23-1.11 (m, 4H), 1.08-0.95 (m, 2H); MS (ESI) *m/z*: 981.3 [M+1]⁺.

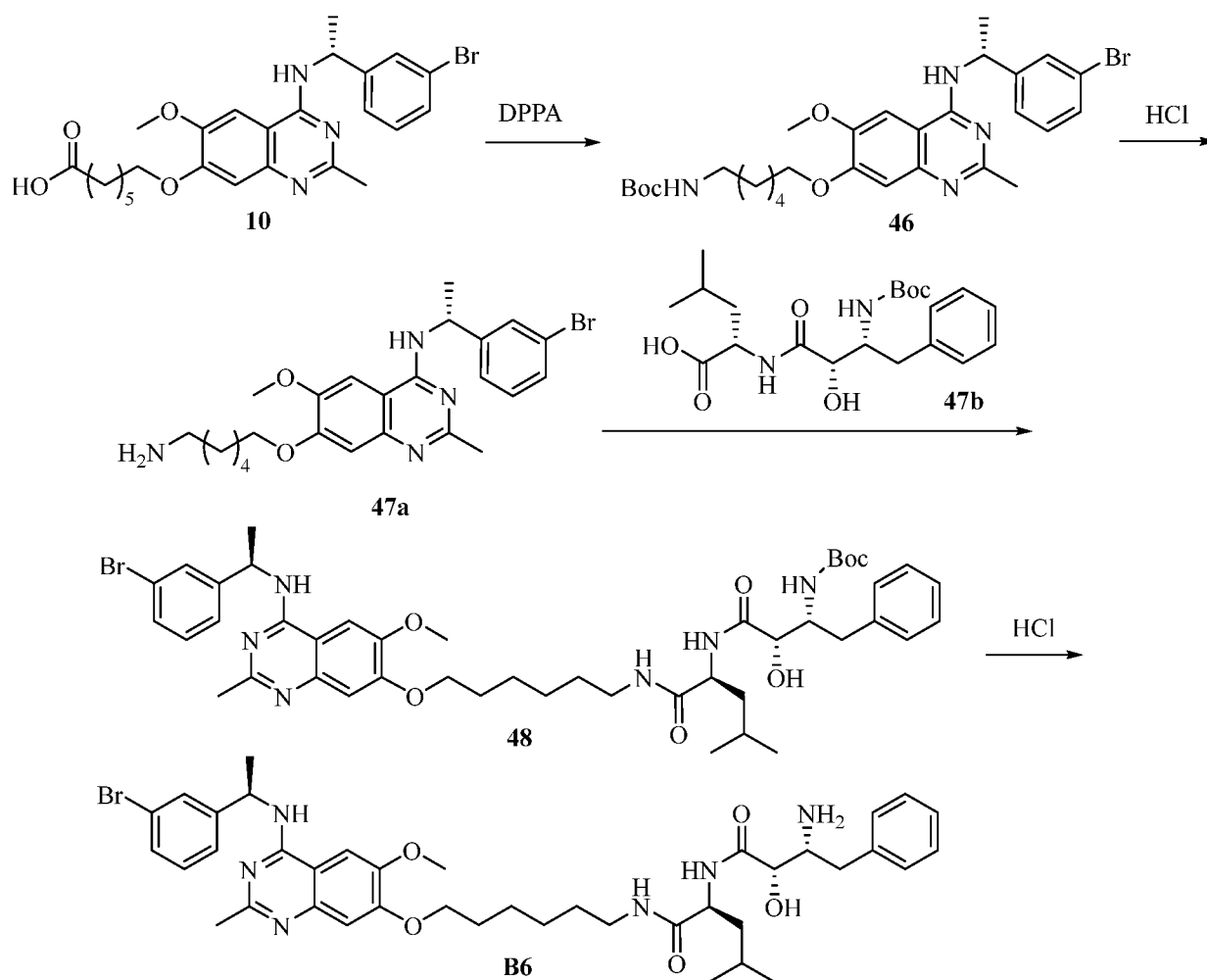
Example 8

Preparation of (*S*)-2-((2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanamido)-*N*-(6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)-4-

methylpentanamide **B6**

[00462] Compound **B6** was synthesized as shown as shown in Scheme 8.

Scheme 8



[00463] (*R*)-*Tert*-butyl (6-((4-((1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)carbamate **46**. To a solution of (*R*)-7-((4-((1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanoic acid **10** (94 mg,

0.18 mmol) in *t*BuOH/Toluene (3/3 mL) were added DPPA (74 mg, 0.27 mmol), (Boc)₂O (78 mg, 0.36 mmol) and TEA (55 mg, 0.54 mmol). After stirred at room temperature for 1 h and at 80 °C overnight, the mixture was concentrated and purified by silica-gel column chromatography eluting with MeOH/DCM to afford compound **46** (80 mg) in 76% yield. MS (ESI) *m/z*: 587.2 [M+1]⁺.

[00464] (*R*)-7-((6-Aminohexyl)oxy)-*N*-(1-(3-bromophenyl)ethyl)-6-methoxy-2-methylquinazolin-4-amine **47a**. To a solution of compound **46** (80 mg, 0.14 mmol) in MeOH (1 mL) was added HCl in EtOAc (2 mL). After stirred at room temperature for 2 h, the mixture was concentrated and the residue was purified by prep-TLC (MeOH/DCM: 10/1) to afford compound **47a** (64 mg) in 94% yield. MS (ESI) *m/z*: 487.1 [M+H]⁺.

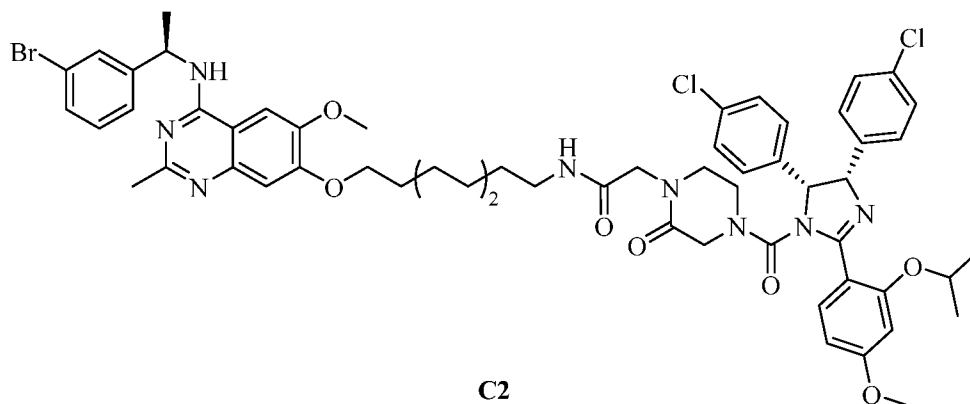
[00465] *Tert*-butyl ((2*R*,3*S*)-4-(((*S*)-1-((6-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-hydroxy-4-oxo-1-phenylbutan-2-yl)carbamate **48**. To a solution of compound **47a** (64 mg, 0.13 mmol) and (*S*)-2-((2*S*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-4-phenylbutanamido)-4-methylpentanoic acid **47b** (54 mg, 0.13 mmol) in DMF (4 mL) were added HOBt (35 mg, 0.26 mmol), EDCI (50 mg, 0.26 mmol), and TEA (50 mg, 0.39 mmol). After the mixture was stirred at room temperature for 2 h, water was added. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica-gel column chromatography eluting with MeOH in DCM from 0% to 10% and then by prep-HPLC to afford compound **48** (32 mg) in 28% yield. MS (ESI) *m/z*: 877.3 [M+H]⁺.

[00466] (*S*)-2-((2*S*,3*R*)-3-Amino-2-hydroxy-4-phenylbutanamido)-*N*-(6-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)-4-methylpentanamide **B6**. To a solution of compound **48** (32 mg, 0.037 mmol) in DCM (2 mL) was added HCl in EtOAc (0.5 mL). After stirred at room temperature for 30 min, the mixture was concentrated to afford compound **B6** (25 mg) in 89% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.43 (s, 1H), 9.91 (s, 1H), 8.16-8.06 (m, 2H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.97-7.88 (m, 2H), 7.75-7.67 (m, 1H), 7.53-7.47 (m, 2H), 7.38-7.32 (m, 3H), 7.30-7.24 (m, 3H), 7.21-7.17 (m, 1H), 6.68-6.59 (m, 1H), 5.83-5.72 (m, 1H), 4.30-4.20 (m, 1H), 4.11(t, *J* = 6.4 Hz, 2H), 4.02-3.93 (m, 4H),

3.59-3.50 (m, 2H), 3.09-2.99 (m, 2H), 2.96-2.90 (m, 1H), 2.86-2.80 (m, 1H), 2.60-2.55 (m, 4H), 2.04-1.95 (m, 1H), 1.81-1.73 (m, 2H), 1.68(d, $J = 6.8$ Hz, 3H), 1.46-1.39 (m, 4H), 1.34-1.24 (m, 4H), 0.89-0.85 (m, 6H); MS (ESI) m/z : 777.3 $[M+H]^+$.

Example 9

Preparation of 2-(4-((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)-2-oxopiperazin-1-yl)-*N*-(8-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)acetamide **C2**



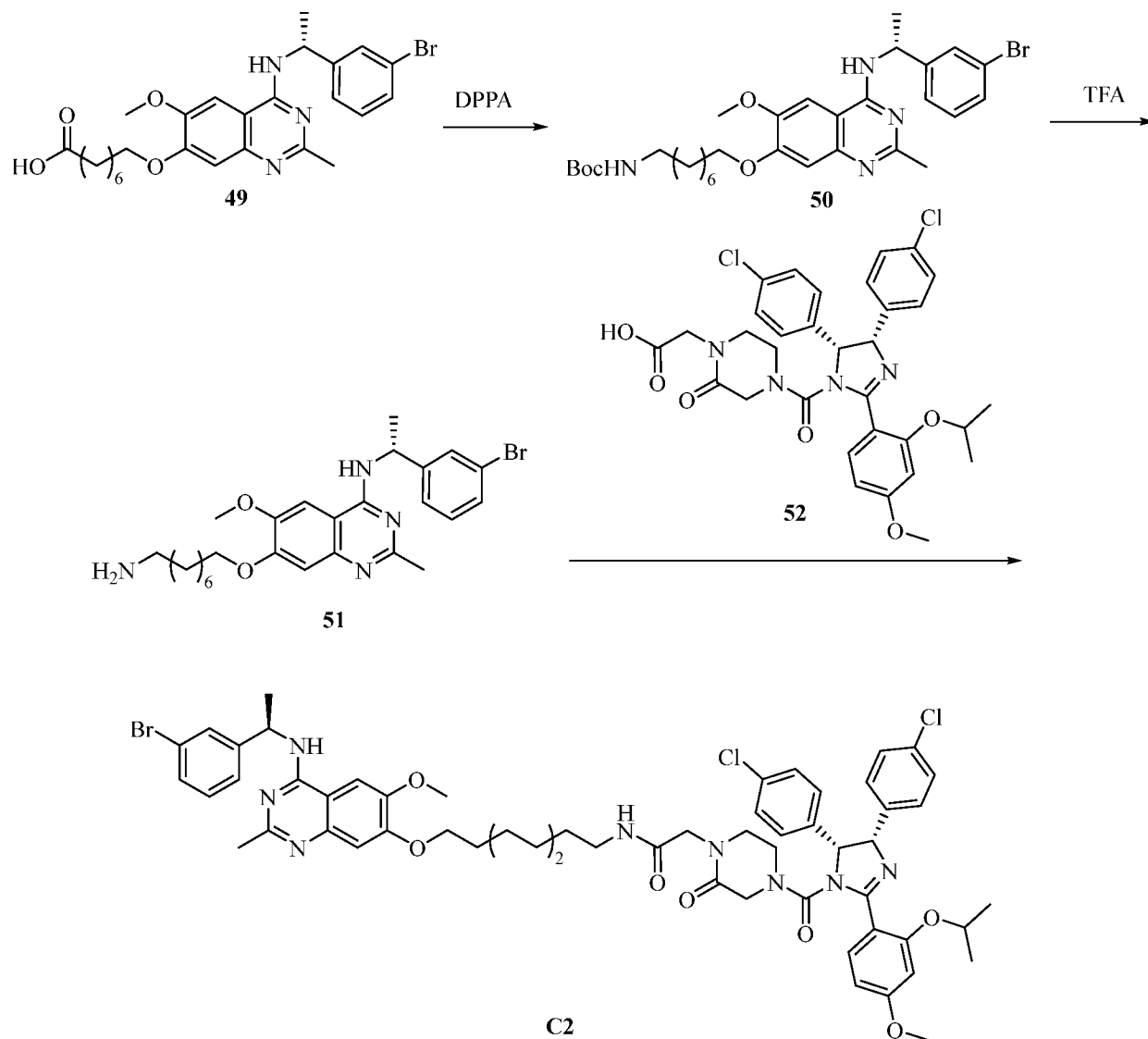
[00467] Compound **C2** was synthesized as shown in Scheme 9.

[00468] (*R*)-*Tert*-butyl (8-((4-((1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)carbamate **50**. To a solution of (*R*)-9-((4-((1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoic acid **49** (507 mg, 0.933 mmol) in toluene/*tert*-butanol (5 mL/5 mL) was added DPPA (513 mg, 1.86 mmol), (Boc)₂O (305 mg, 1.40 mmol), and TEA (283 mg, 2.80 mmol). After stirred at room temperature for 1 h and at 100 °C for 12 h under N₂, the mixture was concentrated. The residue was purified by silica-gel column chromatography eluting with MeOH in DCM from 0% to 10% to afford compound **52** (340 mg). MS (ESI) m/z : 615.6 $[M+H]^+$.

[00469] (*R*)-7-((8-Aminooctyl)oxy)-*N*-(1-(3-bromophenyl)ethyl)-6-methoxy-2-methylquinazolin-4-amine **51**. To a solution of compound **50** (340 mg, 0.553 mmol) in DCM (4 mL) at room temperature was added TFA (1 mL). After stirred at room temperature for 1 h, the mixture was concentrated and the residue was purified by silica-gel column chromatography eluting with MeOH in DCM from 0% to 10% to afford compound **53** (140 mg). MS (ESI) m/z : 515.4

[M+H]⁺.

Scheme 9

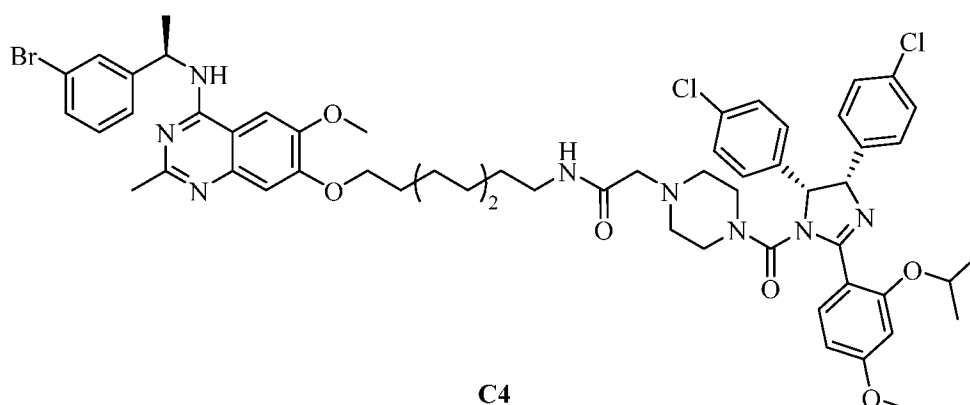


[00470] 2-(4-(((4*S*,5*R*)-4,5-Bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-*N*-(8-(((4-(((*R*)-1-(3-bromophenyl)ethyl)-amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)acetamide **C2**. To a solution of compound **51** (70 mg, 0.136 mmol) in DMF (5 mL) was added 2-(4-(((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)acetic acid at room temperature **52**, DIPEA (53 mg, 0.408 mmol), HOBt (28 mg, 0.204 mmol), and EDCI·HCl (39 mg, 0.204 mmol). After stirred at room temperature overnight, the

mixture was concentrated and the residue was purified by pre-HPLC to afford compound **C2** (21.8 mg) in 14% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.67-7.63 (m, 3H), 7.45-7.38 (m, 3H), 7.30-7.26 (m, 1H), 7.15-7.09 (m, 4H), 7.03-7.00 (m, 3H), 6.95-6.93 (m, 2H), 6.63-6.59 (m, 2H), 5.64-5.58 (m, 2H), 5.51-5.48 (m, 1H), 4.72-4.66 (m, 1H), 4.06 (t, *J* = 6.4 Hz, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.06-2.99 (m, 6H), 2.75-2.66 (m, 2H), 2.33 (s, 3H), 2.07-1.90 (m, 4H), 1.77-1.72 (m, 2H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.40-1.33 (m, 4H), 1.28-1.22 (m, 12H); MS (ESI) *m/z*: 1137.0 [M+H]⁺.

Example 10

Preparation of 2-(4-((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-*N*-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)-amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)acetamide **C4**



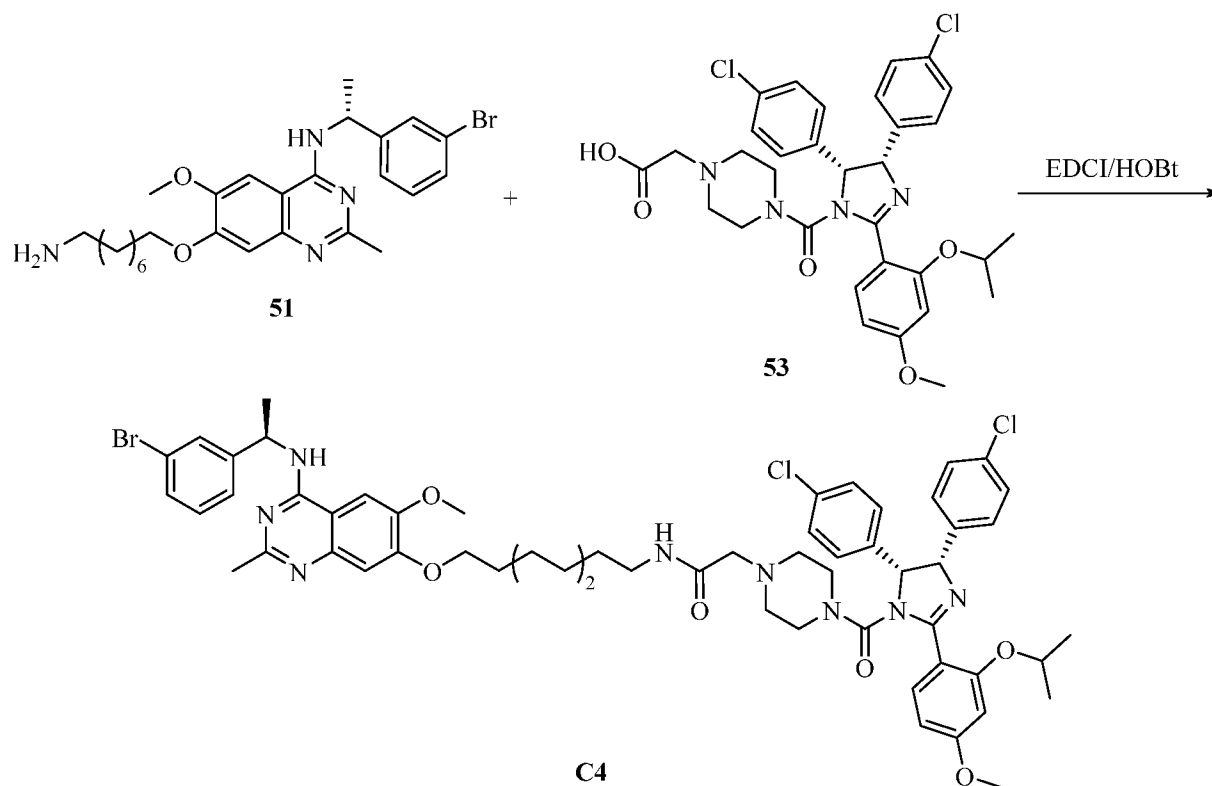
C4

[00471] Compound **C4** was synthesized as shown in Scheme 10.

[00472] 2-(4-((4*S*,5*R*)-4,5-Bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-*N*-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)-amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)acetamide **C4**. To a stirred solution of (*R*)-7-((8-aminooctyl)oxy)-*N*-(1-(3-bromophenyl)ethyl)-6-methoxy-2-methylquinazolin-4-amine **51** (70 mg, 0.136 mmol) in DMF (5 mL) were added at room temperature 2-(4-((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)acetic acid **53**, DIPEA (53 mg, 0.408 mmol), HOBt (28 mg, 0.204 mmol), and EDCI (39 mg, 0.204 mmol). After stirred at room temperature overnight, the mixture was concentrated and the residue was purified by pre-HPLC to afford compound **C4**

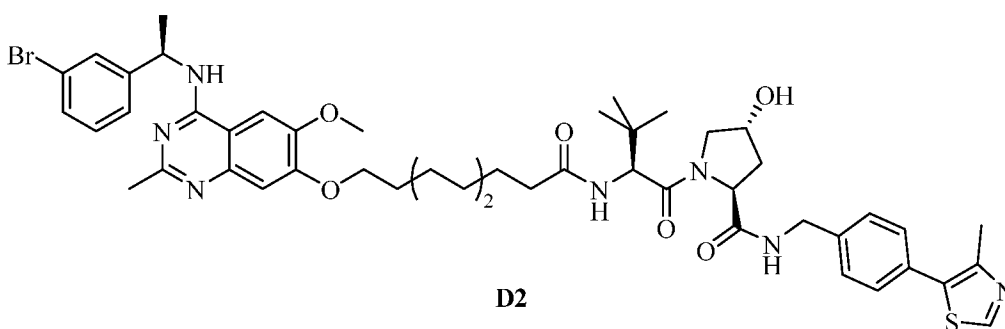
(21.8 mg) in 14% yield. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.98 (d, $J = 8.0$ Hz, 1H), 7.67-7.63 (m, 3H), 7.45-7.38 (m, 3H), 7.30-7.26 (m, 1H), 7.15-7.09 (m, 4H), 7.03-7.00 (m, 3H), 6.95-6.93 (m, 2H), 6.63-6.59 (m, 2H), 5.64-5.58 (m, 2H), 5.51-5.48 (m, 1H), 4.72-4.66 (m, 1H), 4.06 (t, $J = 6.4$ Hz, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.06-2.99 (m, 6H), 2.75-2.66 (m, 2H), 2.33 (s, 3H), 2.07-1.90 (m, 4H), 1.77-1.72 (m, 2H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.40-1.33 (m, 4H), 1.28-1.22 (m, 12H); MS (ESI) m/z : 1121.1, 1123.1 $[\text{M}+1, \text{M}+3]^+$

Scheme 10



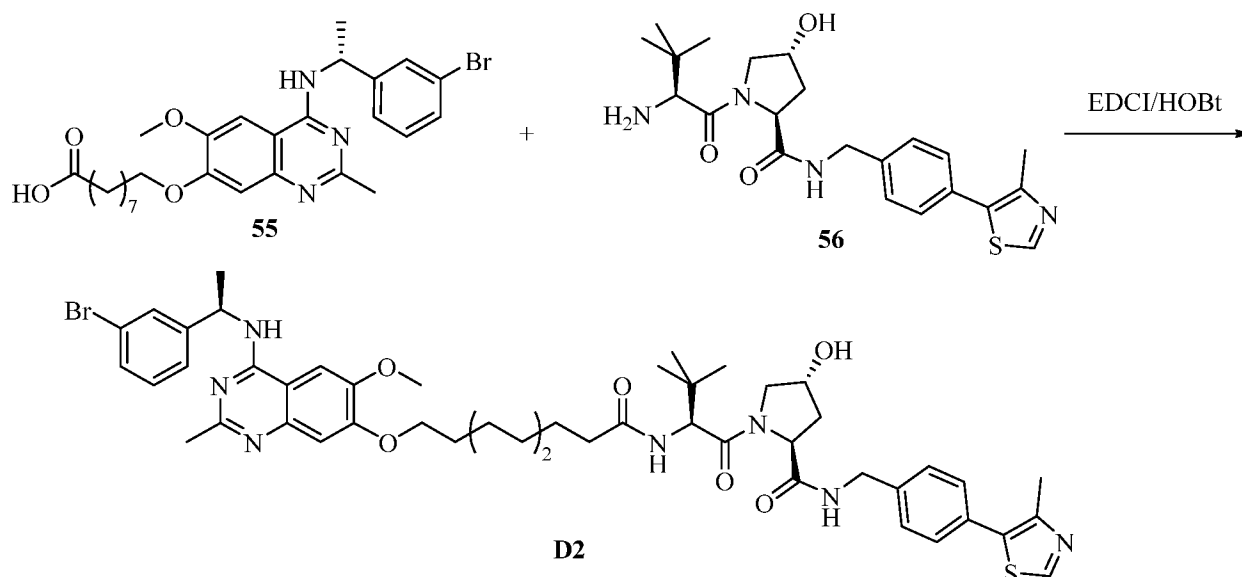
Example 11

Preparation of (2*S*,4*R*)-1-((*S*)-2-(9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D2**



[00473] Compound **D2** was synthesized as shown in Scheme 11.

Scheme 11

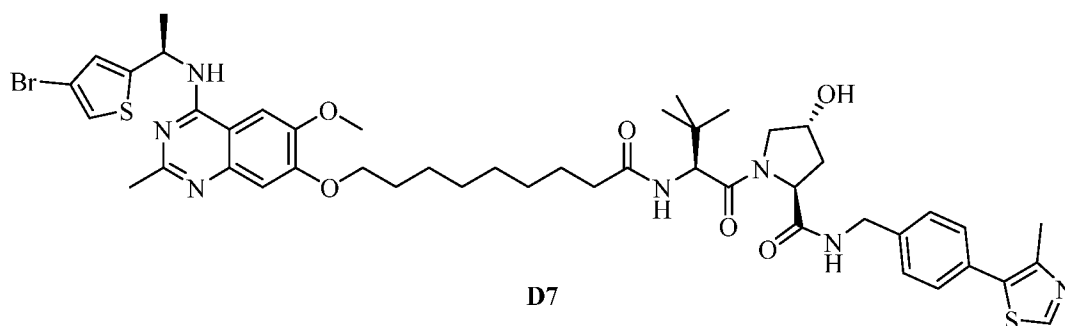


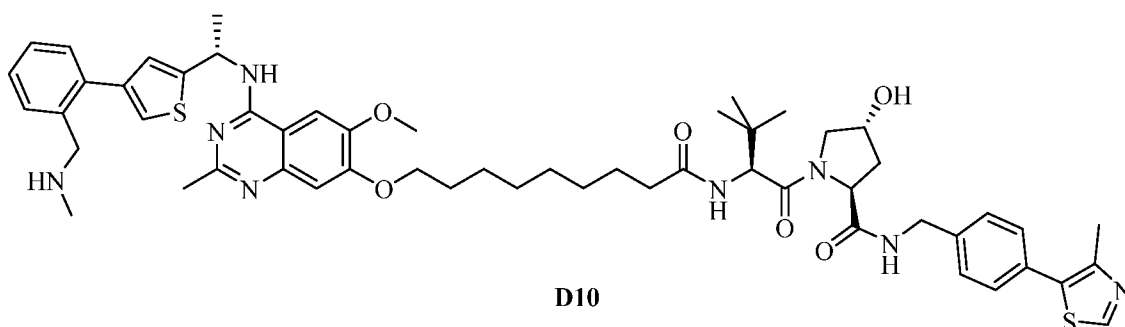
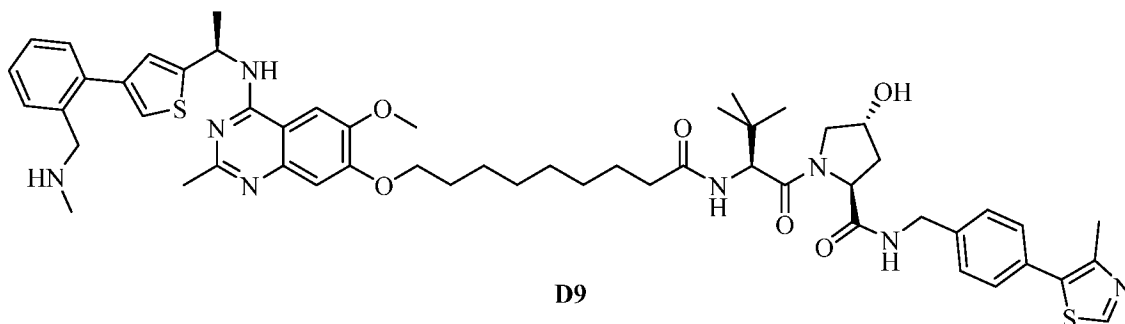
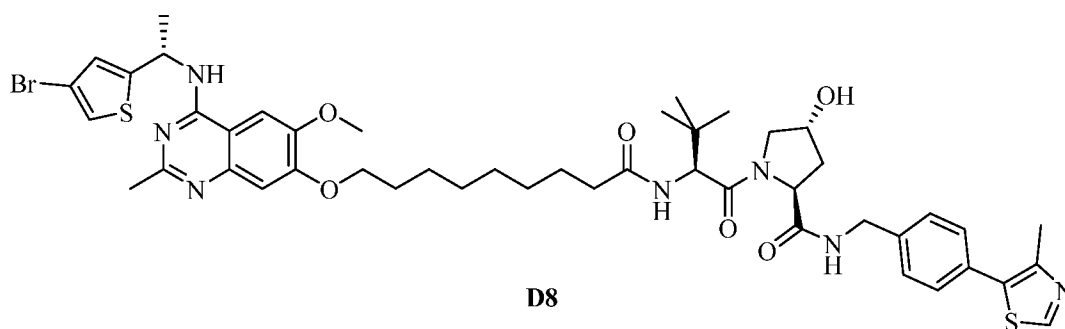
[00474] (2*S*,4*R*)-1-((*S*)-2-(9-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D2**. To a solution of (*R*)-9-((4-((1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoic acid **55** (143 mg, 0.26 mmol) and (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **56** (123 mg, 0.26 mmol) in DMF (4 mL) were added DIPEA (101 mg, 0.78 mmol), EDCI (100 mg, 0.52 mmol), and HOBt (94 mg, 0.616 mmol). After stirred at room temperature overnight, the mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by silica-gel column

chromatography eluting with MeOH in DCM from 0% to 10% and further purified by pre-HPLC to afford compound **D2** (37.9 mg) in 15% yield. ^1H NMR (400 MHz, DMSO- d_6) δ 8.99 (s, 1H), 8.58 (s, 1H), 8.01 (d, $J = 7.2$ Hz, 1H), 7.86 (d, $J = 8.8$ Hz, 1H), 7.69 (s, 1H), 7.65 (s, 1H), 7.46-7.39 (m, 6H), 7.32-7.28 (m, 1H), 7.02 (s, 1H), 5.61 (t, $J = 6.0$ Hz, 1H), 5.16 (s, 1H), 4.56 (d, $J = 8.4$ Hz, 1H), 4.46-4.42 (m, 2H), 4.37 (s, 1H), 4.24-4.21 (m, 1H), 4.12-3.99 (m, 2H), 3.92 (s, 3H), 3.79-3.57 (m, 3H), 2.46 (s, 3H), 2.35 (s, 3H), 2.29-2.26 (m, 1H), 2.15-2.03 (m, 2H), 1.94-1.85 (m, 1H), 1.83-1.71 (m, 2H), 1.59 (d, $J = 5.6$ Hz, 3H), 1.51-1.42 (m, 4H), 1.35-1.26 (m, 5H), 0.94 (s, 9H); MS (ESI) m/z : 956.4, 958.3 [$M+1$, $M+3$] $^+$.

Example 12

Preparation of (2*S*,4*R*)-1-((*S*)-2-(9-((4-(((*R*)-1-(4-bromothiophen-2-yl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D7**; (2*S*,4*R*)-1-((*S*)-2-(9-((4-(((*S*)-1-(4-bromothiophen-2-yl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D8**; (2*S*,4*R*)-4-hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D9**; (2*S*,4*R*)-4-hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D10**

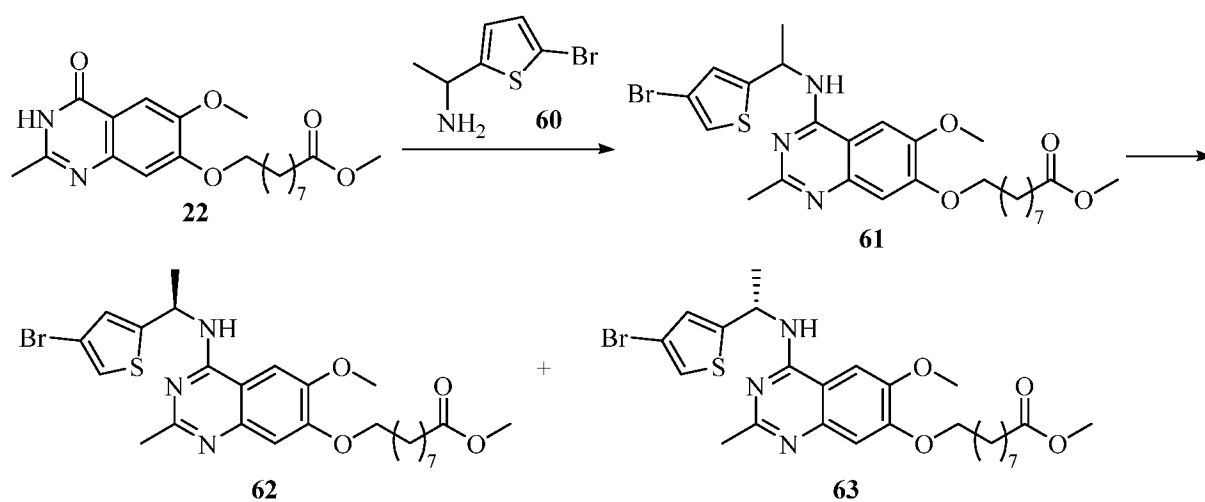




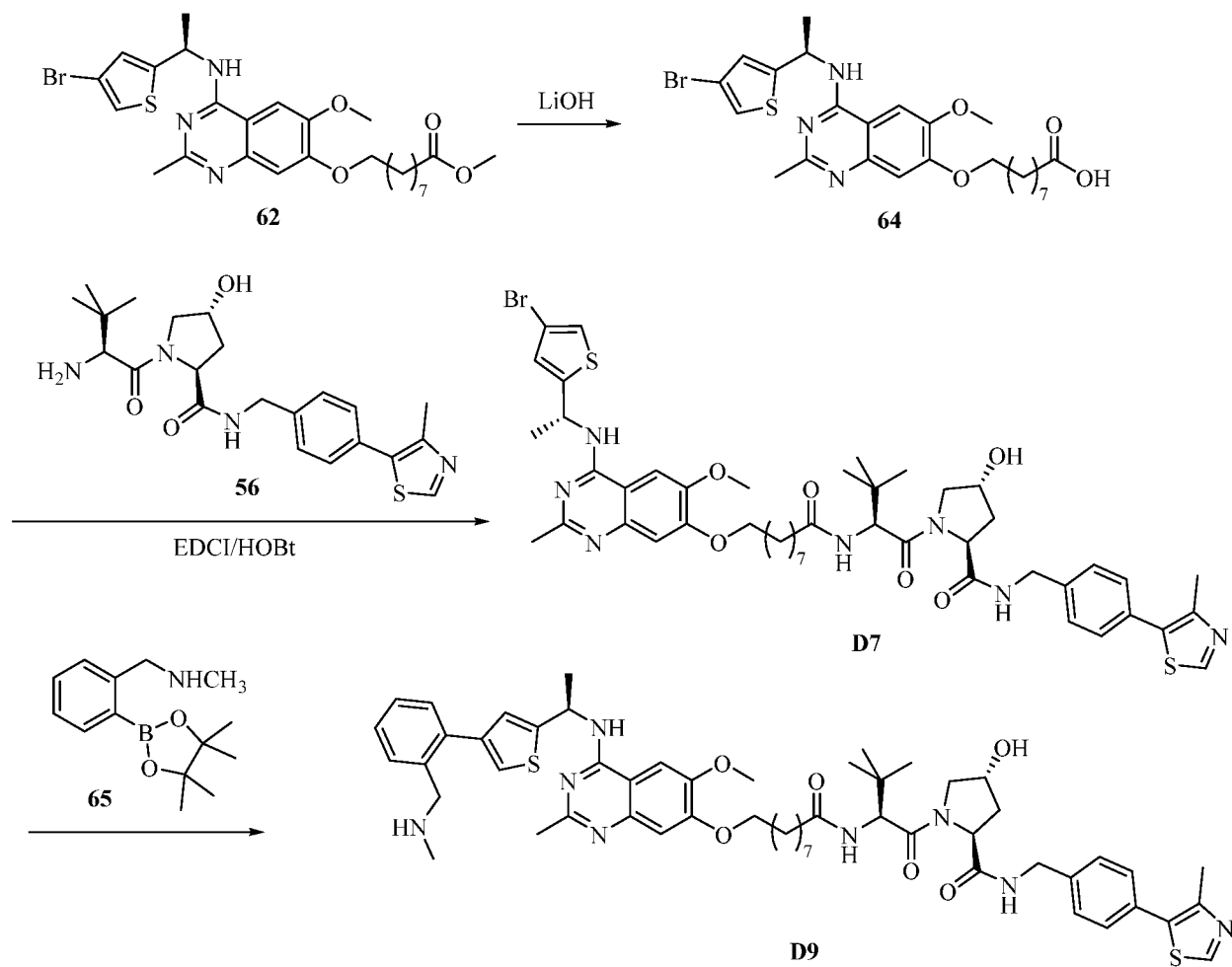
[00475] Compounds **D7** to **D9** were synthesized as shown in Schemes 12 and 13.

[00476] Methyl 9-((4-((1-(4-bromothiophen-2-yl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)nonanoate **61**. To a solution of methyl 9-((6-methoxy-2-methyl-4-oxo-3,4-dihydroquinazolin-7-yl)oxy)nonanoate **22** (1.2 g, 3.19 mmol) in DMF (20 mL) were added BOP (1.83 g, 4.15 mmol), DBU (727 mg, 4.79 mmol), and 1-(5-bromothiophen-2-yl)ethanamine **60** (785 mg, 3.83 mmol). After stirred at 60 °C for 48 h, the mixture was diluted with water (20 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by silica-gel column chromatography to afford compound **61** (466 mg, yield: 25%) in 25%. MS (ESI) *m/z*: 564.5 [M+H]⁺.

Scheme 12



Scheme 13



[00477] Methyl-9-((4-((1-(4-bromothiophen-2-yl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoate **61** was resolved by chiral column chromatography to afford (*R*)-methyl-9-((4-((1-(4-bromothiophen-2-yl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoate **62** (246 mg) and (*S*)-methyl-9-((4-((1-(4-bromothiophen-2-yl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoate **63** (220 mg).

[00478] (*R*)-9-((4-((1-(4-Bromothiophen-2-yl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoic acid **64**. To a solution of compound **62** (246 mg, 0.437 mmol) in THF/MeOH/H₂O (4 mL/1mL/1mL) was added LiOH (37 mg, 0.873 mmol). After stirred at room temperature for 8 h, the mixture was concentrated and water (10 mL) was added. The mixture was adjusted pH 5-6 with 1N HCl and the resulting precipitate was collected and dried to afford compound **64** (290 mg). MS (ESI) *m/z*: 550.5 [M+H]⁺.

[00479] (2*S*,4*R*)-1-((*S*)-2-(9-((4-(((*R*)-1-(4-Bromothiophen-2-yl)ethyl) amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D7**. To a solution of compound **64** (226 mg, 0.411 mmol) and DIPEA (160 mg, 1.23 mmol) in DMF (15 mL) were added EDCI (118 mg, 0.616 mmol), HOBT (94 mg, 0.616 mmol), and (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **56** (288 mg, 0.616 mmol). After stirred at room temperature for 8 h, the mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by silica-gel column chromatography eluting with MeOH in DCM from 0% to 8% to afford compound **D7** (400 mg) in 93% yield. MS (ESI) *m/z*: 962.3 [M+H]⁺.

[00480] (2*S*,4*R*)-1-((*S*)-2-(9-((4-(((*S*)-1-(4-Bromothiophen-2-yl)ethyl) amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D8** was prepared similarly as shown in Scheme 13.

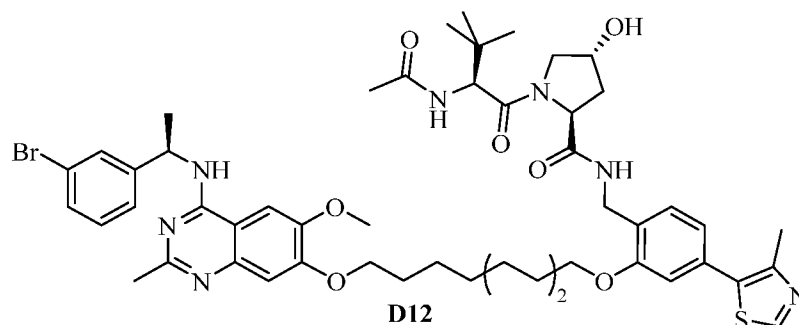
[00481] (2*S*,4*R*)-4-Hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D9**. To a

solution of compound **D7** (100 mg, 0.104 mmol) in dioxane/H₂O (4 mL/0.8 mL) were added potassium carbonate (58 mg, 0.416 mmol), Pd(PPh₃)₄ (12 mg, 0.0104 mmol), and *N*-methyl-1-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine **65** (31 mg, 0.125 mmol). After stirred at 100 °C overnight under N₂, the mixture was diluted with water (10 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by silica-gel column chromatography eluting with MeOH in DCM from 0% to 8% to afford compound **D9** (25.4 mg) in 16% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.55 (t, *J* = 6.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.64 (s, 1H), 7.46-7.37 (m, 6H), 7.32-7.27 (m, 4H), 7.03 (s, 1H), 5.97 (t, *J* = 7.2 Hz, 1H), 5.12 (s, 1H), 4.54 (d, *J* = 10 Hz, 1H), 4.46-4.40 (m, 2H), 4.35 (s, 1H), 4.24-4.19 (m, 1H), 4.06 (t, *J* = 6.4 Hz, 2H), 3.87 (s, 3H), 3.66-3.65 (m, 2H), 3.58 (s, 2H), 2.44-2.42 (m, 8H), 2.28-2.25 (m, 1H), 2.23 (s, 3H), 2.15-2.10 (m, 1H), 2.03-1.97 (m, 2H), 1.78-1.74 (m, 1H), 1.72 (d, *J* = 7.2 Hz, 3H), 1.48-1.40 (m, 4H), 1.31-1.27 (m, 6H), 0.93 (s, 9H); MS (ESI) *m/z*: 1003.5 [M+H]⁺.

[00482] (2*S*,4*R*)-4-Hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D10** was prepared similarly as shown in Scheme 13. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.55 (t, *J* = 6.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.64 (s, 1H), 7.46-7.37 (m, 6H), 7.32-7.27 (m, 4H), 7.03 (s, 1H), 5.97 (t, *J* = 7.2 Hz, 1H), 5.12 (s, 1H), 4.54 (d, *J* = 10.0 Hz, 1H), 4.46-4.40 (m, 2H), 4.35 (s, 1H), 4.24-4.19 (m, 1H), 4.06 (t, *J* = 6.4 Hz, 2H), 3.87 (s, 3H), 3.66-3.65 (m, 2H), 3.58 (s, 2H), 2.44-2.42 (m, 8H), 2.28-2.25 (m, 1H), 2.23 (s, 3H), 2.15-2.10 (m, 1H), 2.03-1.97 (m, 1H), 1.78-1.76 (m, 2H), 1.72 (d, *J* = 7.2 Hz, 3H), 1.52-1.40 (m, 4H), 1.31-1.27 (m, 6H), 0.93 (s, 9H); MS (ESI) *m/z*: 1003.5 [M+H]⁺.

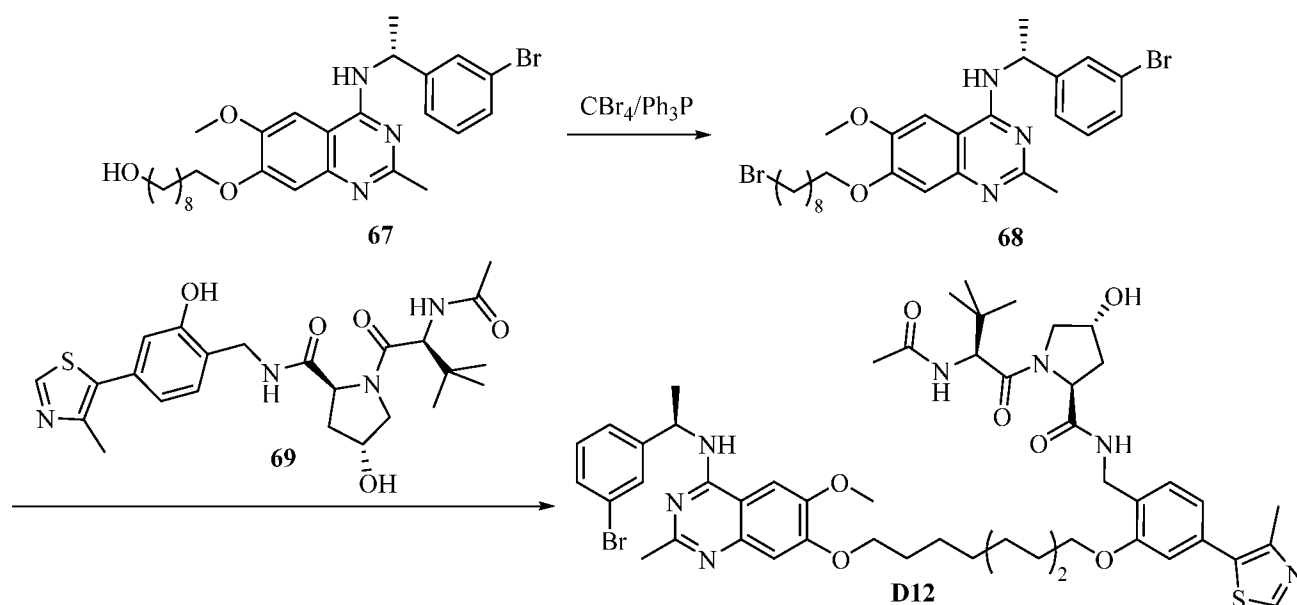
Example 13

Preparation of (2*S*,4*R*)-1-((*S*)-2-acetamido-3,3-dimethylbutanoyl)-*N*-(2-((9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonyl)oxy)-4-(4-

methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D12**

[00483] Compound **D12** was synthesized as shown in Scheme 14.

Scheme 14

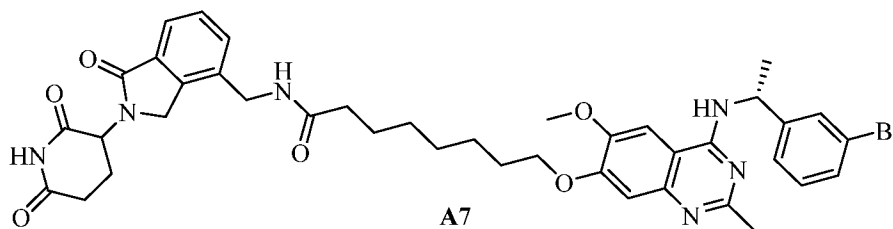


[00484] (R)-7-((9-Bromononyl)oxy)-N-(1-(3-bromophenyl)ethyl)-6-methoxy-2-methylquinazolin-4-amine **68**. To a solution of (R)-9-(((1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonan-1-ol **67** (154 mg, 0.291 mmol) in THF (5 mL) at 0 °C were added CBr₄ (145 mg, 0.436 mmol), Ph₃P (115 mg, 0.436 mmol), and imidazole (107 mg, 0.582 mmol). After stirred at room temperature overnight, the mixture was filtered off and the filtrate was concentrated and the residue was purified by silica-gel column chromatography eluting with EtOAc/PE to give compound **68** (224 mg, crude), which was used directly in the next step without further purification. MS (ESI) *m/z*: 594.1 [M+H]⁺.

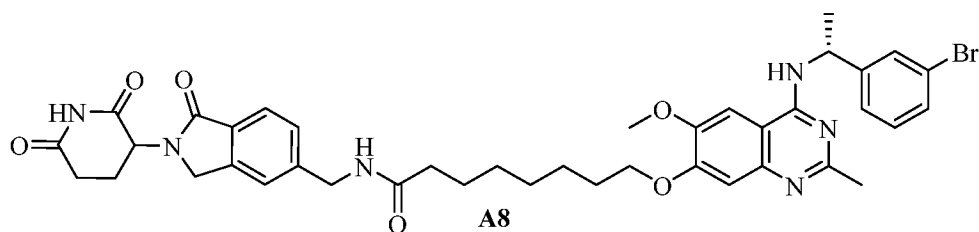
[00485] (2*S*,4*R*)-1-((*S*)-2-Acetamido-3,3-dimethylbutanoyl)-*N*-(2-((9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D12**. To a solution of compound **68** (224 mg, crude) in DMF (5 mL) at room temperature was added (2*R*,4*S*)-1-((*R*)-2-acetamido-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **69** (147 mg, 0.303 mmol), KI (63 mg, 0.379 mmol), and K₂CO₃ (104 mg, 0.758 mmol). After stirred at 50 °C overnight, the mixture was concentrated and the residue was purified by pre-HPLC to afford compound **D12** (31.5 mg) in 11% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.46 (t, *J* = 6.0 Hz, 1H), 8.19 (s, 0.32H), 7.99-7.75 (m, 2H), 7.67 (s, 1H), 7.63 (s, 1H), 7.47-7.39 (m, 3H), 7.30-7.26 (m, 1H), 7.00-2.98 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 5.61-5.58 (m, 1H), 5.13-5.12 (m, 1H), 4.54-4.44 (m, 2H), 4.35-4.29 (m, 2H), 4.17-4.11 (m, 1H), 4.07-4.02 (m, 4H), 3.90 (s, 3H), 3.64-3.61 (m, 2H), 2.45 (s, 3H), 2.33 (s, 3H), 1.88 (s, 3H), 1.77-1.73 (m, 4H), 1.57 (d, *J* = 7.6 Hz, 3H), 1.44-1.23 (m, 12H), 0.91 (s, 9H); MS (ESI) *m/z* = 1000.2 [M+H]⁺.

[00486] The following compounds were prepared similarly.

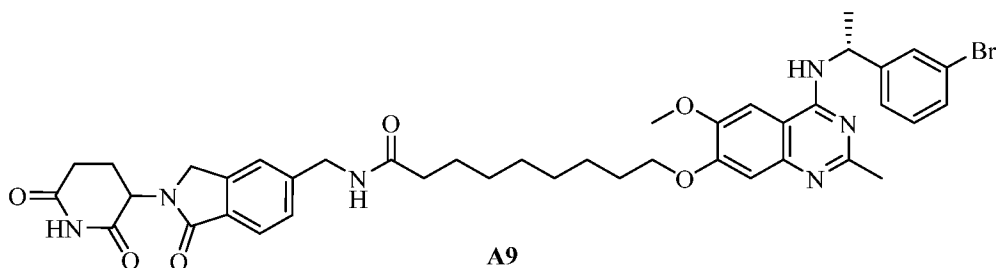
[00487] 8-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)methyl)octanamide **A7**: MS (ESI) *m/z*: 785.7 [M+1]⁺.



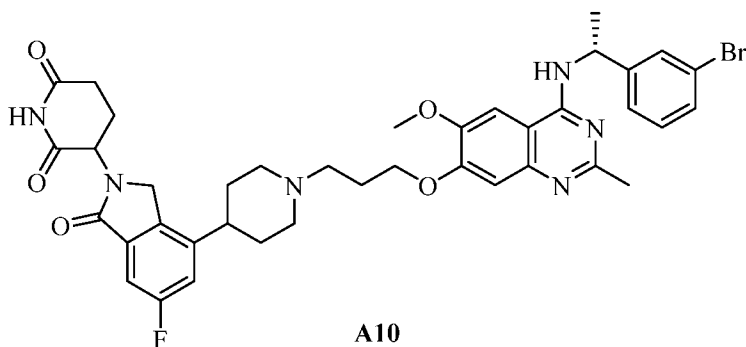
[00488] 8-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)octanamide **A8**: MS (ESI) *m/z*: 785.7 [M+1]⁺.



[00489] 9-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)nonanamide **A9**: MS (ESI) m/z : 799.7 $[M+1]^+$.

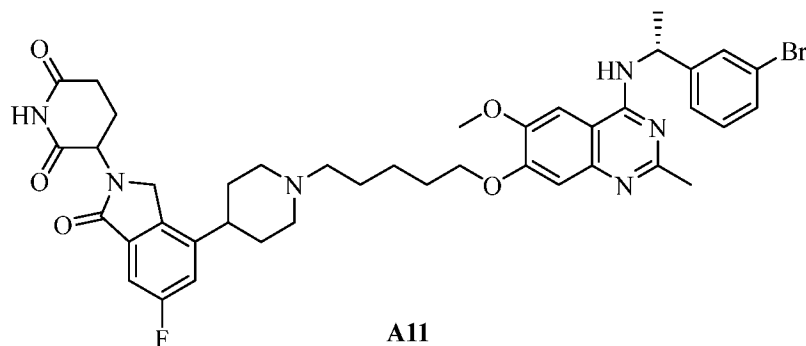


[00490] 3-(4-(1-(3-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)propyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A10**. ^1H NMR (400 MHz, DMSO- d_6) δ 14.27 (s, 1H), 11.05 (s, 1H), 9.73 (d, $J = 6.0$ Hz, 1H), 9.53 (s, 1H), 8.00 (s, 1H), 7.68 (s, 1H), 7.49 (d, $J = 7.6$ Hz, 2H), 7.45 (dd, $J = 2.0, 7.2$ Hz, 1H), 7.37-7.30 (m, 2H), 7.17 (s, 1H), 5.82-5.75 (m, 1H), 5.18 (dd, $J = 4.8$ Hz, 13.2 Hz, 1H), 4.57-4.36 (m, 2H), 4.26 (t, $J = 4.8$ Hz, 2H), 3.97 (s, 3H), 3.70 (d, $J = 10.8$ Hz, 2H), 3.13-2.89 (m, 5H), 2.67-2.65 (m, 1H), 2.59 (s, 3H), 2.35-2.29 (m, 3H), 2.08-1.89 (m, 6H), 1.66 (d, $J = 7.2$ Hz, 3H); MS (ESI) m/z : 774.3, 776.3 $[M+1, M+3]^+$.



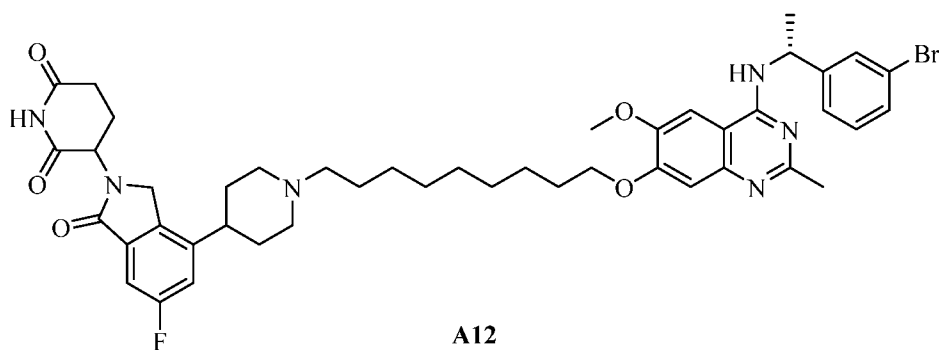
[00491] 3-(4-(1-(5-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione

A11. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.99 (s, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 7.68 (s, 1H), 7.63 (t, $J = 1.2$ Hz, 1H), 7.46-7.27 (m, 5H), 7.03 (s, 1H), 5.64-5.56 (m, 1H), 5.10 (dd, $J = 5.2$, 13.2 Hz, 1H), 4.53-4.32 (m, 2H), 4.08 (t, $J = 6.8$ Hz, 2H), 3.91 (s, 3H), 3.00-2.97 (m, 2H), 2.93-2.87 (m, 1H), 2.67-2.52 (m, 2H), 2.46-2.41 (m, 1H), 2.33-2.31 (m, 5H), 2.02-1.94 (m, 3H), 1.81-1.74 (m, 6H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.53-1.45 (m, 4H); MS (ESI) m/z : 801.3, 803.3 $[\text{M}+1, \text{M}+3]^+$.



[00492] 3-(4-(1-(9-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione

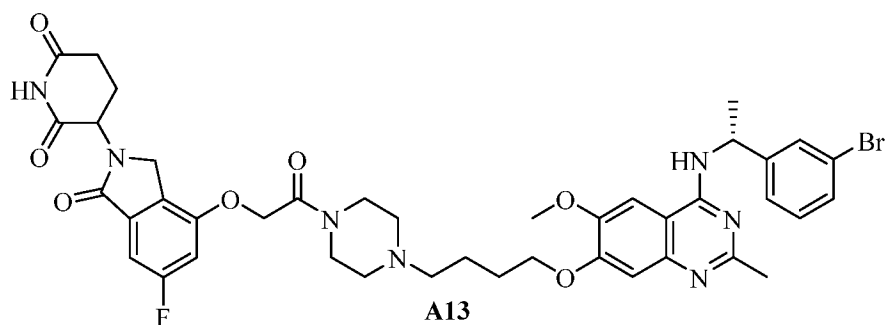
A12. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.01 (s, 1H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.46-7.27 (m, 4H), 7.01 (s, 1H), 5.60 (t, $J = 7.6$ Hz, 1H), 5.14 (dd, $J = 5.2$, 13.2 Hz, 1H), 4.52-4.31 (m, 2H), 4.06 (t, $J = 6.0$ Hz, 2H), 3.91 (s, 3H), 3.01-2.88 (m, 5H), 2.67-2.58 (m, 3H), 2.45-2.41 (m, 2H), 2.33 (s, 3H), 2.06-1.99 (m, 2H), 1.91-1.75 (m, 6H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.44-1.30 (m, 12H); MS (ESI) m/z : 857.4 $[\text{M}+\text{H}]^+$.



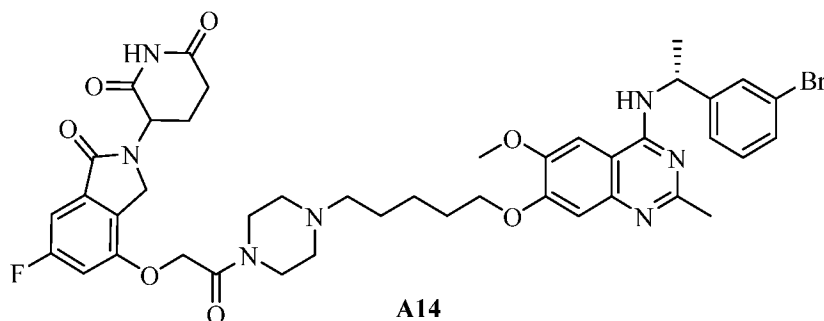
[00493] 3-(4-(2-(4-(4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione

A13. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.98 (s, 1H), 8.00 (d, $J = 7.6$ Hz, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.45-7.40 (m, 2H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.15-7.09 (m, 2H),

7.04 (s, 1H), 5.62-5.58 (m, 1H), 5.10 (dd, $J = 4.8, 13.2$ Hz, 1H), 5.04 (s, 2H), 4.39-4.22 (m, 2H), 4.10 (t, $J = 6.4$ Hz, 2H), 3.91 (s, 3H), 3.44-3.31 (m, 4H), 3.29-3.25 (m, 1H), 2.89-2.87 (m, 1H), 2.60-2.56 (m, 1H), 2.49-2.42 (m, 6H), 2.36 (s, 3H), 2.02-1.99 (m, 1H), 1.82-1.77 (m, 2H), 1.64-1.63 (m, 2H), 1.57 (d, $J = 7.2$ Hz, 3H); MS (ESI) m/z : 846.4 $[M+1]^+$.

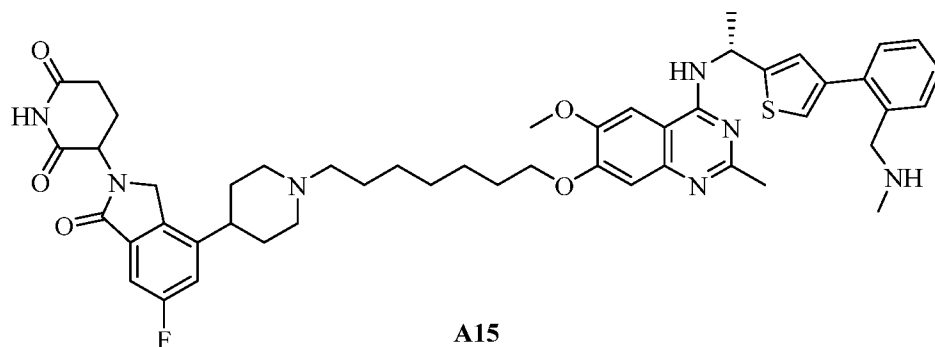


[00494] 3-(4-(2-(4-(5-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A14**. ^1H NMR (400 MHz, DMSO- d_6) δ 10.99 (s, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 7.67 (s, 1H), 7.64 (s, 1H), 7.63-7.39 (m, 2H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.15-7.09 (m, 2H), 7.02 (s, 1H), 5.60 (m, 1H), 5.10 (dd, $J = 5.2, 13.2$ Hz, 1H), 5.04 (s, 2H), 4.39-4.22 (m, 2H), 4.07 (t, $J = 6.4$ Hz, 2H), 3.91 (s, 3H), 3.43-3.31 (m, 4H), 2.94-2.86 (m, 1H), 2.60-2.57 (m, 1H), 2.49-2.42 (m, 3H), 2.40-2.30 (m, 7H), 2.07-1.90 (m, 1H), 1.81-1.76 (m, 2H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.52-1.44 (m, 4H); MS (ESI) m/z : 860.2, 862.2 $[M+1, M+3]^+$.

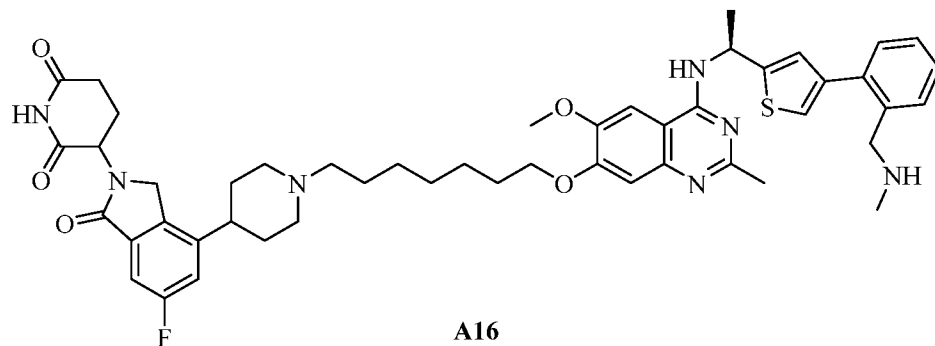


[00495] 3-(6-Fluoro-4-(1-(7-((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A15**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.04 (s, 1H), 9.88 (s, 1H), 9.48 (s, 1H), 8.90 (s, 2H), 7.93 (s, 1H), 7.61-7.59 (m, 1H), 7.51-7.22 (m, 8H), 6.11 (t, $J = 7.6$ Hz, 1H), 5.18 (dd, $J = 5.6, 13.6$ Hz, 1H), 4.56-4.35 (m, 2H), 4.16 (s, 4H), 3.93 (s, 3H), 3.61-3.58 (m, 3H), 3.08-2.96 (m, 7H), 2.64-2.63 (m, 4H), 2.35-2.32 (m, 1H), 2.06-1.98 (m, 5H),

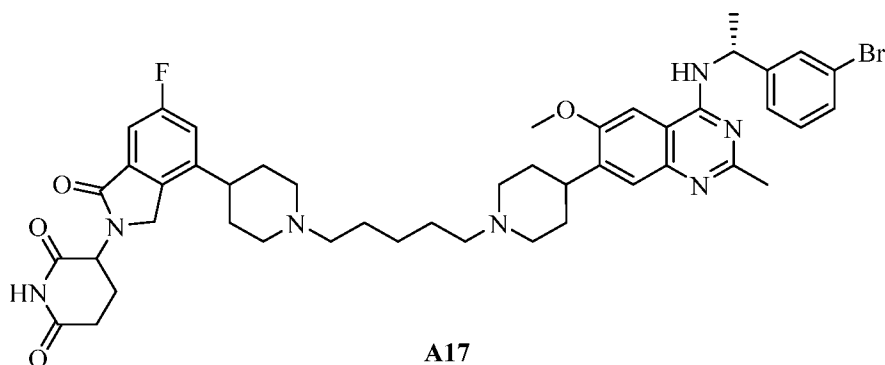
1.81-1.79 (m, 5H), 1.71-1.69 (m, 2H), 1.47-1.24 (m, 7H); MS (ESI) m/z : 438.9 $[1/2M+H]^+$.



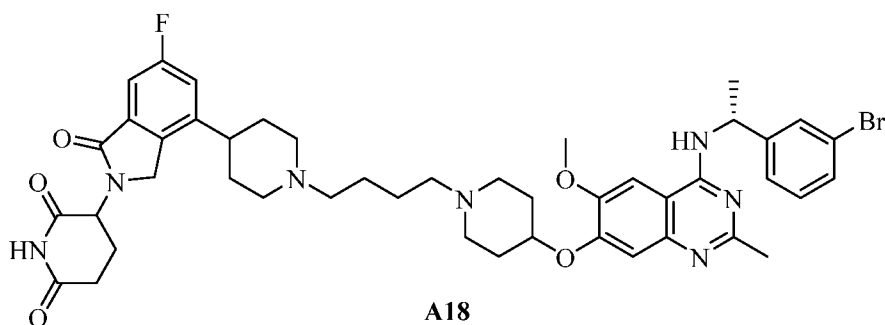
[00496] 3-(6-Fluoro-4-(1-(7-((6-methoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A16**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.13 (d, $J = 8.0$ Hz, 1H), 7.65 (s, 1H), 7.48-7.44 (m, 2H), 7.42 (d, $J = 10.8$ Hz, 1H), 7.35-7.27 (m, 5H), 7.04 (s, 1H), 5.97 (t, $J = 7.6$ Hz, 1H), 5.14 (dd, $J = 13.6, 5.6$ Hz, 1H), 4.53-4.32 (m, 2H), 4.08 (t, $J = 6.4$ Hz, 2H), 3.87 (s, 3H), 3.65 (d, $J = 9.2$ Hz, 2H), 2.99-2.96 (m, 2H), 2.67-2.62 (m, 3H), 2.42 (s, 3H), 2.33-2.31 (m, 3H), 2.27 (s, 3H), 2.03-1.98 (m, 4H), 1.79-1.71 (m, 10H), 1.46-1.38 (m, 4H), 1.35-1.24 (m, 3H); MS (ESI) m/z : 438.9 $[1/2M+H]^+$.



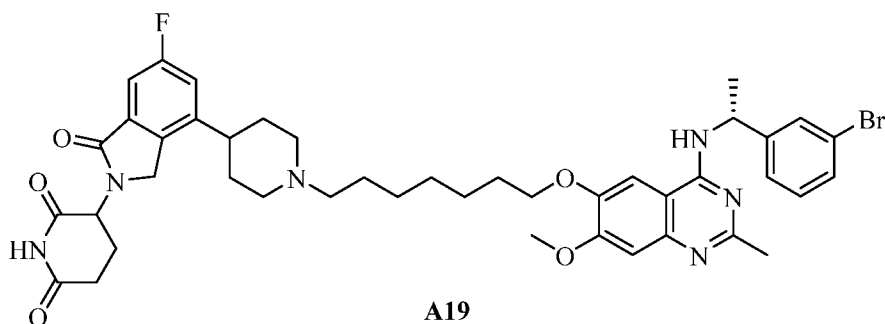
[00497] 3-(4-(1-(5-(4-(4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)piperidin-1-yl)pentyl)piperidin-4-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A17**; MS (ESI) m/z : 869.8 $[M+1]^+$.



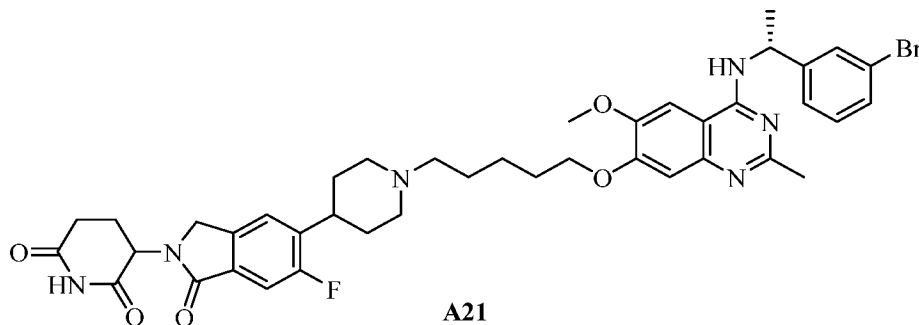
[00498] 3-(4-(1-(4-(4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)piperidin-1-yl)butyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A18**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.04 (s, 1H), 9.98-9.76 (m, 3H), 8.03-8.00 (m, 1H), 7.67 (s, 1H), 7.53-7.43 (m, 4H), 7.36-7.30 (m, 2H), 5.81-5.75 (m, 1H), 5.18 (dd, $J = 5.2, 13.6$ Hz, 1H), 4.93-4.76 (m, 1H), 4.56-4.35 (m, 2H), 4.03 (s, 3H), 3.69-3.59 (m, 4H), 3.14-2.90 (m, 10H), 2.65-2.61 (m, 1H), 2.57 (s, 3H), 2.44-2.29 (m, 3H), 2.17 (s, 2H), 2.05-1.95 (m, 5H), 1.82-1.74 (m, 4H), 1.66 (d, $J = 7.2$ Hz, 3H); MS (ESI) m/z : 870.3 $[\text{M}+1]^+$.



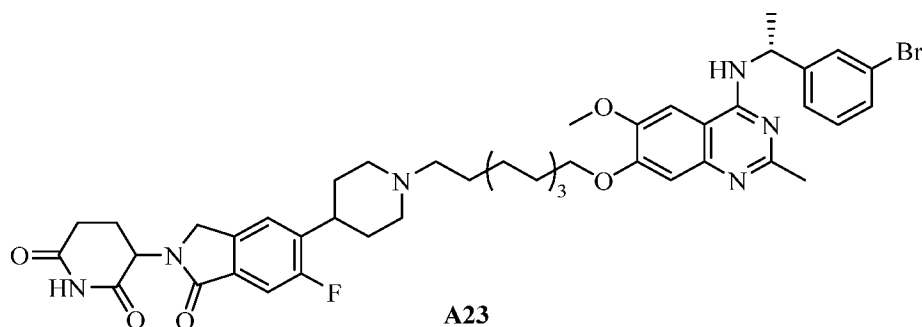
[00499] 3-(4-(1-(7-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-7-methoxy-2-methyl-quinazolin-6-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A19**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 10.95 (s, 1H), 9.70-8.63 (m, 1H), 7.76 (s, 1H), 7.57 (s, 1H), 7.39-7.33 (m, 3H), 7.21 (t, $J = 7.8$ Hz, 2H), 6.97 (s, 1H), 5.62-5.54 (m, 1H), 5.07 (dd, $J = 4.8, 12.8$ Hz, 1H), 4.47-4.25 (m, 2H), 4.04-4.03 (m, 2H), 3.81 (s, 3H), 3.45 (s, 2H), 2.96-2.87 (m, 5H), 2.56-2.51 (m, 2H), 2.34 (s, 3H), 2.26-2.23 (m, 1H), 1.96-1.87 (m, 5H), 1.75-1.72 (m, 2H), 1.61-1.55 (m, 2H), 1.52 (d, $J = 6.8$ Hz, 3H), 1.44-1.37 (m, 2H), 1.33-1.25 (m, 4H); MS (ESI) m/z : 829.3 $[\text{M}+1]^+$.



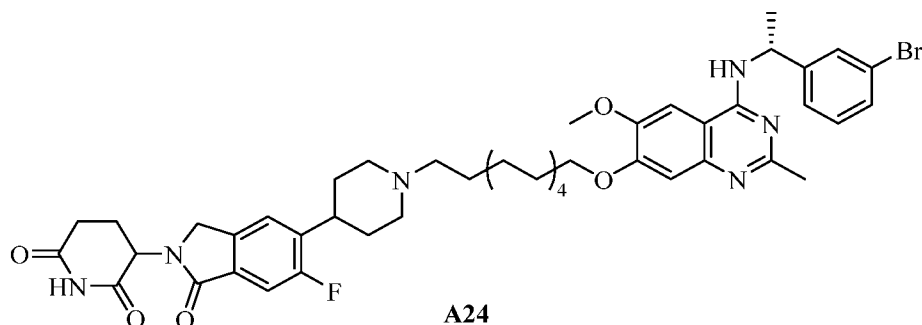
[00500] 3-(5-(1-(5-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)pentyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A21**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.98 (s, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 7.68 (s, 1H), 7.63 (t, $J = 1.6$ Hz, 1H), 7.61 (d, $J = 6.0$ Hz, 1H), 7.47-7.39 (m, 3H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.03 (s, 1H), 5.64-5.56 (m, 1H), 5.10 (dd, $J = 4.8, 13.2$ Hz, 1H), 4.43-4.26 (m, 2H), 4.08 (t, $J = 6.4$ Hz, 2H), 3.91 (s, 3H), 3.01-2.98 (m, 2H), 2.95-2.85 (m, 2H), 2.61-2.57 (m, 1H), 2.37-2.31 (m, 6H), 2.04-1.98 (m, 3H), 1.81-1.73 (m, 6H), 1.57 (d, $J = 6.8$ Hz, 3H), 1.54-1.45 (m, 4H) MS (ESI) m/z : 801.3, 803.3 [$\text{M}+1$, $\text{M}+3$] $^+$.



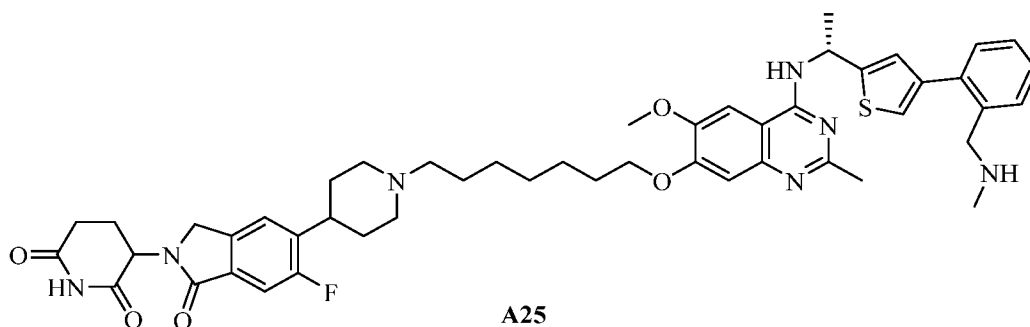
[00501] 3-(5-(1-(9-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)nonyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A23**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.98 (s, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 7.67 (s, 1H), 7.63 (t, $J = 1.6$ Hz, 1H), 7.60 (d, $J = 6.0$ Hz, 1H), 7.47-7.39 (m, 3H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.01 (s, 1H), 5.63-5.56 (m, 1H), 5.10 (dd, $J = 5.2, 13.2$ Hz, 1H), 4.43-4.26 (m, 2H), 4.06 (t, $J = 6.4$ Hz, 2H), 3.91 (s, 3H), 2.98-2.95 (m, 2H), 2.92-2.84 (m, 2H), 2.61-2.56 (m, 1H), 2.41-2.36 (m, 1H), 2.33 (s, 3H), 2.29-2.26 (m, 2H), 2.01-1.95 (m, 3H), 1.78-1.72 (m, 6H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.45-1.40 (m, 4H), 1.36-1.24 (m, 8H); MS (ESI) m/z : 857.3, 859.3 [$\text{M}+1$, $\text{M}+3$] $^+$.



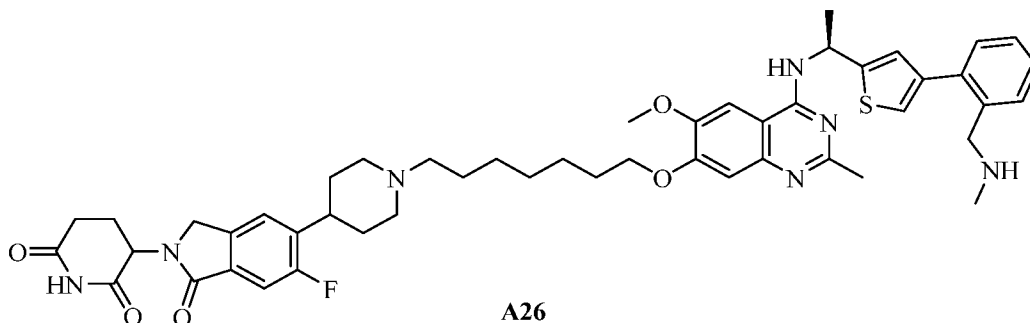
[00502] 3-(5-(1-(11-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)undecyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A24**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 14.26 (s, 1H), 10.99 (s, 1H), 9.84 (s, 2H), 8.06 (d, J = 5.6 Hz, 1H), 7.69 (s, 1H), 7.54-7.47 (m, 4H), 7.34 (t, J = 8.0 Hz, 1H), 7.16 (d, J = 4.4 Hz, 1H), 5.81-5.74 (m, 1H), 5.11 (dd, J = 5.2, 13.6 Hz, 1H), 4.48-4.30 (m, 2H), 4.13 (t, J = 6.4 Hz, 2H), 3.97 (s, 3H), 3.59-3.56 (m, 2H), 3.14-3.04 (m, 2H), 2.96-2.86 (m, 2H), 2.67-2.62 (m, 2H), 2.57 (s, 3H), 2.41-2.36 (m, 1H), 2.08-1.98 (m, 6H), 1.84-1.77 (m, 2H), 1.67 (d, J = 7.2 Hz, 3H), 1.47-1.40 (m, 2H), 1.35-1.30 (m, 14H); MS (ESI) m/z : 886.5 $[\text{M}+1]^+$.



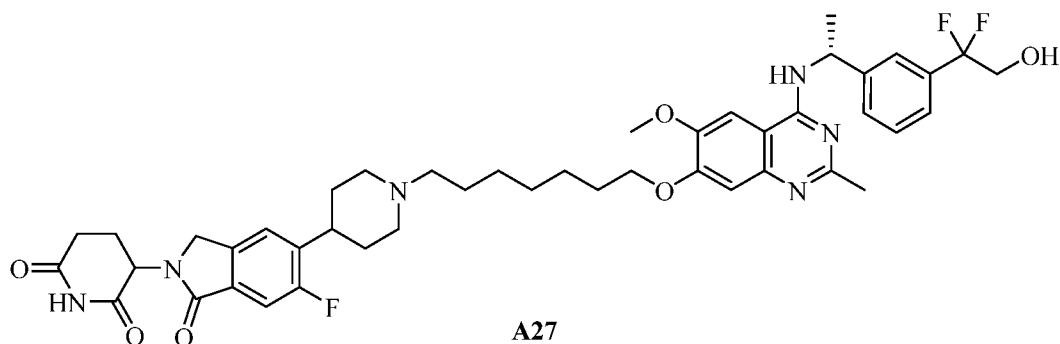
[00503] 3-(6-Fluoro-5-(1-(7-((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A25**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.99 (s, 1H), 9.89 (s, 1H), 9.37 (s, 1H), 8.87 (s, 2H), 7.94 (s, 1H), 7.61-7.59 (m, 1H), 7.55-7.37 (m, 6H), 7.28 (s, 1H), 7.21 (s, 1H), 6.11 (t, J = 7.6 Hz, 1H), 5.13 (dd, J = 13.6, 5.6 Hz, 1H), 4.47-4.18 (m, 2H), 4.17-4.14 (m, 4H), 3.93 (s, 3H), 3.62-3.58 (m, 2H), 3.22-3.20 (m, 1H), 3.16-3.09 (m, 3H), 2.91-2.88 (m, 1H), 2.65 (s, 3H), 2.55-2.52 (m, 4H), 2.41-2.33 (m, 1H), 2.02-1.99 (m, 5H), 1.85-1.79 (m, 5H), 1.71-1.69 (m, 2H), 1.47-1.38 (m, 7H); MS (ESI) m/z : 438.8 $[\text{1/2M}+\text{H}]^+$.



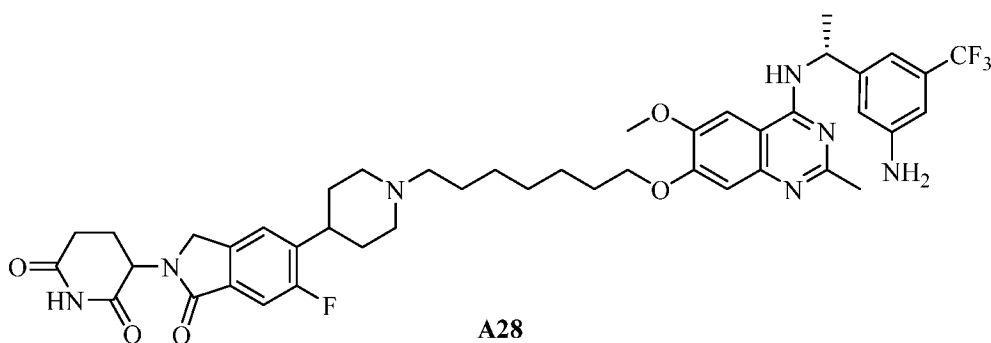
[00504] 3-(6-Fluoro-5-(1-(7-((6-methoxy-2-methyl-4-(((S)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A26**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.00 (s, 1H), 9.93 (d, $J = 6.4$ Hz, 1H), 9.51 (s, 1H), 8.94 (s, 2H), 7.95 (s, 1H), 7.62-7.60 (m, 1H), 7.53-7.26 (m, 8H), 6.11 (t, $J = 7.6$ Hz, 1H), 5.13 (dd, $J = 13.6, 5.6$ Hz, 1H), 4.48-4.30 (m, 2H), 4.17-4.15 (m, 4H), 3.93 (s, 3H), 3.627-3.62 (m, 2H), 3.24-3.20 (m, 1H), 3.13-3.09 (m, 3H), 2.95-2.87 (m, 1H), 2.65 (s, 3H), 2.62-2.52 (m, 4H), 2.41-2.33 (m, 1H), 2.02-2.00 (m, 5H), 1.85-1.73 (m, 5H), 1.70-1.45 (m, 2H), 1.43-1.38 (m, 7H); MS (ESI) m/z : 438.8 $[1/2\text{M}+\text{H}]^+$.



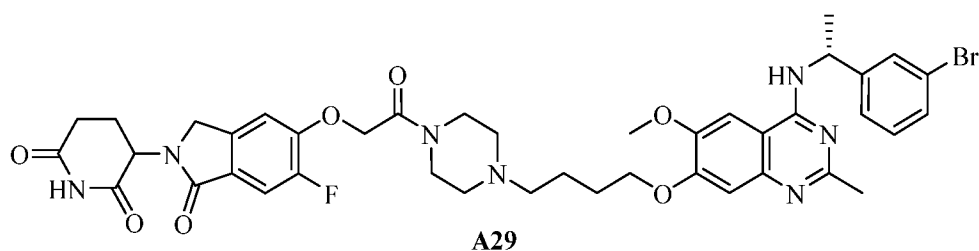
[00505] 3-(5-(1-(7-((4-(((R)-1-(3-(1,1-Difluoro-2-hydroxyethyl)phenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A27**. ^1H NMR (400 MHz, DMSO- d_6) δ 10.98 (s, 1H), 8.01 (d, $J = 8.0$ Hz, 1H), 7.68 (s, 1H), 7.63-7.56 (m, 3H), 7.47-7.41 (m, 2H), 7.37-7.35 (m, 1H), 7.01 (s, 1H), 5.66 (t, $J = 7.6$ Hz, 1H), 5.10 (dd, $J = 5.2, 13.2$ Hz, 1H), 4.43-4.26 (m, 2H), 4.07 (t, $J = 6.0$ Hz, 2H), 3.91 (s, 3H), 3.82 (t, $J = 14.4$ Hz, 2H), 3.04 ($J = 11.2$ Hz, 2H), 2.93-2.87 (m, 2H), 2.67-2.57 (m, 1H), 2.41-2.37 (m, 3H), 2.34 (s, 3H), 2.12 (s, 2H), 2.03-1.99 (m, 1H), 1.79-1.73 (m, 6H), 1.60 (d, $J = 7.2$ Hz, 3H), 1.48-1.45 (m, 4H), 1.37-1.32 (m, 4H); MS (ESI) m/z : 831.2 $[\text{M}+1]^+$.



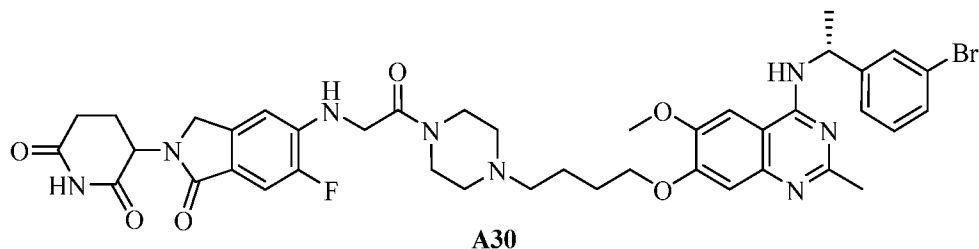
[00506] 3-(5-(1-(7-((4-(((*R*)-1-(3-Amino-5-(trifluoromethyl)phenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A28**. MS (ESI) m/z : 834.5 $[M+1]^+$.



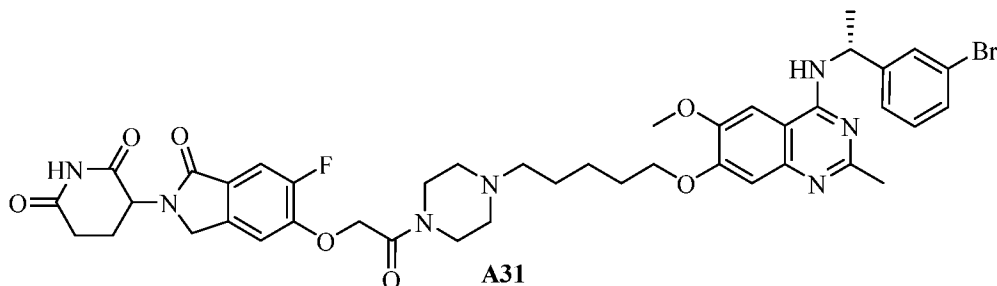
[00507] 3-(5-(2-(4-(4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A29**. ^1H NMR (400 MHz, DMSO- d_6) δ 14.50 (s, 1H), 10.97 (s, 1H), 10.83 (s, 1H), 9.96 (s, 1H), 8.14 (s, 1H), 7.71 (s, 1H), 7.56-7.47 (m, 3H), 7.38-7.32 (m, 2H), 7.22 (s, 1H), 5.76 (t, $J = 7.2$ Hz, 1H), 5.14-5.06 (m, 3H), 4.40-4.19 (m, 4H), 3.99 (s, 3H), 3.63-3.48 (m, 4H), 3.22-3.18 (m, 2H), 2.93-2.86 (m, 1H), 2.63-2.60 (m, 1H), 2.58 (s, 3H), 2.43-2.31 (m, 2H), 2.02-1.95 (m, 1H), 1.90 (s, 4H), 1.68 (d, $J = 6.8$ Hz, 3H), 1.23 (s, 2H); MS (ESI) m/z : 846.3, 848.3 $[M+1, M+3]^+$.



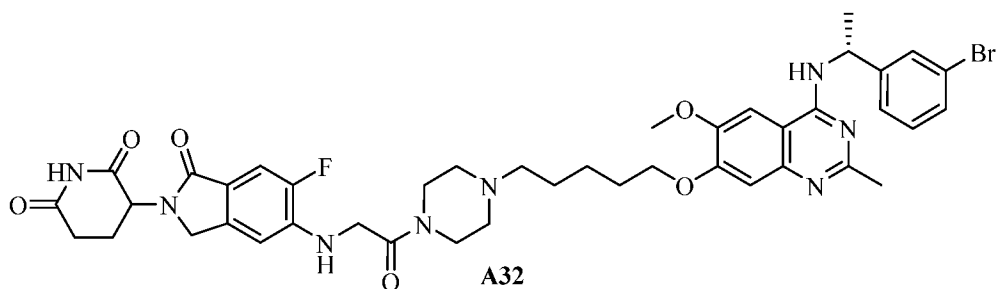
[00508] 3-(5-((2-(4-(4-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A30**; MS (ESI) m/z : 845.0 $[M+1]^+$.



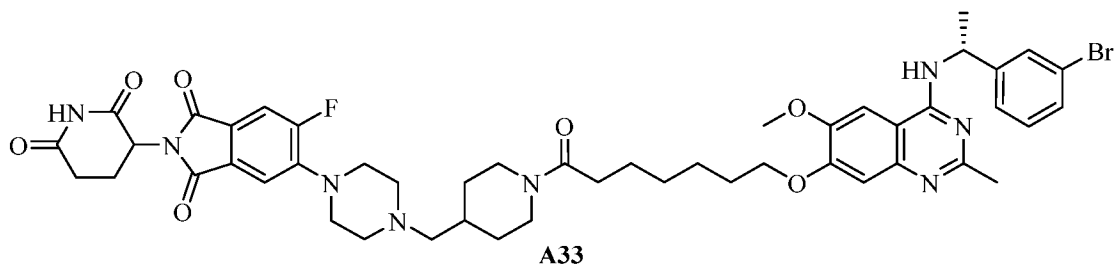
[00509] 3-(5-(2-(4-(5-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A31**. ^1H NMR (400 MHz, DMSO- d_6) δ 10.98 (s, 1H), 8.01 (d, $J = 7.6$ Hz, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.54 (d, $J = 10.0$ Hz, 1H), 7.46-7.40 (m, 2H), 7.32-7.29 (m, 2H), 7.02 (s, 1H), 5.63-5.56 (m, 1H), 5.11-5.06 (m, 3H), 4.45-4.27 (m, 2H), 4.08 (t, $J = 6.4$ Hz, 2H), 3.91 (s, 3H), 3.75-3.64 (m, 4H), 2.95-2.86 (m, 1H), 2.61-2.57 (m, 1H), 2.42-2.37 (m, 3H), 2.33-2.30 (m, 8H), 2.01-1.97 (m, 1H), 1.83-1.74 (m, 2H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.52-1.45 (m, 4H); MS (ESI) m/z : 860.3 $[M+1]^+$.



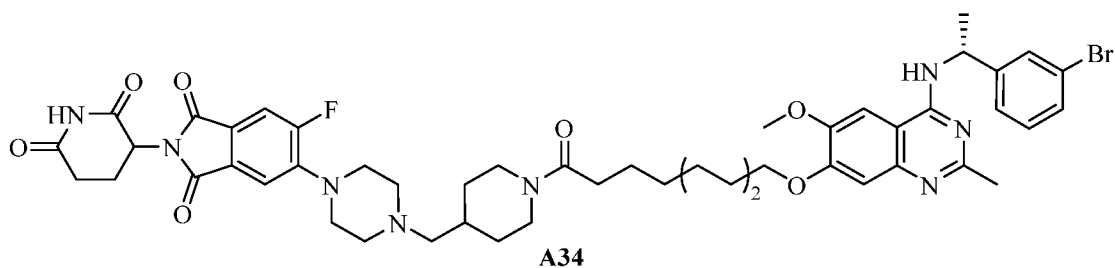
[00510] 3-(5-((2-(4-(5-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A32**; MS (ESI) m/z : 860.8 $[M+1]^+$.



[00511] 5-(4-((1-(7-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione **A33**. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 11.10 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.73-7.63 (m, 3H), 7.44-7.39 (m, 3H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 5.64-5.56 (m, 1H), 5.10 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.36 (d, *J* = 11.2 Hz, 1H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.92 (s, 3H), 3.84 (d, *J* = 13.6 Hz, 1H), 3.23-3.19 (m, 6H), 3.02-2.84 (m, 4H), 2.62-2.51 (m, 3H), 2.35 (s, 3H), 2.31-2.27 (m, 2H), 2.17-2.16 (m, 2H), 2.05-2.02 (m, 1H), 1.78-1.68 (m, 5H), 1.58 (d, *J* = 6.8 Hz, 3H), 1.53-1.35 (m, 6H), 1.04-0.86 (m, 2H); MS (ESI) *m/z*: 955.9 [M+1]⁺.

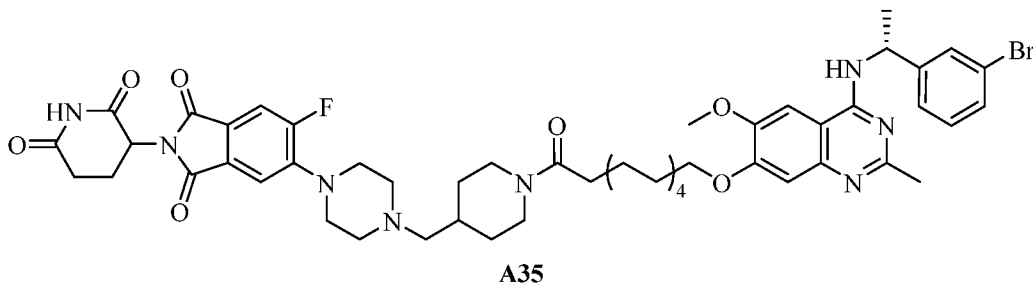


[00512] 5-(4-((1-(9-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione **A34**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.00 (s, 1H), 8.13 (s, 1H), 8.03 (s, 1H), 7.73-7.63 (m, 3H), 7.45-7.39 (m, 3H), 7.30-7.26 (m, 1H), 7.00 (s, 1H), 5.62-5.59 (m, 1H), 5.10 (dd, *J* = 5.6, 12.8 Hz, 1H), 4.37-4.34 (m, 1H), 4.06 (t, *J* = 6.4 Hz, 2H), 3.91 (s, 3H), 3.84-3.81 (m, 1H), 3.31-3.22 (m, 8H), 2.93-2.85 (m, 2H), 2.61-2.53 (m, 2H), 2.50-2.49 (m, 1H), 2.34 (s, 3H), 2.27 (t, *J* = 7.2 Hz, 2H), 2.17-2.16 (m, 2H), 2.04-2.00 (m, 1H), 1.78-1.67 (m, 5H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.50-1.23 (m, 12H); MS (ESI) *m/z*: 983.3 [M+1]⁺.

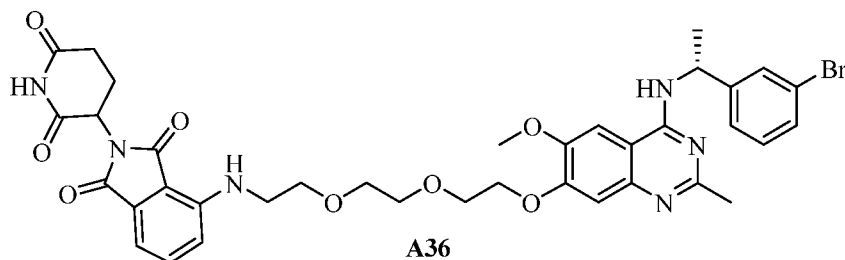


[00513] 5-(4-((1-(11-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecanoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione **A35**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.10 (s, 1H), 8.14 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.73-7.68 (m, 2H), 7.63 (s, 1H), 7.46-7.40 (m, 3H), 7.29 (t, *J* = 8.0

Hz, 1H), 7.01(s, 1H), 5.62-5.58 (m, 1H), 5.10 (dd, $J = 5.6, 13.2$ Hz, 1H), 4.36 (d, $J = 12.8$ Hz, 1H), 4.06 (t, $J = 6.4$ Hz, 1H), 3.82 (d, $J = 13.2$ Hz, 1H), 3.35-3.23 (m, 8H), 2.99-2.85 (m, 3H), 2.62-2.56 (m, 2H), 2.34 (s, 3H), 2.26 (t, $J = 6.8$ Hz, 2H), 2.17 (d, $J = 6.8$ Hz, 2H), 2.05-1.99 (m, 1H), 1.78-1.68 (m, 4H), 1.57(d, $J = 7.2$ Hz, 3H), 1.47-1.40 (m, 4H), 1.33-1.24 (m, 12H); MS (ESI) m/z : 1011.1 $[M+1]^+$.

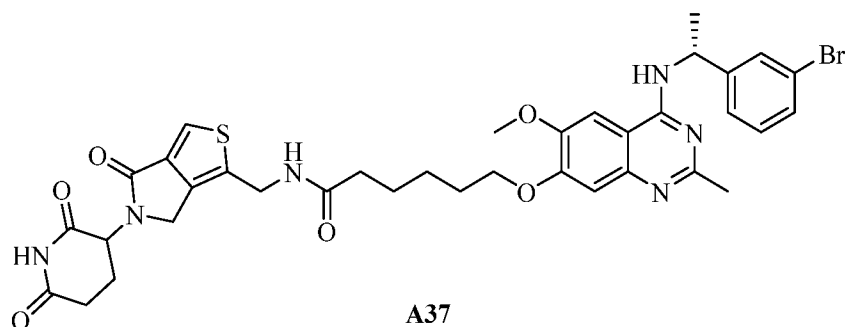


[00514] 4-((2-(2-(2-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione **A36**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.17 (s, 1H), 7.99 (d, $J = 7.6$ Hz, 1H), 7.65 (d, $J = 8.4$ Hz, 2H), 7.54 (dd, $J = 7.6, 16.0$ Hz, 1H), 7.46-7.40 (m, 2H), 7.31-7.27 (m, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.10-6.97 (m, 2H), 6.58 (t, $J = 5.8$ Hz, 1H), 5.60 (t, $J = 7.4$ Hz, 1H), 5.04 (dd, $J = 5.2, 12.8$ Hz, 1H), 4.18-4.16 (m, 2H), 3.89 (s, 3H), 3.82-3.80 (m, 2H), 3.65-3.60 (m, 6H), 3.47-3.43 (m, 2H), 2.87-2.81 (m, 1H), 2.59-2.54 (m, 2H), 2.33 (s, 3H), 2.03- 1.97 (m, 1H), 1.58 (d, $J = 7.2$ Hz, 3H); MS (ESI) m/z : 775.3 $[M+1]^+$.

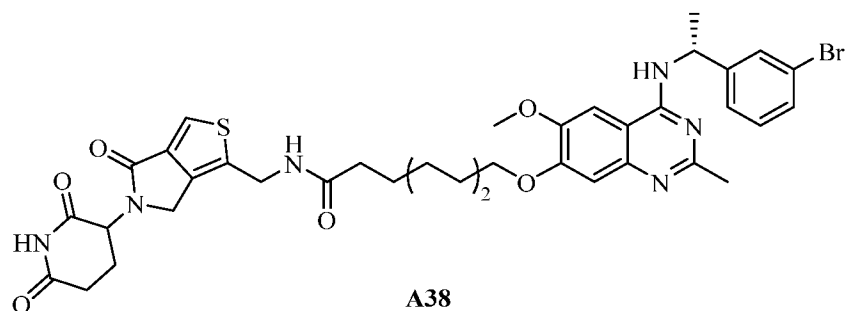


[00515] 6-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methyl)-hexanamide **A37**. ^1H NMR (400 MHz, DMSO- d_6) δ 10.99 (s, 1H), 8.48 (t, $J = 5.9$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.85 (s, 1H), 7.65 (d, $J = 16.7$ Hz, 2H), 7.43 (dd, $J = 16.0, 8.2$ Hz, 2H), 7.29 (t, $J = 7.8$ Hz, 1H), 7.01 (s, 1H), 5.65-5.54 (m, 1H), 5.00 (dd, $J = 13.2, 5.0$ Hz, 1H), 4.39 (d, $J = 5.8$ Hz, 2H), 4.29-4.15 (m, 2H), 4.05 (t, $J = 6.4$ Hz, 2H), 3.90 (s, 3H), 2.92-2.83 (m, 2H), 2.60-

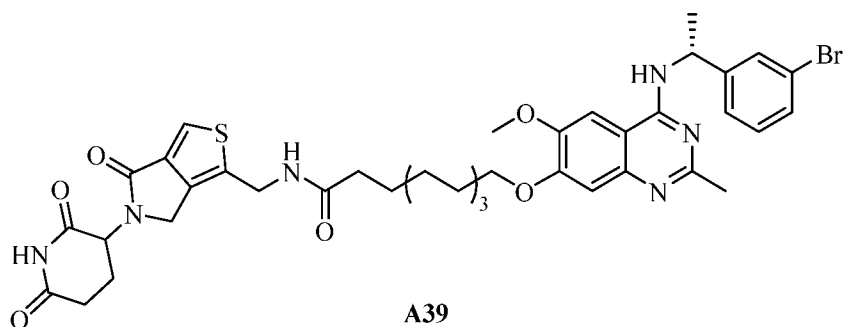
2.55 (m, 1H), 2.38-2.29 (m, 4H), 2.15 (t, $J = 7.6$ Hz, 2H), 2.03-1.96 (m, 2H), 1.80-1.73 (m, 2H), 1.63-1.54 (m, 5H), 1.48-1.37 (m, 2H), 1.28-1.23 (m, 2H); MS (ESI) m/z : 763.0 $[M+1]^+$.



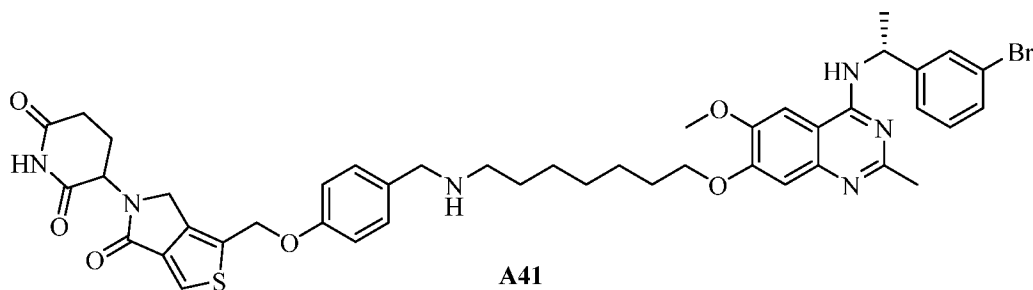
[00516] 8-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methyl)-octanamide **A38**: MS (ESI) m/z : 791.7 $[M+1]^+$.



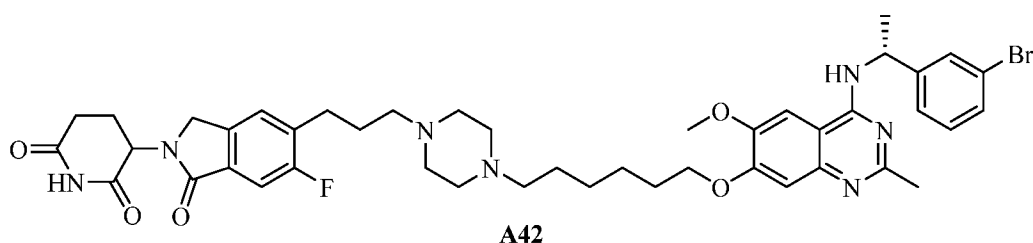
[00517] 10-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)-methyl)decanamide **A39**. ^1H NMR (DMSO- d_6 , 400 MHz) δ 10.97 (s, 1H), 8.44 (t, $J = 6.0$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.85 (s, 1H), 7.67 (d, $J = 16.8$ Hz, 2H), 7.43 (dd, $J = 14.8, 8.0$ Hz, 2H), 7.28 (t, $J = 8.0$ Hz, 1H), 7.00 (s, 1H), 5.62-5.58 (m, 1H), 5.02 (dd, $J = 13.6, 5.2$ Hz, 1H), 4.37 (d, $J = 5.6$ Hz, 2H), 4.29-4.14 (m, 2H), 4.06 (t, $J = 6.4$ Hz, 2H), 3.90 (s, 3H), 2.88-2.85 (m, 1H), 2.60-2.55 (m, 1H), 2.33-2.28 (m, 4H), 2.10 (t, $J = 7.6$ Hz, 2H), 2.00-1.96 (m, 1H), 1.77-1.73 (m, 2H), 1.58 (d, $J = 7.2$ Hz, 3H), 1.52-1.37 (m, 4H), 1.31-1.25 (m, 8H); MS (ESI) m/z : 819.0 $[M+1]^+$.



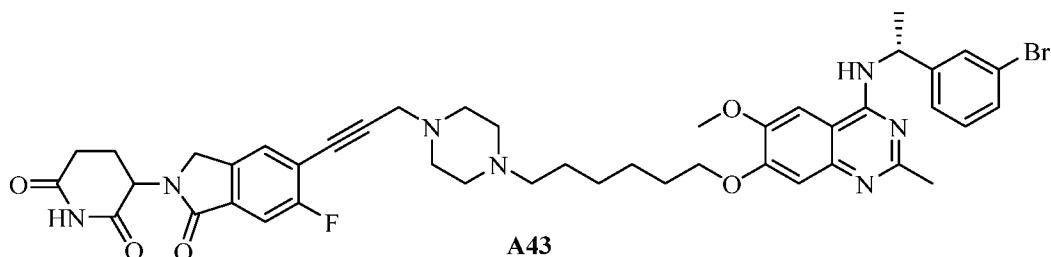
[00518] 3-(1-((4-(((7-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)amino)methyl)phenoxy)methyl)-4-oxo-4*H*-thieno[3,4-*c*]pyrrol-5(6*H*)-yl)piperidine-2,6-dione **A41**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.97 (s, 1H), 9.71 (d, *J* = 7.2 Hz, 1H), 8.73 (s, 2H), 8.03 (s, 1H), 7.97 (s, 1H), 7.68 (s, 1H), 7.50-7.48 (m, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.17 (s, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 5.81-5.74 (m, 1H), 5.35 (s, 2H), 5.02 (dd, *J* = 4.8, 13.2 Hz, 1H), 4.39-4.21 (m, 2H), 4.14 (t, *J* = 6.0 Hz, 2H), 4.08 (t, *J* = 4.4 Hz, 2H), 3.96 (s, 3H), 2.89-2.85 (m, 3H), 2.61-2.58 (m, 1H), 2.57 (s, 3H), 2.39-2.28 (m, 1H), 2.09-1.97 (m, 1H), 1.83-1.79 (m, 2H), 1.66 (d, *J* = 7.2 Hz, 3H), 1.62-1.57 (m, 2H), 1.45-1.42 (m, 2H), 1.34-1.33 (m, 4H); MS (ESI) *m/z*: 869.3, 871.3 [*M*+1, *M*+3]⁺.



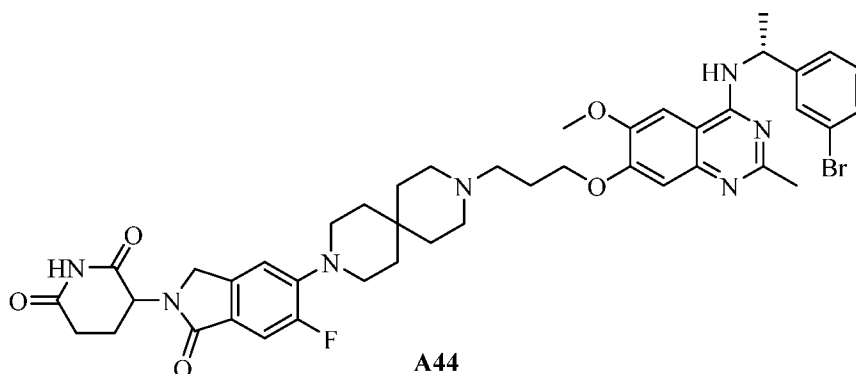
[00519] 3-(5-(3-(4-(6-(((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)piperazin-1-yl)propyl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A42**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.99 (s, 1H), 8.13 (s, 1H), 7.73 (s, 1H), 7.64 (s, 1H), 7.57 (d, *J* = 6.4 Hz, 1H), 7.49-7.41 (m, 3H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 5.62-5.59 (m, 1H), 5.11 (dd, *J* = 5.2, 13.6 Hz, 1H), 4.44-4.27 (m, 2H), 4.08 (t, *J* = 6.8 Hz, 2H), 3.92 (s, 3H), 2.96-2.87 (m, 3H), 2.76-2.58 (m, 5H), 2.36-2.30 (m, 12H), 2.01-1.99 (m, 1H), 1.80-1.77 (m, 4H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.47-1.35 (m, 6H); MS (ESI) *m/z*: 858.1, 860.1 [*M*+1, *M*+3]⁺.



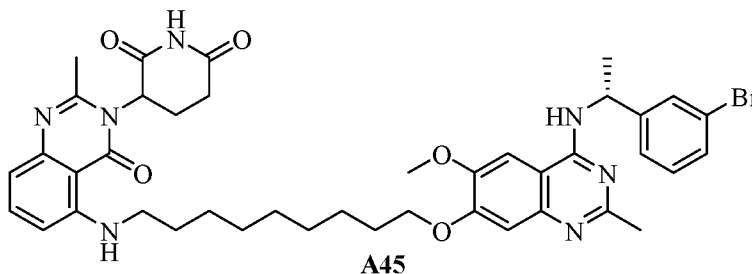
[00520] 3-(5-(3-(4-(6-(((4-(((R)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)hexyl)piperazin-1-yl)prop-1-yn-1-yl)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A43**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.01 (s, 1H), 8.01 (d, $J = 7.6$ Hz, 1H), 7.78 (d, $J = 6.0$ Hz, 1H), 7.69 (s, 1H), 7.64-7.60 (m, 2H), 7.46-7.40 (m, 2H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.01 (s, 1H), 5.62-5.59 (m, 1H), 5.11 (dd, $J = 5.2$ Hz, 13.6 Hz, 1H), 4.45-4.29 (m, 2H), 4.06 (t, $J = 6.0$ Hz, 2H), 3.91 (s, 3H), 3.61 (s, 2H), 2.94-2.87 (m, 1H), 2.67-2.58 (m, 8H), 2.44-2.38 (m, 4H), 2.35 (s, 3H), 2.03-2.01 (m, 1H), 1.78-1.75 (m, 2H), 1.58 (d, $J = 6.8$ Hz, 3H), 1.46-1.44 (m, 4H), 1.35-1.34 (m, 2H); MS (ESI) m/z : 854.1, 856.1 [$M+1$, $M+3$] $^+$ MS (ESI) m/z : 854.1 [$M+1$] $^+$.



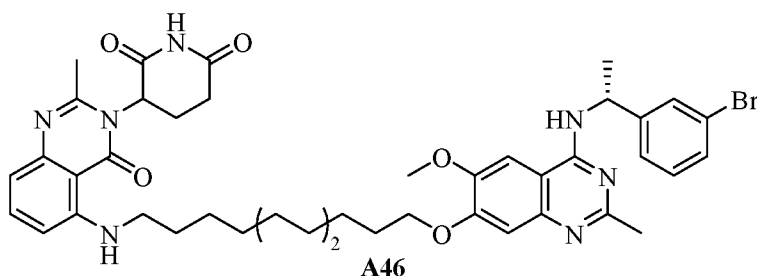
[00521] 3-(5-(9-(3-(((4-(((R)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)propyl)-3,9-diazaspiro[5.5]undecan-3-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A44**. ^1H NMR (400 MHz, DMSO- d_6) δ 10.98 (s, 1H), 8.17 (s, 1H), 8.01 (d, $J = 8.0$ Hz, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.46-7.38 (m, 2H), 7.30 (d, $J = 7.6$ Hz, 1H), 7.25 (t, $J = 7.2$ Hz, 1H), 7.03 (s, 1H), 5.63-5.56 (m, 1H), 5.07 (dd, $J = 4.8$, 12.8 Hz, 1H), 4.37-4.20 (m, 2H), 4.12 (t, $J = 6.0$ Hz, 2H), 3.91 (s, 3H), 3.50 (s, 2H), 3.08 (s, 5H), 2.94-2.85 (m, 1H), 2.60-2.59 (m, 5H), 2.38 (d, $J = 4.8$ Hz, 1H), 2.34 (s, 3H), 2.00-1.96 (m, 2H), 1.60-1.55 (m, 11H); MS (ESI) m/z : 843.5, 845.5 [$M+1$, $M+3$] $^+$.



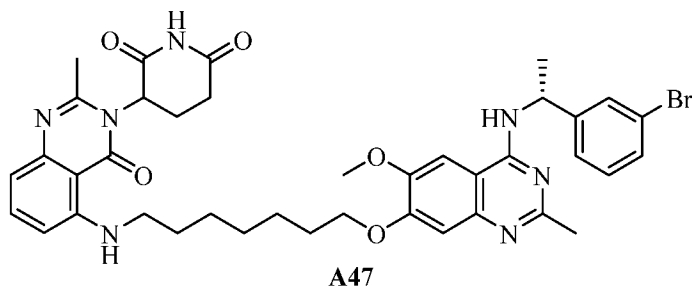
[00522] 3-(5-((9-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)nonyl)amino)-2-methyl-4-oxoquinazolin-3(4*H*)-yl)piperidine-2,6-dione **A45**. ^1H NMR (DMSO- d_6 , 400 MHz) δ 10.98 (s, 1H), 8.31 (t, $J = 5.2$ Hz, 1H), 8.29 (s, 1H), 7.98 (d, $J = 8.0$ Hz, 2H), 7.67 (s, 1H), 7.63 (s, 1H), 7.49-7.39 (m, 3H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.00 (s, 1H), 6.62 (d, $J = 7.6$ Hz, 1H), 6.48 (d, $J = 8.4$ Hz, 1H), 5.61-5.58 (m, 1H), 5.16 (dd, $J = 5.6$, 11.6 Hz, 1H), 4.05 (t, $J = 6.4$ Hz, 2H), 3.90 (s, 3H), 3.16-3.11 (m, 2H), 2.83-2.79 (m, 1H), 2.67-2.60 (m, 1H), 2.54 (s, 3H), 2.33 (s, 3H), 2.16-2.12 (m, 1H), 2.01-1.99 (m, 1H), 1.77-1.71 (m, 2H), 1.61-1.56 (m, 5H), 1.42-1.23 (m, 10H); MS (ESI) m/z : 798.2, 800.2 [$M+1$, $M+3$] $^+$.



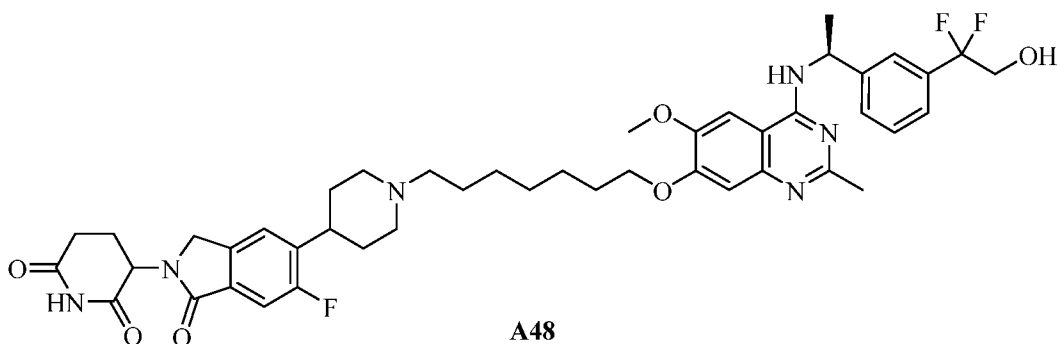
[00523] 3-(5-((11-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)undecyl)amino)-2-methyl-4-oxoquinazolin-3(4*H*)-yl)piperidine-2,6-dione **A46**. ^1H NMR (400 MHz, DMSO- d_6) δ 10.10 (s, 1H), 8.30 (t, $J = 4.4$ Hz, 1H), 8.14 (s, 0.44H), 8.02 (d, $J = 7.6$ Hz, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.49-7.40 (m, 3H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.00 (s, 1H), 6.63 (d, $J = 7.6$ Hz, 1H), 6.48 (d, $J = 8.4$ Hz, 1H), 5.64-5.57 (m, 1H), 5.17 (dd, $J = 5.6$, 11.6 Hz, 1H), 4.06 (t, $J = 6.0$ Hz, 2H), 3.91 (s, 3H), 3.16-3.11 (m, 2H), 2.88-2.79 (m, 1H), 2.59-2.55 (m, 4H), 2.34 (s, 3H), 2.18-2.02 (m, 1H), 2.03-1.95 (m, 1H), 1.79-1.72 (m, 2H), 1.64-1.54 (m, 5H), 1.14-1.40 (m, 2H), 1.31-1.24 (m, 12H); MS (ESI) m/z : 826.1, 828.1 [$M+1$, $M+3$] $^+$.



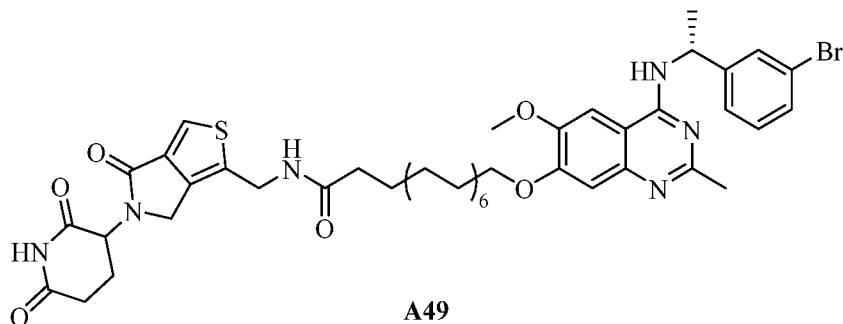
[00524] 3-(5-((7-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)amino)-2-methyl-4-oxoquinazolin-3(4*H*)-yl)piperidine-2,6-dione **A47**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.99 (s, 1H), 8.32 (t, $J = 5.2$ Hz, 1H), 8.19 (s, 0.57H), 7.97 (d, $J = 8.0$ Hz, 1H), 7.67 (s, 1H), 7.63 (t, $J = 1.6$ Hz, 1H), 7.49-7.40 (m, 3H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.01 (s, 1H), 6.63 (d, $J = 7.2$ Hz, 1H), 6.50 (d, $J = 8.4$ Hz, 1H), 5.60 (t, $J = 7.2$ Hz, 1H), 5.19-5.15 (m, 1H), 4.08-4.01 (m, 2H), 3.90 (s, 3H), 3.16 (q, $J = 6.8$ Hz, 2H), 2.86-2.78 (m, 1H), 2.68-2.58 (m, 1H), 2.55 (s, 3H), 2.34 (s, 3H), 2.28 (t, $J = 7.6$ Hz, 1H), 2.18-2.10 (m, 1H), 1.78-1.74 (m, 2H), 1.63-1.57 (m, 5H), 1.53-1.39 (m, 6H); MS (ESI) m/z : 770.0, 772.0 [$\text{M}+1$, $\text{M}+3$] $^+$.



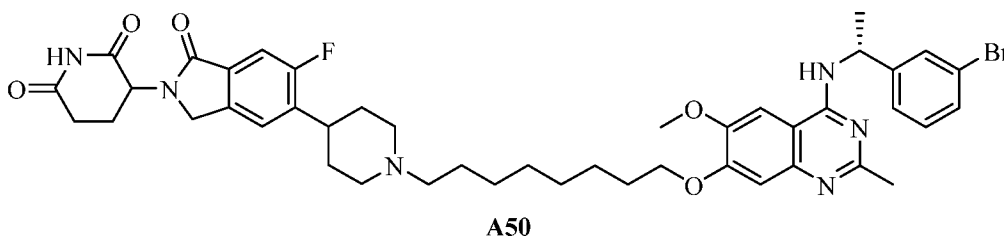
[00525] 3-(5-(1-(7-((4-(((*S*)-1-(3-(1,1-Difluoro-2-hydroxyethyl)phenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A48**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.98 (s, 1H), 8.02 (d, $J = 8.0$ Hz, 1H), 7.68 (s, 1H), 7.63-7.56 (m, 3H), 7.48-7.41 (m, 2H), 7.37-7.35 (m, 1H), 7.01 (s, 1H), 5.66 (t, $J = 7.6$ Hz, 1H), 5.10 (dd, $J = 5.2, 13.2$ Hz, 1H), 4.43-4.26 (m, 2H), 4.07 (t, $J = 6.0$ Hz, 2H), 3.91 (s, 3H), 3.82 (t, $J = 14.4$ Hz, 2H), 3.04 (d, $J = 11.2$ Hz, 2H), 2.93-2.87 (m, 2H), 2.67-2.57 (m, 1H), 2.41-2.37 (m, 3H), 2.34 (s, 3H), 2.12 (s, 2H), 2.03-1.99 (m, 1H), 1.79-1.73 (m, 6H), 1.60 (d, $J = 7.2$ Hz, 3H), 1.48-1.45 (m, 4H), 1.37-1.32 (m, 4H); MS (ESI) m/z : 831.2 [$\text{M}+1$] $^+$.



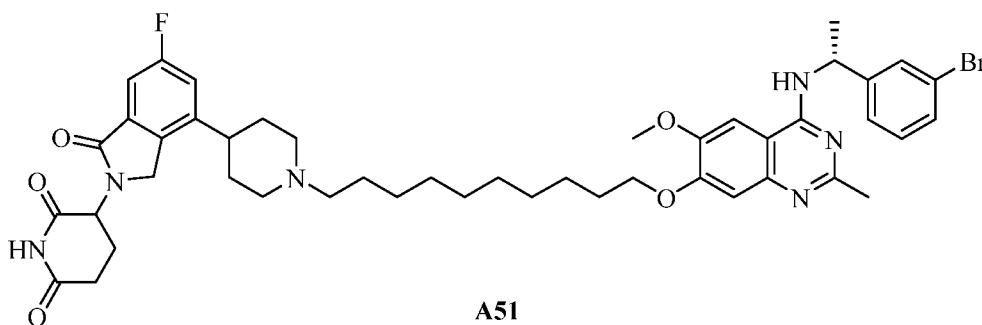
[00526] 16-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methyl)-hexadecanamide **A49**. ^1H NMR (400 MHz, DMSO- d_6) δ 10.10 (s, 1H), 8.43 (t, $J = 5.6$ Hz, 1H), 8.04 (s, 1H), 7.85 (s, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.44 (t, $J = 7.6$ Hz, 1H), 7.40 (s, 1H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.00 (s, 1H), 5.61 (t, $J = 6.8$ Hz, 1H), 5.01 (dd, $J = 4.8$ Hz, 13.2 Hz, 2H), 4.37 (d, $J = 6.0$ Hz, 1H), 4.28-4.14 (m, 2H), 4.06 (t, $J = 6.8$ Hz, 2H), 3.91 (s, 3H), 2.92-2.85 (m, 1H), 2.60-2.59 (m, 1H), 2.34 (s, 3H), 2.32-2.87 (m, 1H), 2.09 (t, $J = 7.2$ Hz, 2H), 2.01-1.97 (m, 1H), 1.77-1.72 (m, 2H), 1.43 (d, $J = 7.2$ Hz, 3H), 1.51-1.46 (m, 4H), 1.42-1.40 (m, 2H), 1.30-1.22 (m, 18H); MS (ESI) m/z : 903.5, 905.5 [$M+1$, $M+3$] $^+$.



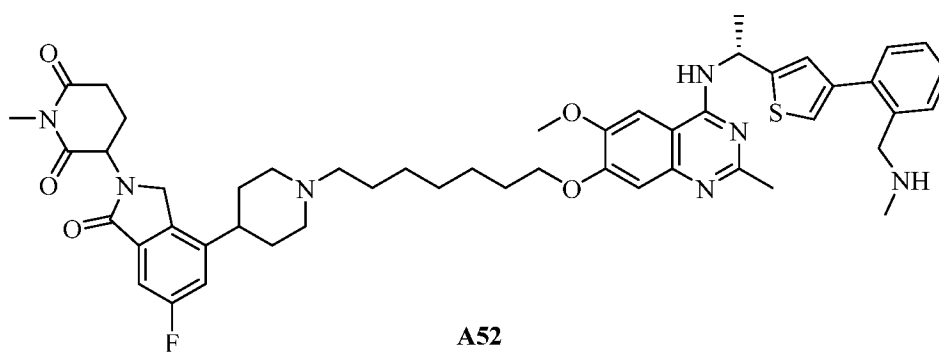
[00527] 3-(5-(1-(8-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A50**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.04 (s, 1H), 10.00 (s, 1H), 9.85 (s, 1H), 8.07 (s, 1H), 7.70 (s, 1H), 7.52-7.41 (m, 3H), 7.36-7.25 (m, 2H), 7.18 (s, 1H), 5.79-5.76 (m, 1H), 5.32 (t, $J = 4.8$ Hz, 1H), 5.17 (dd, $J = 4.8$, 12.8 Hz, 1H), 4.57-4.35 (m, 2H), 4.15 (t, $J = 6.0$ Hz, 1H), 3.98 (s, 3H), 3.58 (d, $J = 10.4$ Hz, 1H), 3.57-2.90 (m, 5H), 2.61-2.55 (m, 4H), 2.40-2.35 (m, 1H), 2.12-2.06 (m, 1H), 2.05-1.96 (m, 6H), 1.86-1.80 (m, 2H), 1.76-1.70 (m, 2H), 1.67 (d, $J = 7.2$ Hz, 3H), 1.51-1.44 (m, 2H), 1.38-1.31 (m, 6H); MS (ESI) m/z : 843.1 [$M+1$] $^+$.



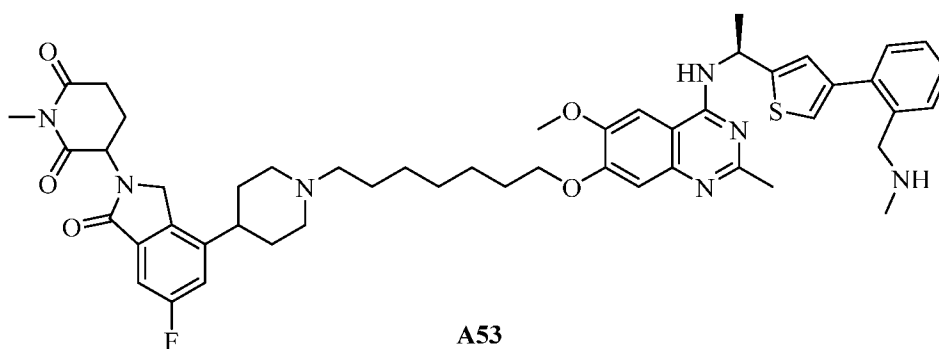
[00528] 3-(4-(1-(10-(((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A51**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 14.56 (s, 1H), 11.04 (s, 1H), 10.47 (s, 1H), 10.04 (s, 1H), 8.18 (s, 1H), 7.73 (s, 1H), 7.54-7.42 (m, 3H), 7.35-7.19 (m, 3H), 5.81-5.74 (m, 1H), 5.17 (dd, $J = 4.8, 13.2$ Hz, 1H), 4.58-4.35 (m, 2H), 4.13 (t, $J = 6.4$ Hz, 2H), 3.99 (s, 3H), 3.58-3.55 (m, 2H), 3.01-2.90 (m, 4H), 2.67-2.64 (m, 1H), 2.58 (s, 3H), 2.38-2.33 (m, 2H), 2.19-1.99 (m, 6H), 1.85-1.67 (m, 8H), 1.45-1.31 (m, 14H); MS (ESI) m/z : 871.5 $[\text{M}+1]^+$.



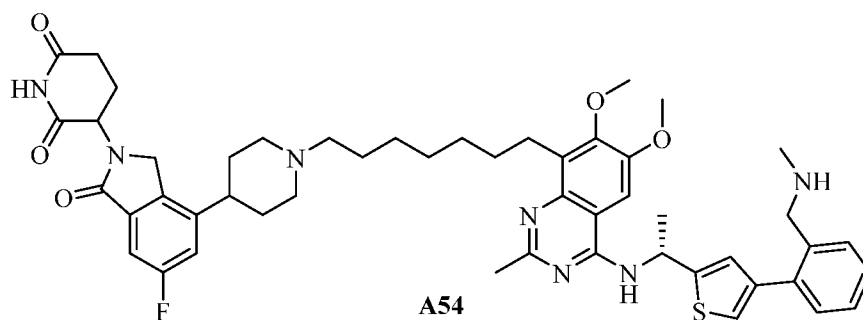
[00529] 3-(6-Fluoro-4-(1-(7-(((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)-1-methylpiperidine-2,6-dione **A52**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 14.73 (s, 1H), 10.41 (s, 1H), 10.19 (s, 1H), 9.23 (s, 2H), 8.14 (s, 1H), 7.75-7.65 (m, 1H), 7.55-7.51 (m, 1H), 7.48-7.42 (m, 3H), 7.39-7.36 (m, 1H), 7.34-7.28 (m, 3H), 6.15-6.07 (m, 1H), 5.24 (dd, $J = 4.8, 13.6$ Hz, 1H), 4.58-4.32 (m, 1H), 4.19-4.09 (m, 4H), 3.96 (s, 3H), 3.61-3.54 (m, 2H), 3.08-2.94 (m, 9H), 2.83-2.74 (m, 1H), 2.66 (s, 3H), 2.40-2.27 (m, 2H), 2.21-2.12 (m, 2H), 2.09-1.95 (m, 4H), 1.87-1.78 (m, 6H), 1.77-1.67 (m, 2H), 1.49-1.35 (m, 6H); MS (ESI) m/z : 890.2 $[\text{M}+1]^+$.



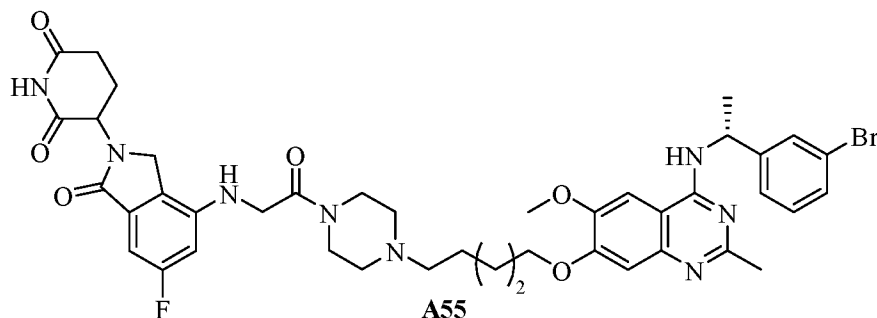
[00530] 3-(6-Fluoro-4-(1-(7-((6-methoxy-2-methyl-4-(((S)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)-1-methylpiperidine-2,6-dione **A53**. ^1H NMR (400 MHz, DMSO- d_6) δ 14.77 (s, 1H), 10.46 (s, 1H), 10.20 (s, 1H), 9.26 (s, 2H), 8.15 (s, 1H), 7.73-7.70 (m, 1H), 7.55-7.51 (m, 1H), 7.48-7.43 (m, 3H), 7.38-7.36 (m, 1H), 7.34-7.27 (m, 3H), 6.15-6.07 (m, 1H), 5.24 (dd, $J = 5.2, 13.6$ Hz, 1H), 4.58-4.35 (m, 2H), 4.16-4.08 (m, 4H), 3.96 (s, 3H), 3.59-3.56 (m, 2H), 3.10-2.94 (m, 9H), 2.81-2.76 (m, 1H), 2.66 (s, 3H), 2.42-2.31 (m, 2H), 2.21-2.13 (m, 2H), 2.09-1.96 (m, 4H), 1.89-1.78 (m, 6H), 1.77-1.69 (m, 2H), 1.51-1.36 (m, 6H); MS (ESI) m/z : 890.6 $[\text{M}+1]^+$.



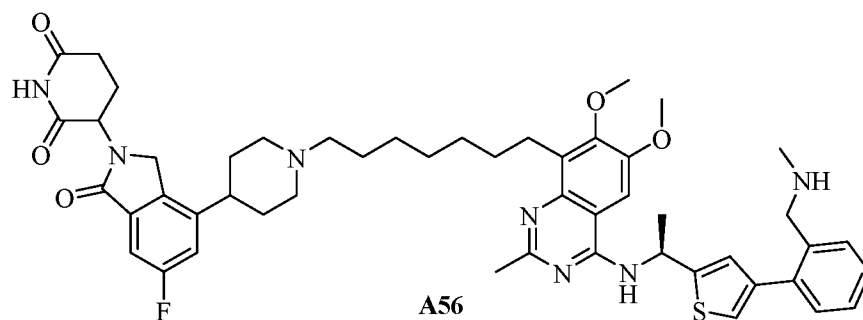
[00531] 3-(4-(1-(7-(6,7-Dimethoxy-2-methyl-4-(((R)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-8-yl)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A54**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.04 (s, 1H), 9.43 (s, 2H), 8.28 (s, 1H), 7.80-7.75 (m, 1H), 7.54 (s, 1H), 7.50-7.41 (m, 3H), 7.39-7.33 (m, 2H), 7.28 (dd, $J = 2.0$ Hz, 10.4 Hz, 1H), 6.20-6.10 (m, 1H), 5.17 (dd, $J = 5.2$ Hz, 13.2 Hz, 1H), 4.57 (d, $J = 17.2$ Hz, 1H), 4.38 (d, $J = 17.2$ Hz, 1H), 4.12 (t, $J = 6.0$ Hz, 2H), 4.02 (s, 3H), 3.92 (s, 3H), 3.56 (d, $J = 11.6$ Hz, 2H), 3.33-3.28 (m, 1H), 3.15-2.88 (m, 8H), 2.82 (s, 3H), 2.68-2.58 (m, 2H), 2.44-2.29 (m, 2H), 2.29-2.13 (m, 2H), 2.10-1.92 (m, 3H), 1.85 (d, $J = 6.4$ Hz, 3H), 1.80-1.65 (m, 2H), 1.55-1.27 (m, 8H); MS (ESI) m/z : 890.2 $[\text{M}+1]^+$.



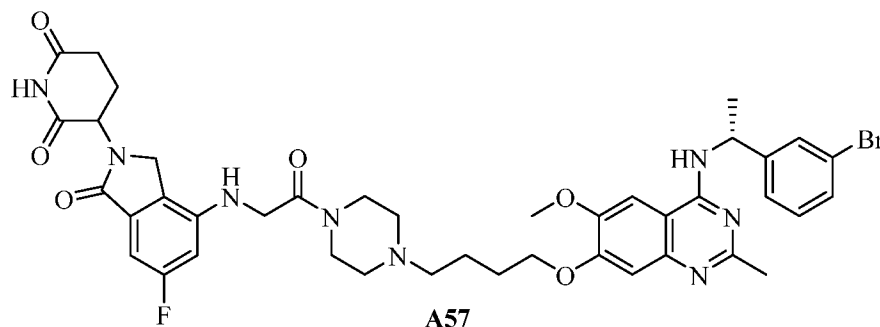
[00532] 3-(4-((2-(4-(5-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A55**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.00 (s, 1H), 8.01 (brs, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.46-7.40 (m, 2H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.02 (s, 1H), 6.67-6.59 (m, 2H), 5.89-5.88 (m, 1H), 5.62-5.57 (m, 1H), 5.10-5.08 (m, 1H), 4.30-4.13 (m, 2H), 4.12-4.04 (m, 4H), 3.91 (s, 3H), 3.52 (brs, 4H), 2.95-2.86 (m, 1H), 2.66-2.58 (m, 1H), 2.49-2.32 (m, 9H), 2.07-1.98 (m, 2H), 1.95-1.90 (m, 2H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.53-1.45 (m, 4H); MS (ESI) *m/z*: 859.3, 861.3 [*M*+1, *M*+3]⁺.



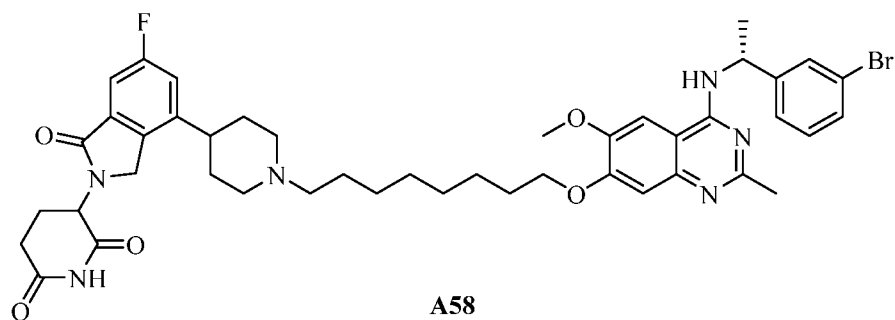
[00533] 3-(4-(1-(7-(6,7-Dimethoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-8-yl)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A56**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.04 (s, 1H), 9.34 (s, 2H), 8.25 (s, 1H), 7.78-7.68 (m, 1H), 7.54 (s, 1H), 7.49-7.42 (m, 3H), 7.49-7.32 (m, 2H), 7.28 (dd, *J* = 2.0 Hz, 10.4 Hz, 1H), 6.21-6.08 (m, 1H), 5.17 (dd, *J* = 4.8 Hz, 13.2 Hz, 1H), 4.56 (d, *J* = 17.2 Hz, 1H), 4.38 (d, *J* = 17.2 Hz, 1H), 4.12 (t, *J* = 5.6 Hz, 2H), 4.01 (s, 3H), 3.92 (s, 3H), 3.56 (d, *J* = 10.4 Hz, 2H), 3.28-3.18 (m, 1H), 3.15-2.88 (m, 8H), 2.82 (s, 3H), 2.70-2.57 (m, 1H), 2.43-2.10 (m, 5H), 2.08-1.92 (m, 3H), 1.84 (d, *J* = 5.6 Hz, 3H), 1.79-1.64 (m, 2H), 1.55-1.26 (m, 8H); MS (ESI) *m/z*: 890.2 [*M*+1]⁺.



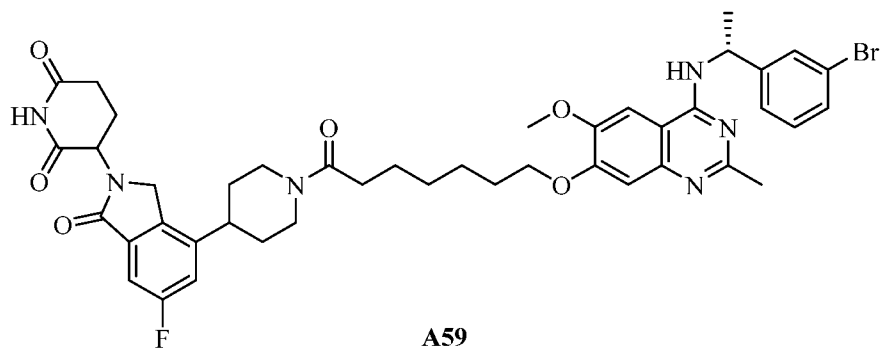
[00534] 3-(4-((2-(4-(4-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A57**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.00 (s, 1H), 8.06 (brs, 1H), 7.69 (s, 1H), 7.63 (s, 1H), 7.46-7.40 (m, 2H), 7.29 (t, $J = 8.4$ Hz, 1H), 7.05 (s, 1H), 6.69-6.60 (m, 2H), 5.90 (d, $J = 4.8$ Hz, 1H), 5.61 (t, $J = 7.6$ Hz, 1H), 5.10-5.08 (m, 1H), 4.30-4.05 (m, 6H), 3.92 (s, 3H), 3.52 (brs, 4H), 2.96-2.87 (m, 1H), 2.67-2.63 (m, 1H), 2.50-2.38 (m, 5H), 2.34 (s, 3H), 2.04-1.91 (m, 3H), 1.82-1.79 (m, 2H), 1.64-1.62 (m, 2H), 1.58 (d, $J = 7.2$ Hz, 3H); MS (ESI) m/z : 845.3, 847.3 [$\text{M}+1$, $\text{M}+3$] $^+$.



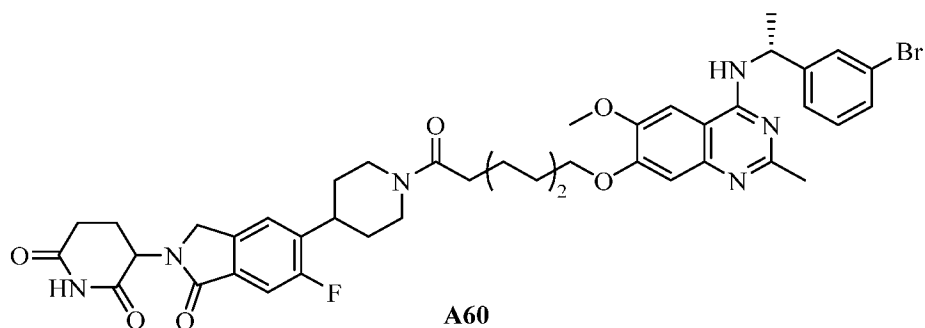
[00535] 3-(4-(1-(8-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)octyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A58**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.00 (s, 1H), 8.17-8.14 (m, 1H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.68 (s, 1H), 7.63-7.58 (m, 2H), 7.49-7.39 (m, 3H), 7.29 (t, $J = 4.0$ Hz, 1H), 7.02 (s, 1H), 5.63-5.55 (m, 1H), 5.11 (dd, $J = 5.2, 13.2$ Hz, 1H), 4.43-4.26 (m, 2H), 4.07 (t, $J = 6.4$ Hz, 2H), 3.91 (s, 3H), 3.12-3.04 (m, 2H), 2.95-2.86 (m, 2H), 2.43-2.38 (m, 2H), 2.33 (s, 3H), 2.26-2.13 (m, 2H), 2.02-1.97 (m, 1H), 1.82-1.71 (m, 6H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.52-1.41 (m, 4H), 1.38-1.19 (m, 8H); MS (ESI) m/z : 843.1, 845.1 [$\text{M}+1$, $\text{M}+3$] $^+$.



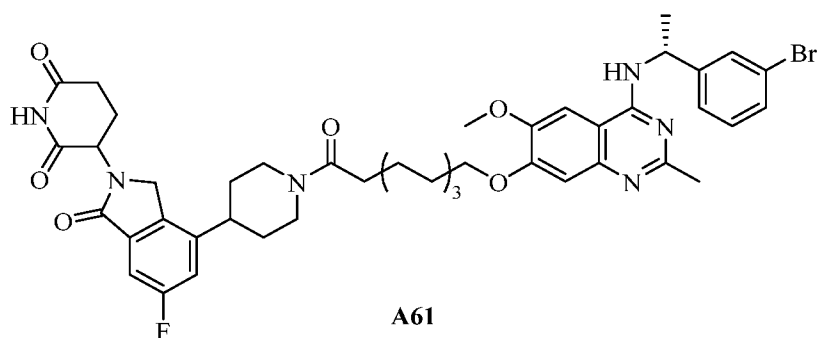
[00536] 3-(4-(1-(7-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanoyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A59**; MS (ESI) m/z : 844.8 $[M+1]^+$.



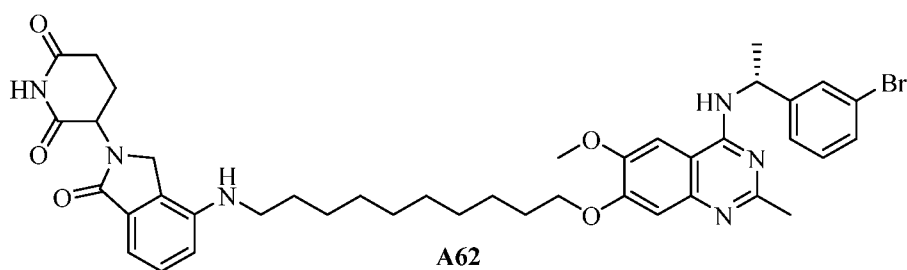
[00537] 3-(5-(1-(7-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanoyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A60**; MS (ESI) m/z : 844.8 $[M+1]^+$.



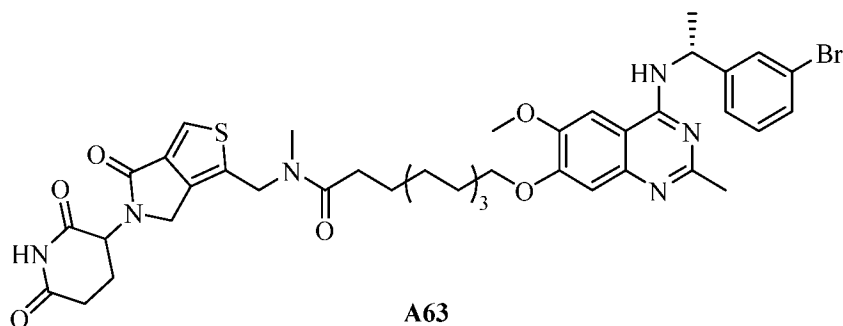
[00538] 3-(4-(1-(9-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A61**; MS (ESI) m/z : 872.8 $[M+1]^+$.



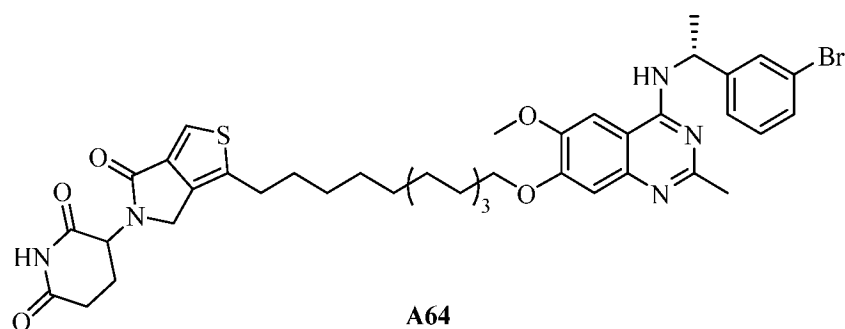
[00539] 3-(4-((10-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A62**; MS (ESI) m/z : 785.1 $[M+1]^+$.



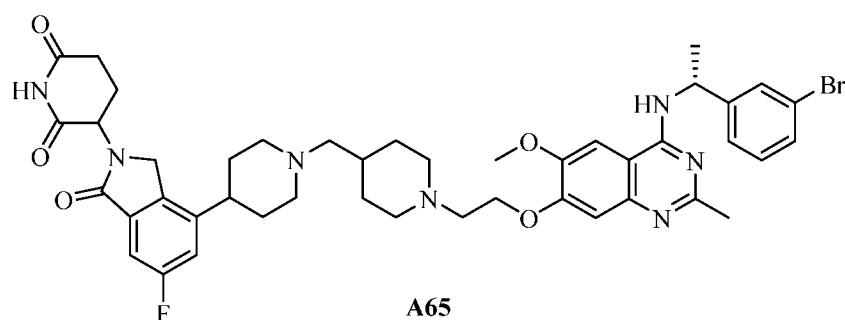
[00540] 6-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methyl)-*N*-methylhexanamide **A63**; MS (ESI) m/z : 833.0 $[M+1]^+$.



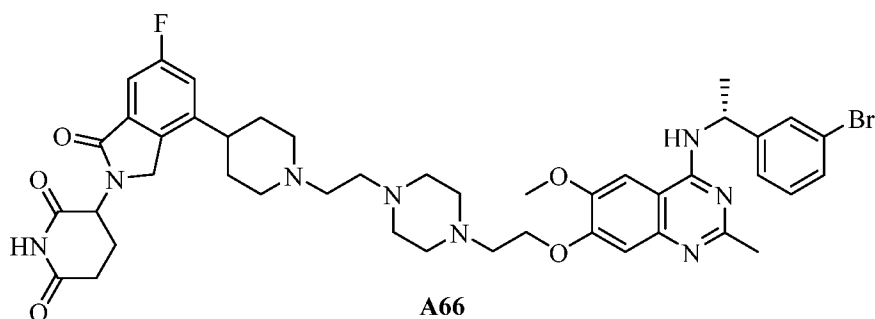
[00541] 3-(1-(12-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)dodecyl)-4-oxo-4*H*-thieno[3,4-*c*]pyrrol-5(6*H*)-yl)piperidine-2,6-dione **A64**; MS (ESI) m/z : 804.1 $[M+1]^+$.



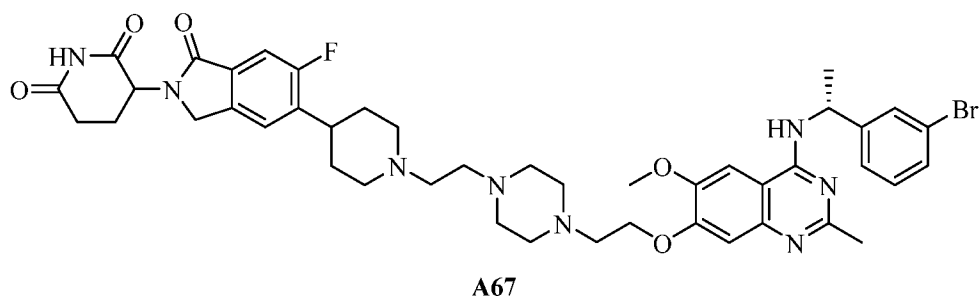
[00542] 3-(4-(1-((1-(2-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)ethyl)piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A65**; MS (ESI) m/z : 856.1 $[M+1]^+$.



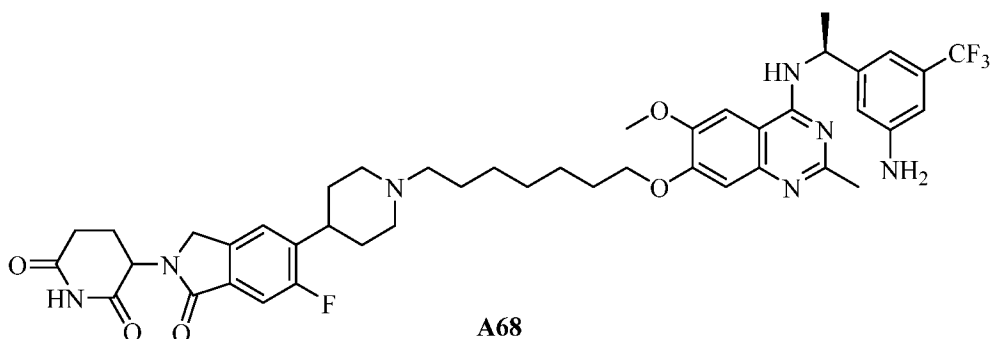
[00543] 3-(4-(1-(2-(4-(2-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)ethyl)piperazin-1-yl)ethyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A66**; MS (ESI) m/z : 871.1 $[M+1]^+$.



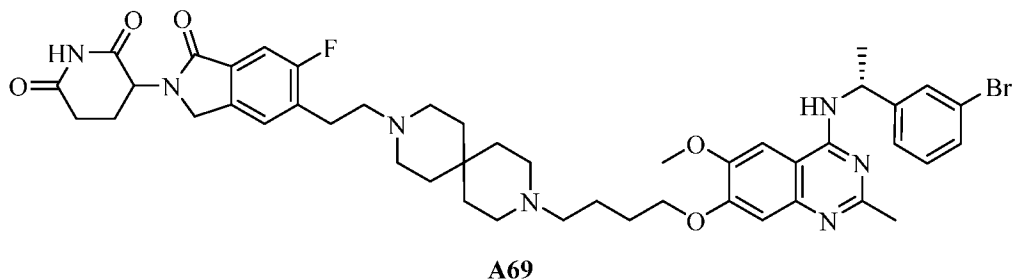
[00544] 3-(5-(1-(2-(4-(2-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)ethyl)piperazin-1-yl)ethyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A67**; MS (ESI) m/z : 871.1 $[M+1]^+$.



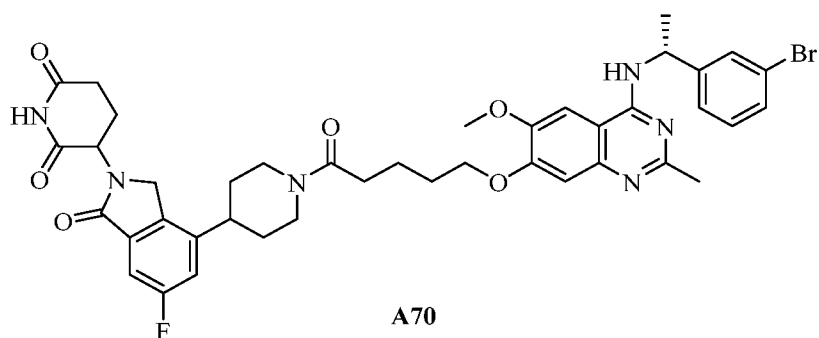
[00545] 3-(5-(1-(7-((4-(((S)-1-(3-Amino-5-(trifluoromethyl)phenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A68**; MS (ESI) m/z : 834.2 $[M+1]^+$.



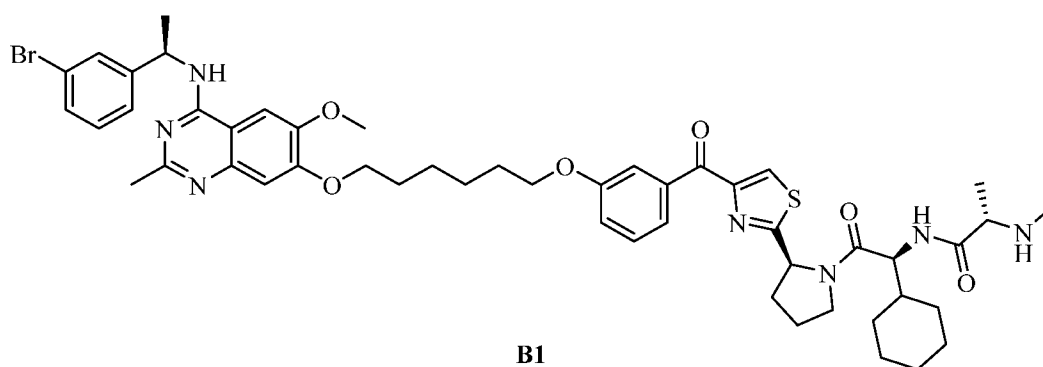
[00546] 3-(5-(2-(9-(4-((4-(((R)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)butyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A69**; MS (ESI) m/z : 884.1 $[M+1]^+$.



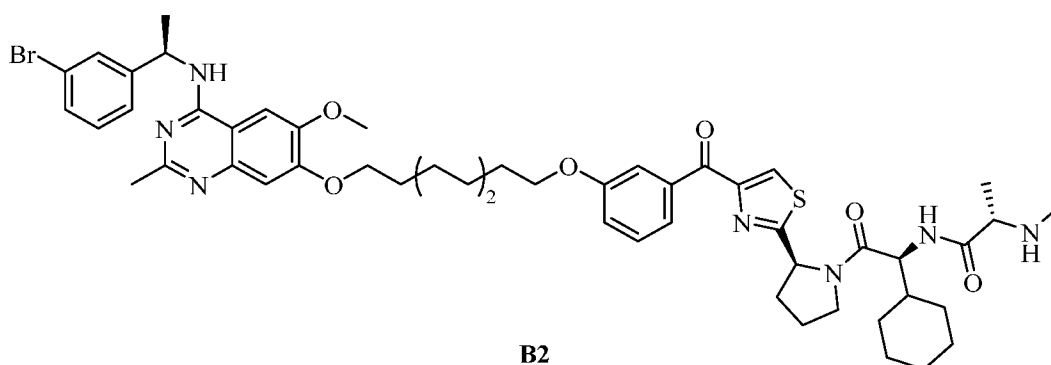
[00547] 3-(4-(1-(5-((4-(((R)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentanoyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A70**; MS (ESI) m/z : 816.7 $[M+1]^+$.



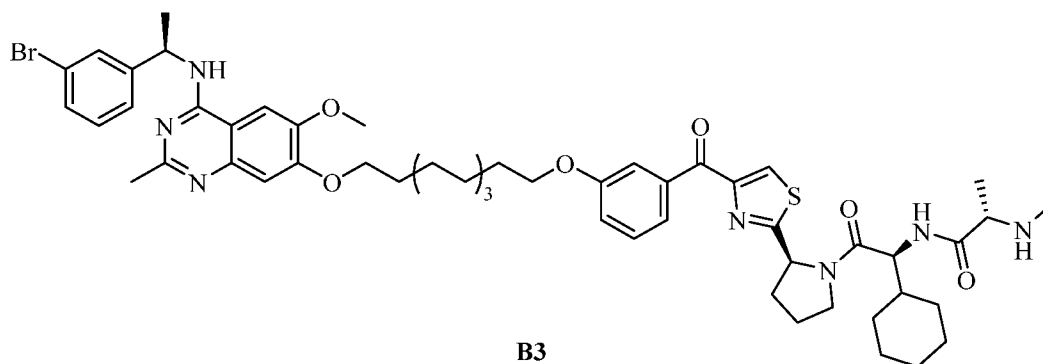
[00548] (S)-N-((S)-2-((S)-2-(4-(3-((6-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B1**. MS (ESI) m/z : 970.0 $[M+1]^+$.



[00549] (S)-N-((S)-2-((S)-2-(4-(3-((8-((4-(((R)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B2**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.60 (s, 1H), 10.07 (s, 1H), 9.34 (s, 1H), 8.95 (d, $J = 8.0$ Hz, 1H), 8.85-8.83 (m, 1H), 8.44 (s, 1H), 8.20 (s, 1H), 7.73 (s, 1H), 7.67-7.43 (m, 5H), 7.35-7.31 (m, 1H), 7.25-7.22 (m, 2H), 5.80-5.73 (m, 1H), 5.38 (d, $J = 8.0$ Hz, 1H), 4.42 (t, $J = 8.8$ Hz, 1H), 4.12 (t, $J = 6.4$ Hz, 2H), 4.05-4.00 (m, 3H), 3.98 (s, 3H), 3.79-3.68 (m, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.33-1.95 (m, 6H), 1.83-1.67 (m, 11H), 1.63-1.45 (m, 8H), 1.39-1.38 (m, 6H), 1.15-1.08 (m, 2H); MS (ESI) m/z : 996.5, 998.4 $[M+1, M+3]^+$.

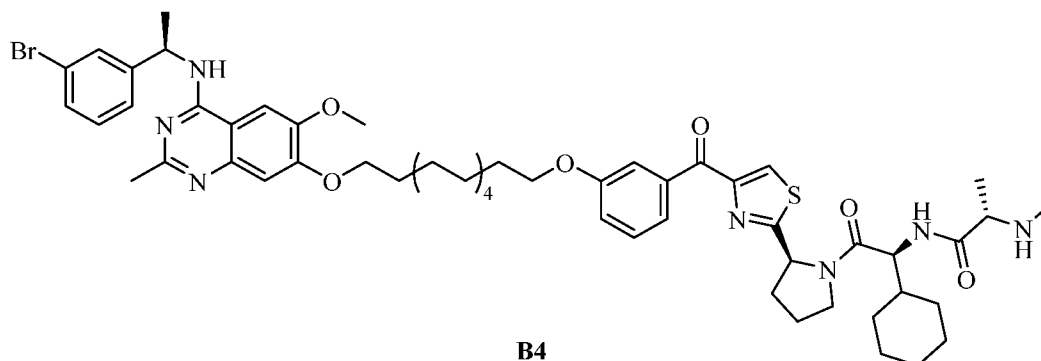


[00550] (S)-N-((S)-2-((S)-2-(4-(3-((10-((4-(((R)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B3**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.14 (s, 1H), 9.48 (s, 1H), 8.97 (d, $J = 8.4$ Hz, 1H), 8.84 (s, 1H), 8.44 (s, 1H), 8.25 (s, 1H), 7.74 (s, 1H), 7.64-7.53 (m, 3H), 7.47-7.43 (m, 2H), 7.38-7.22 (m, 3H), 5.76 (t, $J = 6.8$ Hz, 1H), 5.39 (d, $J = 8.0$ Hz, 1H), 4.42-4.35 (m, 2H), 4.11 (t, $J = 6.4$ Hz, 2H), 4.04-3.98 (m, 6H), 3.79-3.78 (m, 1H), 3.56-3.54 (m, 1H), 2.57 (s, 3H), 2.38-2.34 (m, 5H), 2.03-1.99 (m, 1H), 1.81-1.80 (m, 2H), 1.75-1.68 (m, 11H), 1.62-1.57 (m, 2H), 1.42-1.36 (m, 8H), 1.34-1.23 (m, 11H); MS (ESI) m/z : 1024.2 $[\text{M}+1]^+$.

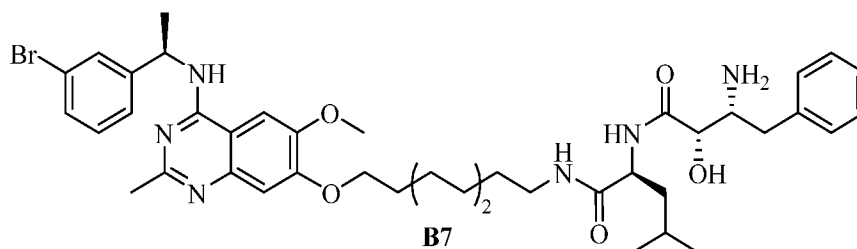


[00551] (S)-N-((S)-2-((S)-2-(4-(3-((12-((4-(((R)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)dodecyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B4**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.55 (s, 1H), 10.04 (s, 1H), 9.33-9.27 (m, 1H), 8.96-8.83 (m, 2H), 8.47 (s, 1H), 8.19 (s, 1H), 7.73 (s, 1H), 7.76-7.43 (m, 5H), 7.33 (t, $J = 7.6$ Hz, 1H), 7.24-7.21 (m, 1H), 5.80-5.73 (m, 1H), 5.38 (dd, $J = 1.6, 8.0$ Hz, 1H), 4.43 (t, $J = 8.4$ Hz, 1H), 4.11 (t, $J = 6.8$ Hz, 2H), 4.02 (t, $J = 6.4$ Hz, 2H), 3.98 (s, 3H), 3.75-3.68 (m, 2H), 2.57 (s, 3H), 2.39 (s, 3H), 2.35-2.22 (m, 2H), 2.04-1.93

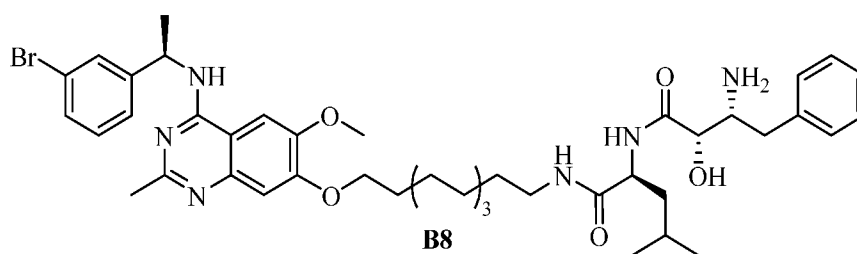
(m, 3H), 1.85-1.67 (m, 11H), 1.63-1.51 (m, 2H), 1.43-1.38 (m, 8H), 1.27-1.23 (m, 15H); MS (ESI) m/z : 1052.6, 1054.6 $[M+1, M+3]^+$.



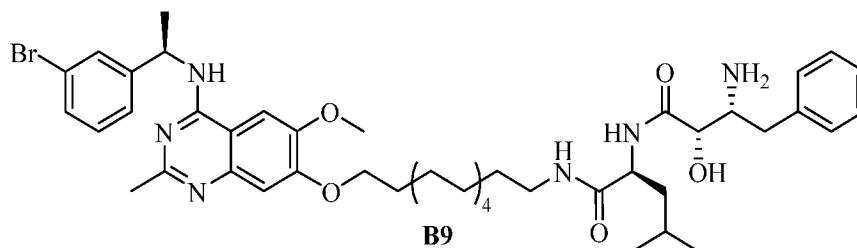
[00552] (S)-2-((2S,3R)-3-Amino-2-hydroxy-4-phenylbutanamido)-N-(8-(((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)-4-methylpentanamide **B7**. ^1H NMR (400 MHz, DMSO- d_6) δ 14.53 (s, 1H), 9.99 (s, 1H), 8.09-7.96 (m, 5H), 7.72 (s, 1H), 7.53-7.46 (m, 2H), 7.36-7.26 (m, 7H), 6.64 (s, 1H), 4.27-4.22 (m, 1H), 4.11 (t, $J = 6.4$ Hz, 2H), 3.97 (s, 3H), 3.54 (s, 1H), 3.08-2.81 (m, 4H), 2.57 (s, 3H), 2.02-1.95 (m, 1H), 1.82-1.75 (m, 2H), 1.68-1.67 (m, 3H), 1.61-1.34 (m, 7H), 1.31-1.23 (m, 8H), 0.88-0.85 (m, 6H) MS (ESI) m/z : 805.5, 807.5 $[M+1, M+3]^+$.



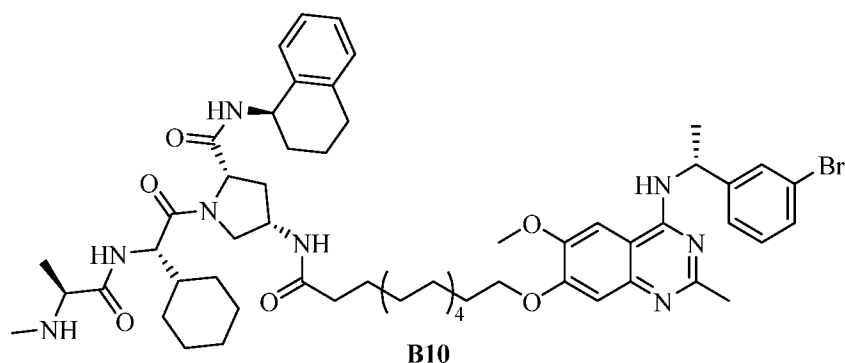
[00553] (S)-2-((2S,3R)-3-Amino-2-hydroxy-4-phenylbutanamido)-N-(10-(((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)-4-methylpentanamide **B8**. ^1H NMR (400 MHz, DMSO- d_6) δ 9.79 (s, 1H), 8.12-8.04 (m, 2H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.97-7.86 (m, 2H), 7.70 (s, 1H), 7.52-7.47 (m, 2H), 7.36-7.33 (m, 3H), 7.30-7.27 (m, 3H), 7.19-7.11 (m, 1H), 6.70-6.56 (m, 1H), 5.82-5.70 (m, 1H), 4.30-4.20 (m, 1H), 4.12 (t, $J = 6.0$ Hz, 2H), 4.02-3.97 (m, 4H), 3.58-3.50 (m, 2H), 3.08-3.03 (m, 1H), 2.99-2.90 (m, 2H), 2.85-2.79 (m, 1H), 2.56 (s, 3H), 2.03-1.98 (m, 1H), 1.84-1.76 (m, 2H), 1.67 (d, $J = 6.4$ Hz, 3H), 1.51-1.41 (m, 4H), 1.28-1.23 (m, 12H), 0.89-0.85 (m, 6H); MS (ESI) m/z : 834.2 $[M+1]^+$.



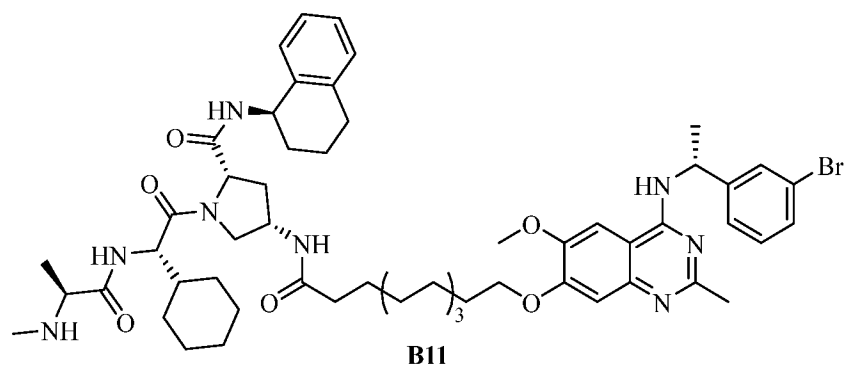
[00554] (S)-2-((2S,3R)-3-Amino-2-hydroxy-4-phenylbutanamido)-N-(12-(((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)dodecyl)-4-methylpentanamide **B9**. ^1H NMR (400 MHz, DMSO- d_6) δ 14.09 (s, 1H), 9.74 (s, 1H), 8.10-7.97 (m, 3H), 7.94-7.84 (m, 2H), 7.71-7.66 (m, 1H), 7.51-7.47 (m, 2H), 7.39-7.31 (m, 3H), 7.30-7.29 (m, 3H), 7.12 (s, 1H), 6.68-6.58 (m, 1H), 5.79-5.72 (m, 1H), 4.25 (q, $J = 8.0$ Hz, 1H), 4.13 (t, $J = 6.4$ Hz, 2H), 4.00-3.96 (m, 4H), 3.54-3.52 (m, 2H), 3.10-3.03 (m, 1H), 2.98-2.90 (m, 2H), 2.84-2.79 (m, 1H), 2.58-2.55 (m, 4H), 2.03-1.97 (m, 1H), 1.83-1.76 (m, 2H), 1.66 (d, $J = 6.8$ Hz, 3H), 1.49-1.39 (m, 4H), 1.36-1.31 (m, 2H), 1.29-1.23 (m, 13H), 0.89-0.85 (m, 6H); MS (ESI) m/z : 861.2, 863.2 [$M+1$, $M+3$] $^+$.



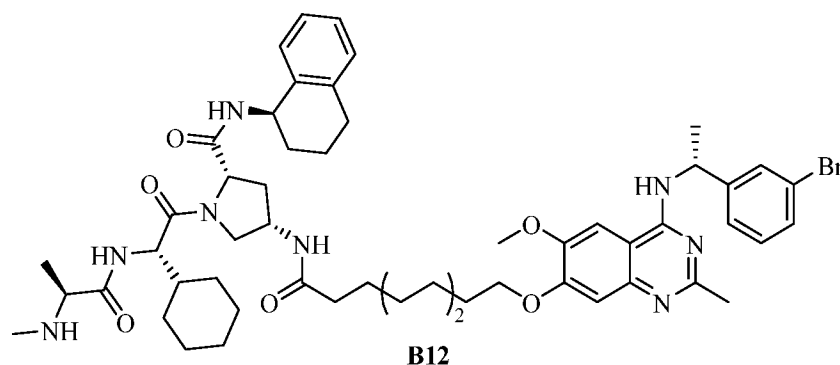
[00555] (2S,4S)-4-(13-(((4-(((R)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)tridecanamido)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)-acetyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide **B10**. ^1H NMR (400 MHz, DMSO- d_6) δ 14.64 (s, 1H), 10.12 (s, 1H), 9.29 (s, 1H), 8.90-8.84 (m, 2H), 8.52 (d, $J = 8.8$ Hz, 1H), 8.26-8.26 (m, 2H), 7.79 (s, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.41-7.34 (m, 2H), 7.30 (s, 2H), 7.22-7.12 (m, 3H), 5.87-5.78 (m, 1H), 4.99 (s, 1H), 4.43 (t, $J = 8.0$ Hz, 1H), 4.37-4.28 (m, 2H), 4.18-4.13 (m, 3H), 4.04 (s, 3H), 3.90 (s, 1H), 3.35-3.28 (m, 2H), 2.82-2.74 (m, 2H), 2.63 (s, 3H), 2.56 (s, 3H), 2.46-2.37 (m, 1H), 2.12-2.09 (m, 2H), 1.98-1.84 (m, 8H), 1.79-1.71 (m, 5H), 1.69-1.67 (m, 2H), 1.56-1.49 (m, 5H), 1.39-1.30 (m, 20H); MS (ESI) m/z : 1065.3, 1067.3 [$M+1$, $M+3$] $^+$.



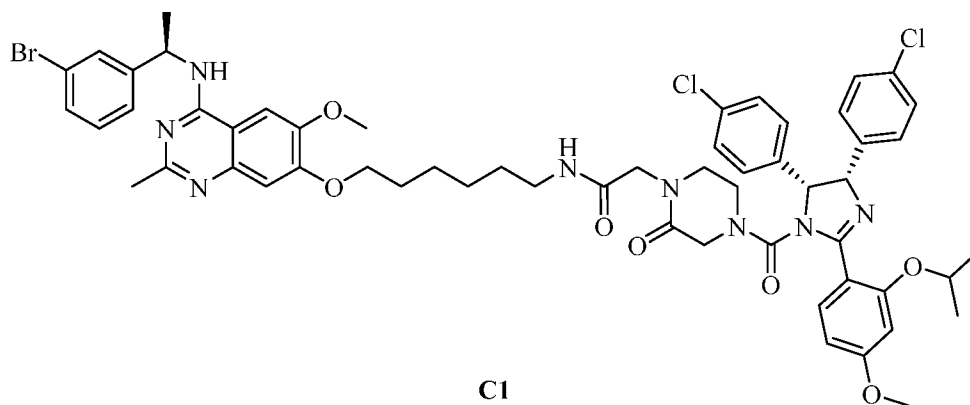
[00556] (2*S*,4*S*)-4-(11-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecanamido)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)-acetyl)-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide **B11**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 (d, *J* = 8.8 Hz, 1H), 8.22 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 16.0 Hz, 2H), 7.46-7.40 (m, 2H), 7.32-7.27 (m, 2H), 7.14-7.06 (m, 3H), 7.00 (s, 1H), 5.62-5.58 (m, 1H), 4.94-4.92 (m, 1H), 4.38 (t, *J* = 16.0 Hz, 1H), 4.32-4.25 (m, 2H), 4.08-4.04 (m, 4H), 3.91 (s, 3H), 4.38 (t, *J* = 1.6 Hz, 2H), 3.34-3.32 (m, 2H), 2.72-2.69 (m, 2H), 2.39-2.35 (m, 1H), 2.34 (s, 3H), 2.07 (s, 3H), 2.03 (t, *J* = 7.2 Hz, 2H), 1.87-1.84 (m, 3H), 1.79-1.69 (m, 8H), 1.61-1.58 (m, 4H), 1.51-1.48 (m, 2H), 1.42-1.39 (m, 2H), 1.39-1.21 (m, 12H), 1.13 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 13.2 Hz, 2H); MS (ESI) *m/z*: 1037.3 [M+1]⁺.



[00557] (2*S*,4*S*)-4-(9-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)-acetyl)-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide **B12**; MS (ESI) *m/z*: 1011.1 [M+1]⁺.

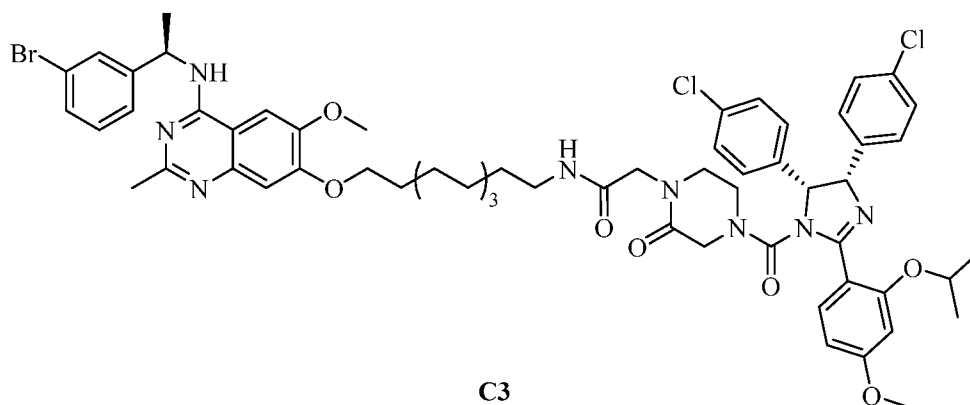


[00558] 2-(4-((4*S*,5*R*)-4,5-Bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)-2-oxopiperazin-1-yl)-*N*-(6-((4-(((*R*)-1-(3-bromophenyl)-ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)acetamide **C1**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.99 (d, *J* = 7.2 Hz, 1H), 7.83 (t, *J* = 5.6 Hz, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.53 (dd, *J* = 2.0, 9.2 Hz, 1H), 7.45-7.36 (m, 8H), 7.29 (td, *J* = 0.8, 8.0 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.01 (s, 1H), 6.60-6.58 (m, 2H), 5.63-5.58 (m, 1H), 4.98 (d, *J* = 8.0 Hz, 1H), 4.84 (d, *J* = 8.0 Hz, 1H), 4.69-4.63 (m, 1H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 3.78-3.55 (m, 4H), 3.39 (s, 1H), 3.11-2.92 (m, 5H), 2.34 (s, 3H), 1.78-1.71 (m, 2H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.43-1.38 (m, 4H), 1.33 (d, *J* = 6.4 Hz, 2H), 1.24-1.20 (m, 6H); MS (ESI) *m/z*: 1108.3 [M+1]⁺.

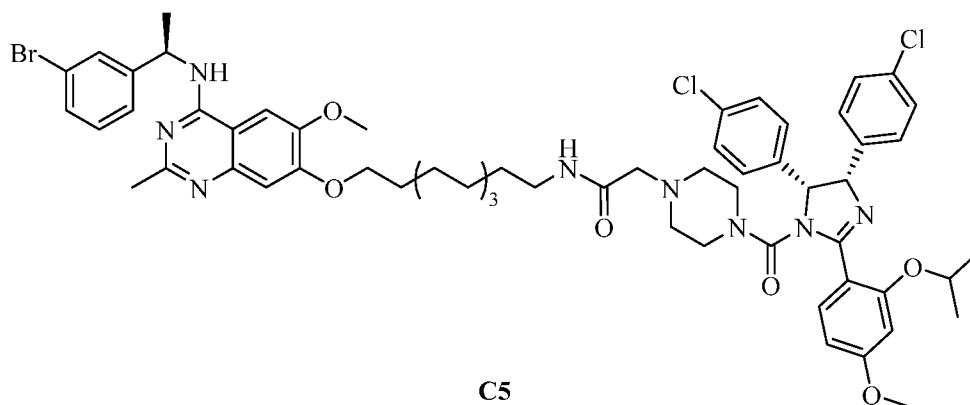


[00559] 2-(4-((4*S*,5*R*)-4,5-Bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)-2-oxopiperazin-1-yl)-*N*-(10-((4-(((*R*)-1-(3-bromophenyl)-ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)acetamide **C3**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 6.0 Hz, 1H), 7.65 (d, *J* = 16.0 Hz, 2H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.45-7.37 (m, 8H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.00 (s,

1H), 6.60-6.59 (m, 2H), 5.64-5.58 (m, 1H), 4.98 (d, $J = 8.0$ Hz, 1H), 4.85 (d, $J = 8.0$ Hz, 1H), 4.70-4.64 (m, 1H), 4.05 (t, $J = 6.8$ Hz, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.77 (s, 1H), 3.69-3.66 (m, 2H), 3.57 (d, $J = 16.8$ Hz, 1H), 3.12-3.08 (m, 1H), 3.02-2.97 (m, 3H), 2.92-2.86 (m, 1H), 2.33 (s, 3H), 2.01-1.97 (m, 1H), 1.77-1.72 (m, 2H), 1.57 (d, $J = 6.8$ Hz, 3H), 1.45-1.38 (m, 2H), 1.35-1.33 (m, 2H), 1.25-1.20 (m, 16H); MS (ESI) m/z : 1165.1 $[M+1]^+$.

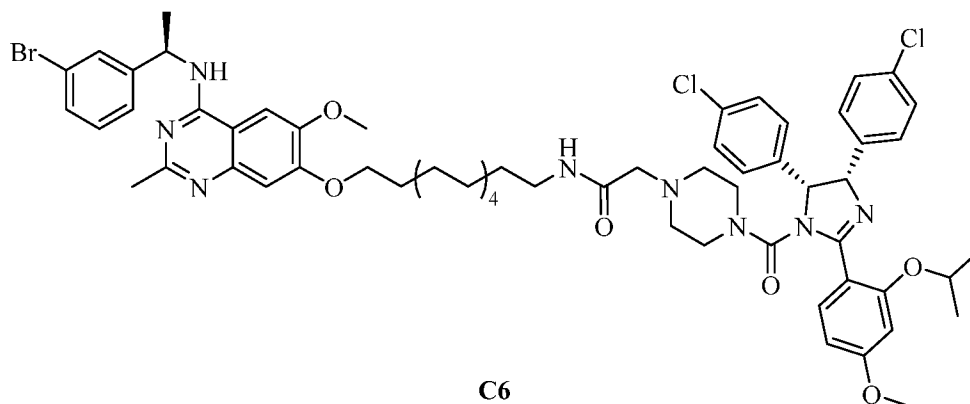


[00560] 2-(4-(((4*S*,5*R*)-4,5-Bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-*N*-(10-((4-(((*R*)-1-(3-bromophenyl)ethyl)-amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)acetamide **C5**. ^1H NMR (400 MHz, DMSO- d_6) δ 7.99 (d, $J = 8.0$ Hz, 1H), 7.67-7.63 (m, 3H), 7.45-7.40 (m, 3H), 7.31-7.27 (m, 1H), 7.16-7.10 (m, 4H), 7.04-7.00 (m, 3H), 6.95 (d, $J = 8.0$ Hz, 2H), 6.63-6.60 (m, 2H), 5.64-5.58 (m, 2H), 5.50 (d, $J = 10.4$ Hz, 1H), 4.73-4.67 (m, 1H), 4.05 (d, $J = 6.4$ Hz, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.07-3.98 (m, 6H), 2.72-2.66 (m, 2H), 2.34 (s, 3H), 2.03-1.97 (m, 4H), 1.77-1.74 (m, 2H), 1.57 (d, $J = 6.8$ Hz, 3H), 1.47-1.40 (m, 4H), 1.37-1.23 (m, 16H); MS (ESI) m/z : 1149.6, 1151.6 $[M+1, M+3]^+$.

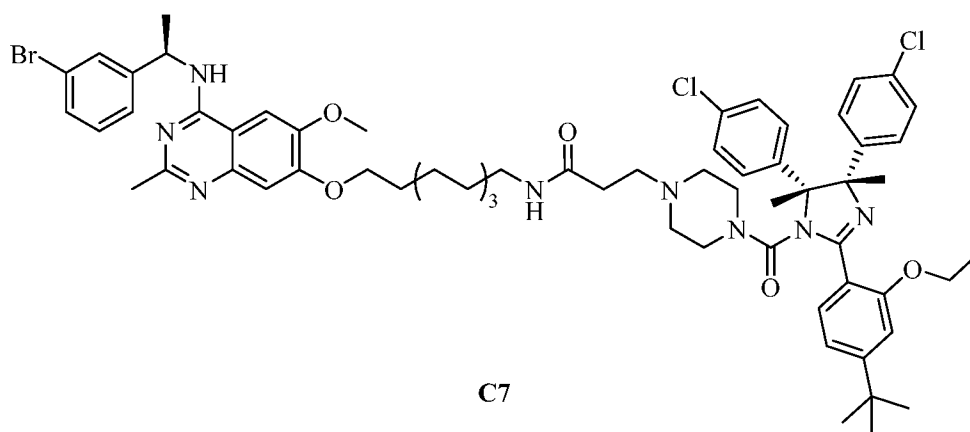


[00561] 2-(4-(((4*S*,5*R*)-4,5-Bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-

dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-*N*-(12-((4-(((*R*)-1-(3-bromophenyl)ethyl)-amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)dodecyl)acetamide **C6**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.67-7.63 (m, 3H), 7.45-7.39 (m, 3H), 7.30-7.26 (m, 1H), 7.15-7.09 (m, 4H), 7.03-7.00 (m, 3H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.63-6.59 (m, 2H), 5.64 -5.58 (m, 2H), 5.50 (d, *J* = 10.0 Hz, 1H), 4.73-4.67 (m, 1H), 4.05 (t, *J* = 6.6 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.44-3.40 (m, 4H), 3.07 (s, 4H), 3.03-2.98 (m, 2H), 2.75-2.66 (m, 2H), 2.33 (s, 3H), 2.05-1.93 (m, 4H), 1.78-1.71 (m, 2H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.45-1.39 (m, 2H), 1.36-1.31 (m, 4H), 1.28 -1.23 (m, 14H); MS (ESI) *m/z*: 590.1 [1/2M+1]⁺.

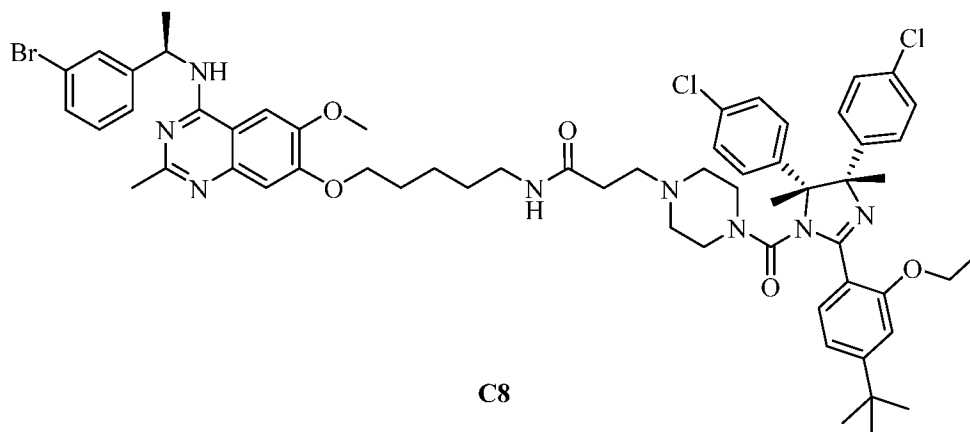


[00562] *N*-(9-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonyl)-3-(4-((4*S*,5*R*)-2-(4-(*tert*-butyl)-2-ethoxyphenyl)-4,5-bis(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)propanamide **C7**; MS (ESI) *m/z*: 1191.2 [M+1]⁺.

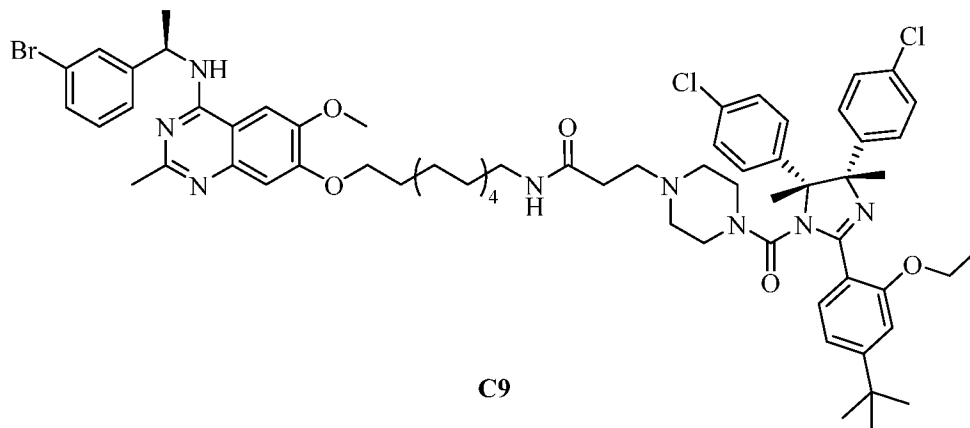


[00563] *N*-(5-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)-3-(4-((4*S*,5*R*)-2-(4-(*tert*-butyl)-2-ethoxyphenyl)-4,5-bis(4-chlorophenyl)-4,5-

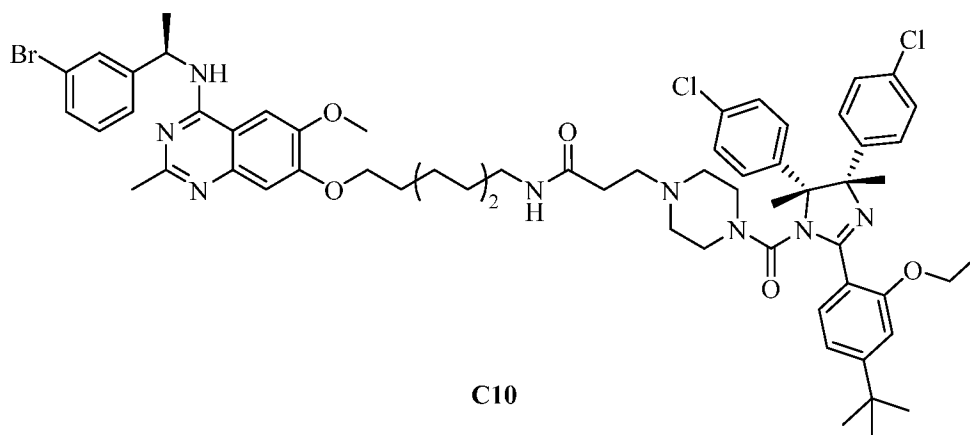
dimethyl-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)propanamide **C8**; MS (ESI) m/z : 1135.1 $[M+1]^+$.



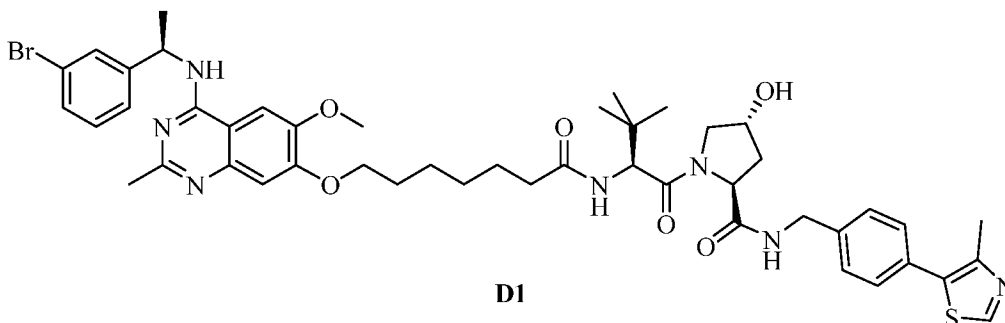
[00564] *N*-(11-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecyl)-3-(4-(((4*S*,5*R*)-2-(4-(tert-butyl)-2-ethoxyphenyl)-4,5-bis(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)propanamide **C9**; MS (ESI) m/z : 1219.2 $[M+1]^+$.



[00565] *N*-(7-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)-3-(4-(((4*S*,5*R*)-2-(4-(tert-butyl)-2-ethoxyphenyl)-4,5-bis(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)propanamide **C10**; MS (ESI) m/z : 1163.1 $[M+1]^+$.

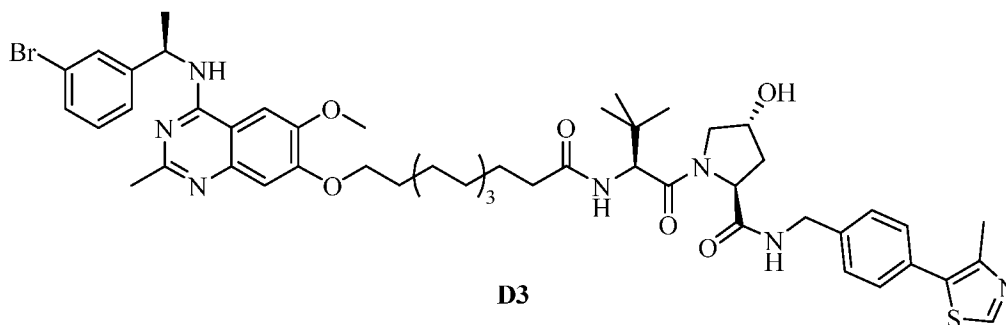


[00566] (2*S*,4*R*)-1-((*S*)-2-(7-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D1**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.55 (t, *J* = 6.0 Hz, 1H), 8.14 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 9.6 Hz, 1H), 7.68 (s, 1H), 7.63 (t, *J* = 1.6 Hz, 1H), 7.46-7.37 (m, 5H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 5.64-5.57 (m, 1H), 4.55 (d, *J* = 9.2 Hz, 1H), 4.58-4.41 (m, 2H), 4.37-4.33 (m, 1H), 4.21 (dd, *J* = 5.6, 16.0 Hz, 1H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.91 (s, 3H), 3.58 (s, 2H), 2.44 (s, 3H), 2.34 (s, 3H), 2.29-2.24 (m, 1H), 2.16-2.10 (m, 1H), 2.06-2.00 (m, 1H), 1.94-1.87 (m, 1H), 1.77-1.73 (m, 2H), 1.59-1.30 (m, 9H), 0.93 (s, 9H); MS (ESI) *m/z*: 928.1 [M+1]⁺.

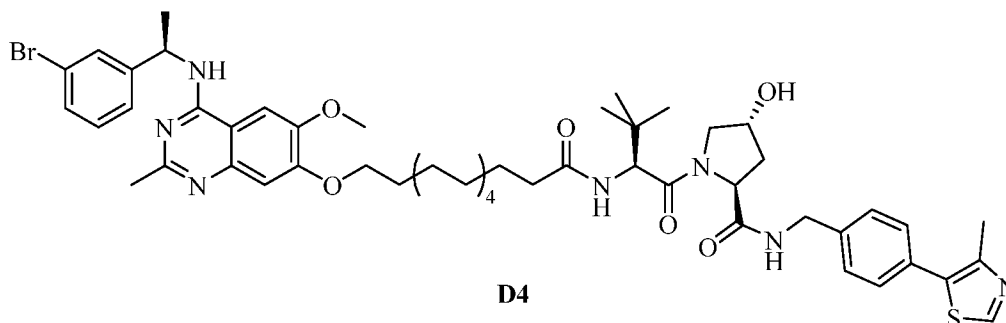


[00567] (2*S*,4*R*)-1-((*S*)-2-(11-((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D3**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.56 (t, *J* = 6.0 Hz, 1H), 7.96 (s, 1H), 7.83 (d, *J* = 9.2 Hz, 1H), 7.69 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.45-7.37 (m, 5H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.12 (s, 1H), 5.71-5.68 (m, 1H), 5.13 (s, 1H), 4.54 (d, *J* = 9.2 Hz, 1H), 4.46-4.40 (m, 2H), 4.35 (s, 1H), 4.22 (dd, *J* = 5.6, 16.0 Hz, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.95 (s, 3H), 3.69-3.57 (m, 2H), 2.47 (s, 3H), 2.44 (s, 3H), 2.30-2.01 (m,

3H), 1.93-1.87 (m, 1H), 1.80-1.74 (m, 2H), 1.64 (d, $J = 7.2$ Hz, 3H), 1.51-1.39 (m, 5H), 1.32-1.23 (m, 12H), 0.93 (s, 9H); MS (ESI) m/z : 984.2 $[M+1]^+$.

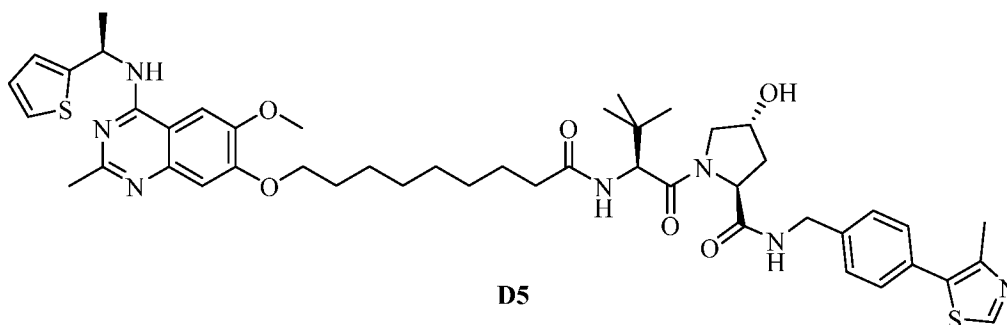


[00568] (2*S*,4*R*)-1-((*S*)-2-(13-(((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)tridecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D4**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.54 (t, $J = 6.0$ Hz, 1H), 8.23 (s, 0.41H), 7.97 (d, $J = 8.0$ Hz 1H), 7.82 (d, $J = 9.6$ Hz, 1H), 7.67 (s, 1H), 7.63 (t, $J = 1.6$ Hz, 1H), 7.46-7.37 (m, 5H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.00 (s, 1H), 5.62-5.58 (m, 1H), 5.11 (d, $J = 2.8$ Hz, 1H), 4.54-4.40 (m, 2H), 4.35 (s, 1H), 4.22 (dd, $J = 5.6, 15.6$ Hz, 1H), 4.05 (t, $J = 6.8$ Hz, 1H), 3.90 (s, 3H), 3.68-3.62 (m, 2H), 2.44 (s, 3H), 2.33 (s, 3H), 2.27-1.90 (m, 4H), 1.79-1.72 (m, 2H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.50-1.24 (m, 18H), 0.93 (s, 9H); MS (ESI) m/z : 1012.1 $[M+1]^+$.

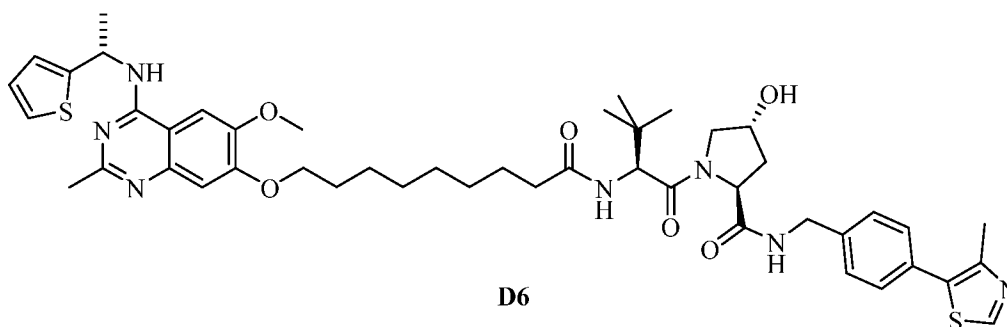


[00569] (2*S*,4*R*)-4-Hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*R*)-1-(thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D5**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.56 (t, $J = 6.0$ Hz, 1H), 8.06 (t, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 9.2$ Hz, 1H), 7.62 (s, 1H), 7.43-7.34 (m, 5H), 7.06 (d, $J = 2.4$ Hz, 1H), 7.01 (s, 1H), 6.99 (dd, $J = 3.6, 5.2$ Hz, 1H), 5.95-5.91 (m, 1H), 5.12 (d, $J = 2.8$ Hz, 1H), 4.54 (d, $J = 9.6$ Hz, 1H), 4.46-4.40 (m, 2H), 4.35 (s, 1H), 4.21 (dd, $J =$

5.2, 16.0 Hz, 1H), 4.06 (t, $J = 6.4$ Hz, 2H), 3.86 (s, 3H), 3.67-3.63 (m, 2H), 2.44 (s, 3H), 2.41 (s, 3H), 2.28-2.25 (m, 1H), 2.15-2.09 (m, 1H), 2.03-1.97 (m, 2H), 1.92-1.88 (m, 1H), 1.78-1.74 (m, 2H), 1.68 (d, $J = 7.2$ Hz, 3H), 1.51-1.41 (m, 4H), 1.30-1.25 (m, 6H), 0.93 (s, 9H); MS (ESI) m/z : 884.1 $[M+1]^+$.

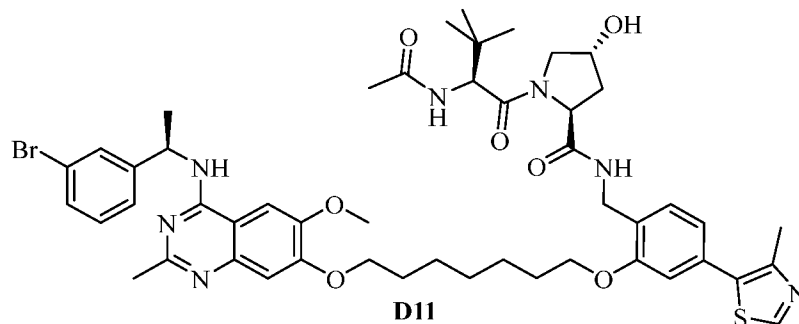


[00570] (2*S*,4*R*)-4-Hydroxy-1-((*S*)-2-(9-(((6-methoxy-2-methyl-4-(((*S*)-1-(thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D6**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.56 (t, $J = 6.0$ Hz, 1H), 8.06 (t, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 9.2$ Hz, 1H), 7.62 (s, 1H), 7.43-7.34 (m, 5H), 7.06 (d, $J = 2.4$ Hz, 1H), 7.01 (s, 1H), 6.99 (dd, $J = 3.6, 5.2$ Hz, 1H), 5.95-5.91 (m, 1H), 5.12 (d, $J = 3.6$ Hz, 1H), 4.54 (d, $J = 9.6$ Hz, 1H), 4.46-4.40 (m, 2H), 4.35 (s, 1H), 4.21 (dd, $J = 5.2, 16.0$ Hz, 1H), 4.06 (t, $J = 6.4$ Hz, 2H), 3.86 (s, 3H), 3.67-3.63 (m, 2H), 2.44 (s, 3H), 2.41 (s, 3H), 2.28-2.23 (m, 1H), 2.13-2.09 (m, 1H), 2.02-1.97 (m, 2H), 1.93-1.87 (m, 1H), 1.78-1.74 (m, 2H), 1.68 (d, $J = 6.8$ Hz, 3H), 1.51-1.41 (m, 4H), 1.30-1.25 (m, 6H), 0.93 (s, 9H); MS (ESI) m/z : 884.1 $[M+1]^+$.

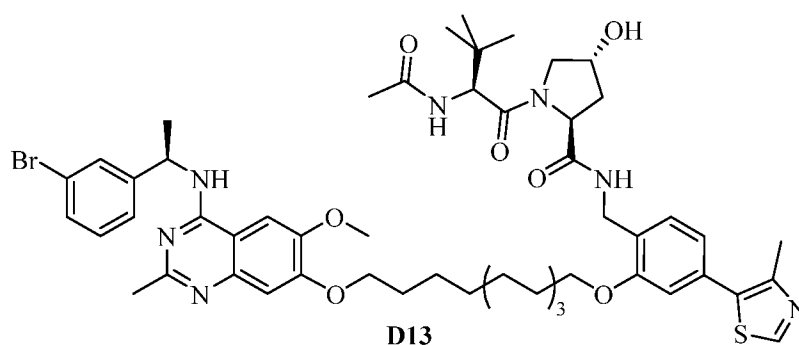


[00571] (2*S*,4*R*)-1-((*S*)-2-Acetamido-3,3-dimethylbutanoyl)-*N*-(2-((7-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D11**. ^1H NMR (400 MHz,

DMSO-*d*₆) δ 8.97 (s, 1H), 8.43 (t, *J* = 6.0 Hz, 1H), 8.26 (s, 1H), 7.98-7.93 (m, 2H), 7.67 (s, 1H), 7.63 (t, *J* = 2.0 Hz, 1H), 7.47-7.40 (m, 3H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.01-7.00 (m, 2H), 6.90 (dd, *J* = 1.2, 7.6 Hz, 1H), 5.62-5.58 (m, 1H), 4.53 (d, *J* = 9.6 Hz, 1H), 4.46 (t, *J* = 8.0 Hz, 1H), 4.36-4.30 (m, 2H), 4.16 (dd, *J* = 5.2, 16.8 Hz, 1H), 4.09-4.04 (m, 4H), 3.90 (s, 3H), 3.67-3.62 (m, 3H), 2.45 (s, 3H), 2.33 (s, 3H), 2.06-1.91 (m, 2H), 1.89 (s, 3H), 1.84-1.77 (m, 4H), 1.58 (d, *J* = 7.2 Hz, 3H), 1.51-1.40 (m, 6H), 0.91 (s, 9H); MS (ESI) *m/z*: 972.3, 974.3[M+1, M+3]⁺.

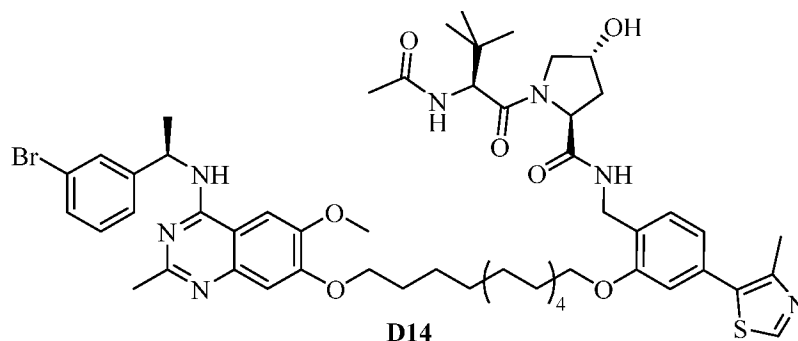


[00572] (2*S*,4*R*)-1-((*S*)-2-Acetamido-3,3-dimethylbutanoyl)-*N*-(2-((11-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D13**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.44 (t, *J* = 6.0 Hz, 1H), 7.99-7.94 (m, 2H), 7.65 (d, *J* = 16.8 Hz, 2H), 7.47-7.39 (m, 3H), 7.29 (t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.62-5.58 (m, 1H), 4.53 (d, *J* = 9.2 Hz, 1H), 4.46 (t, *J* = 8.0 Hz, 1H), 4.35-4.29 (m, 2H), 4.17-4.02 (m, 6H), 3.91 (s, 3H), 3.67-3.62 (m, 2H), 2.45 (s, 3H), 2.33 (s, 3H), 1.89 (s, 3H), 1.77-1.72 (m, 4H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.47-1.42 (m, 4H), 1.40-1.24 (m, 12H), 0.92 (s, 9H); MS (ESI) *m/z*: 1028.2 [M+1]⁺.



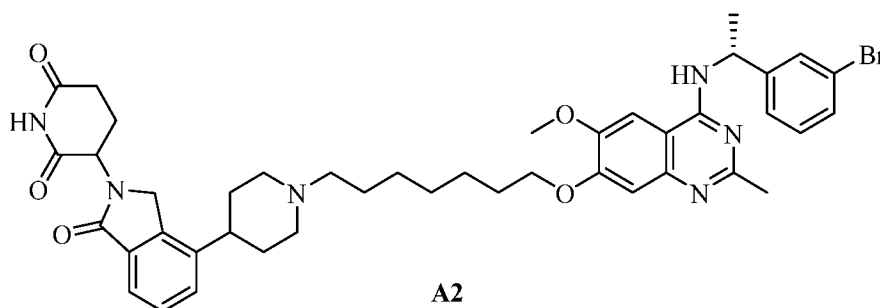
[00573] (2*S*,4*R*)-1-((*S*)-2-Acetamido-3,3-dimethylbutanoyl)-*N*-(2-((13-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)tridecyl)oxy)-4-(4-methyl-

thiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D14**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.97 (s, 1H), 8.44 (t, $J = 5.6$ Hz, 1H), 8.29 (s, 0.52H), 7.97 (dd, $J = 7.6, 16.8$ Hz, 2H), 7.67 (s, 1H), 7.62 (s, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.41-7.39 (m, 1H), 7.30-7.26 (m, 1H), 7.00- 6.98 (m, 2H), 6.90 (d, $J = 7.6$ Hz, 1H), 5.63-5.56 (m, 1H), 4.54 (d, $J = 9.2$ Hz, 1H), 4.66 (t, $J = 8.0$ Hz, 1H), 4.35-4.29 (m, 3H), 4.17-4.11 (m, 1H), 4.07-4.01 (m, 4H), 3.90 (s, 3H), 3.65 (s, 4H), 2.45 (s, 3H), 2.33 (s, 3H), 2.06-2.01 (m, 2H), 1.89 (s, 3H), 1.78-1.69 (m, 4H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.42 (m, 4H), 1.31-1.25 (m, 12H), 0.92 (s, 9H); MS (ESI) m/z : 1056.7, 1058.7 [$\text{M}+1$, $\text{M}+3$] $^+$.

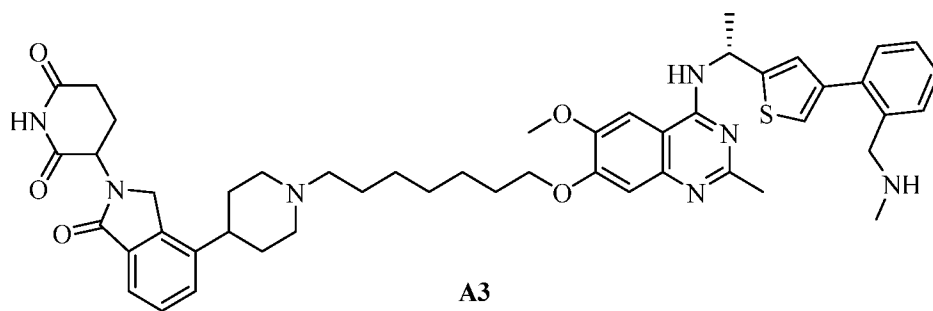


[00574] The following compounds are prepared similarly.

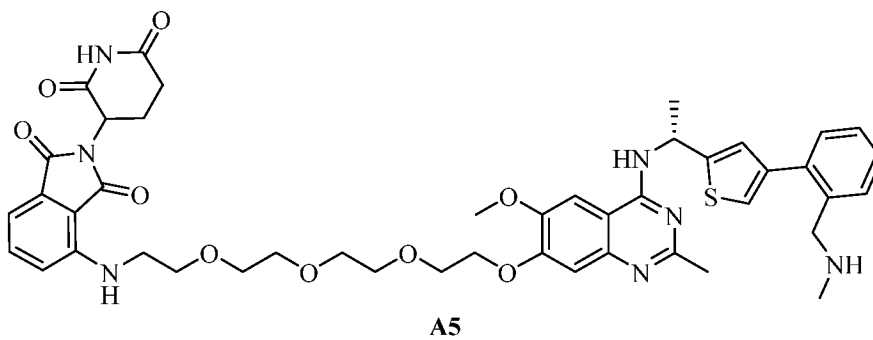
[00575] 3-(4-(1-(7-(((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methyl-quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A2**.



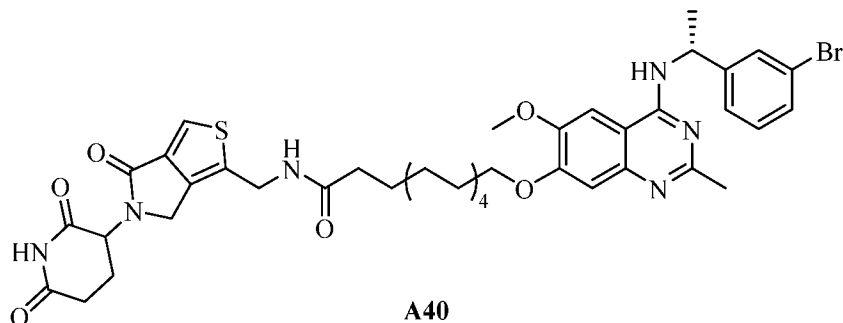
[00576] 3-(4-(1-(7-(((6-Methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)methyl)phenyl)-thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A3**.



[00577] 2-(2,6-Dioxopiperidin-3-yl)-4-(((2-(2-(2-(2-((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)ethoxy)ethoxy)-ethoxy)ethyl)amino)isoindoline-1,3-dione **A5**.



[00578] 12-(((4-(((*R*)-1-(3-Bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)-methyl)dodecanamide **A40**.



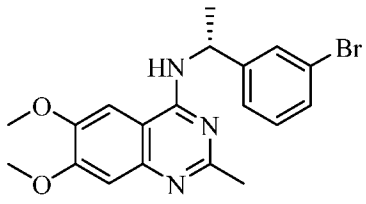
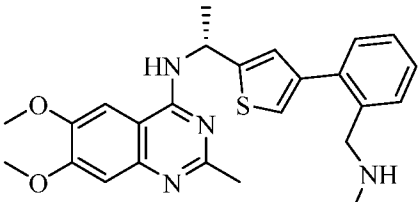
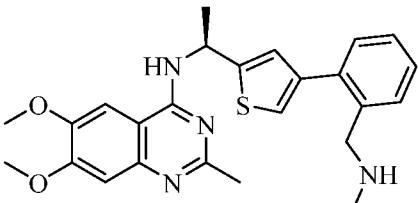
Example B1

Cell Viability Assays

[00579] H358, H23, SW48, and AsPC-1 cells were cultured in RPMI 1640 media supplemented with 10% fetal bovine serum, streptomycin, and penicillin. Lovo and SW480 cells

were cultured in DMEM media supplemented with 10% fetal bovine serum, streptomycin, and penicillin. The cell lines were plated in their respective medium supplemented with 2.5% fetal bovine serum, streptomycin, and penicillin. All cell lines were plated in white walled 96-well plates at 2,000 cells/well or 384-well plates at 500 cells/well, except Lovo, which were plated at 4,000 or 1,000 cells/well, respectively. The cells were incubated in DMSO (control) or a compound for 3 days at 37 °C under 5% CO₂. A CELLTITER-GLO® reagent (100 µL) was then added to each well. After a 10 min incubation with shaking, luminescence was measured using an ENVISION® multimode plate reader. IC₅₀ values are summarized in Table 1 and percentages of inhibition are summarized in Table 2.

Table 1. Inhibition of Cancerous Cells

Compound	IC ₅₀ (µM)					
	Lovo (G13D)	SW480 (G12V)	SW48 (wt)	AsPC-1 (G12D)	H23	H358 (G12C)
 E1	2.2	2.8	3.6		4.8	4.1
 E2					1.5	2.1
 E3					2.3	2.4
A1	0.94	0.58	0.7		1.2	2.8
A4					9	7.2
A6	4.9	8.3	> 10			9.9

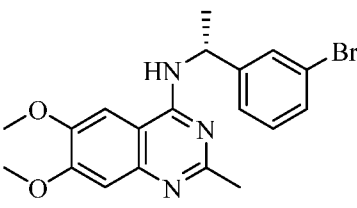
Compound	IC ₅₀ (μM)					
	Lovo (G13D)	SW480 (G12V)	SW48 (wt)	AsPC-1 (G12D)	H23	H358 (G12C)
A7	3.5	6.4	5			5.4
A8	0.97	2.1	0.4			1.6
A9	0.047	1.2	0.022			0.82
A11	0.41	0.56	0.51			1.6
A12					1.2	1.4
A13	9.8	6.6	5.9			7.4
A14	2.8	5	3.1			4.5
A15	0.26	0.37	0.41			0.55
A16	0.23	0.35	0.34			0.43
A17	0.76	0.95	1.1			1.4
A18					2.6	3
A19					1.9	1.7
A20	0.95	1.2	0.81			0.83
A21	0.38	0.43	0.43			1.1
A22					0.9	0.79
A23	0.33	0.29	0.3			0.76
A24	0.4	0.55	1.3			1.2
A25	0.29	0.37	0.42			0.51
A26	0.36	0.4	0.42			0.57
A27	0.58	0.59	0.94			1
A28	0.55	0.5	0.44	1.1		1.2
A29	0.73	5.7	0.89	> 10		6.8
A30	0.04	3.9	0.64	7.8		4.2
A31	0.23	4.9	0.51			4.5
A32	0.06	4.4	0.47	> 10		> 10
A33	0.18	0.57	3.3			> 10
A34	0.3	0.64	3.4			> 10
A35	0.54	2.5	4.1			> 10
A36					8.3	8.8
A37	> 10	> 10	> 10			> 10

Compound	IC ₅₀ (μM)					
	Lovo (G13D)	SW480 (G12V)	SW48 (wt)	AsPC-1 (G12D)	H23	H358 (G12C)
A38	6.1	6.4	7.9			6.3
A39	0.79	2.6	0.21			0.68
A41					1.3	1.5
A42	0.52	0.48	1	1.4		0.89
A43	0.34	0.44	0.62	0.83		1.3
A44	0.53	0.44	0.61	0.98		1.2
A45	1.2	0.90	2	5.2		2.3
A46	0.99	0.72	2.7	> 10		> 10
A47	0.91	0.74	1.4	3.7		3
A48	0.67	0.48	0.82			1.3
A49	0.42	2.8	0.67			> 10
A50	0.43	0.47	0.79			0.96
A51	0.16	0.64	0.29			0.39
A52	0.042	0.17	0.17			0.21
A53	0.068	0.17	0.17			0.23
A54	0.13	0.24	0.2			0.36
A55	0.64	1.8	1.4			2
A56	0.15	0.26	0.19			0.36
A57	0.9	5.2	2.9			3.3
A58	0.3	0.36	0.42			1.2
A59	4.9	4.7	5.3	> 10		> 10
A60	4.3	4	3.8	8.4		> 10
A61	6.6	5.2	5.9	> 10		> 10
A62	4	1.3	2.4	> 10		> 10
A63	< 0.014	0.65	0.02	3.5		0.13
A64	2.6	3.1	1.2	5.5		> 10
A65	1.1	1.1	0.97	3.3		1.6
A66	5.8	9.7	3.8	> 10		8
A67	1	2.7	1.1	2.1		1.7
A68	0.63	0.53	0.5	1.5		0.69

Compound	IC ₅₀ (μM)					
	Lovo (G13D)	SW480 (G12V)	SW48 (wt)	AsPC-1 (G12D)	H23	H358 (G12C)
B1	0.72	0.98	1.1	3		2.4
B2	0.48	0.5	0.98	1.2		0.98
B3	1.4	2.3	4.7	5		2.2
B4	4	> 10	> 10	> 10		7.6
B5	0.77	0.44	0.75	1.5		0.65
B6	1	0.66	0.68			1.2
B7	0.68	0.61	0.92	1.2		1.3
B8	0.39	0.55	1			1.2
B9	0.73	0.96	1.4	2.7		1.2
B10	0.67	0.72	1.3	1.5		1.6
B11	0.39	0.36	0.53	0.96		0.53
B12	0.8	0.45	0.46	2.7		1.1
C1	> 10	> 10	> 10			> 10
C2	> 10	> 10	> 10			> 10
C3	> 10	> 10	> 10			> 10
C4	> 10	> 10	> 10			> 10
C5	> 10	> 10	> 10			> 10
C6	> 10	> 10	> 10			> 10
C7	6.6	> 10	> 10		> 10	> 10
C8	0.54	1.4	1.1		> 10	2.8
D1	6.4	1.3	7.9			1.6
D2					13	15
D3	> 10	> 10	> 10			> 10
D4	> 10	2.7	> 10			> 10
D6					2.7	6.1
D9					1	0.97
D10					0.93	0.75
D11	2.6	1.2	5.9	> 10		1.6
D12	3.1	3.5	5.4			4.3
D13	1.6	2.9	> 10			> 10

Compound	IC ₅₀ (μM)					
	Lovo (G13D)	SW480 (G12V)	SW48 (wt)	AsPC-1 (G12D)	H23	H358 (G12C)
D14	0.64	3.3	> 10	> 10		> 10

Table 2. Inhibition of Molm-13 Cells

Compound	Molm-13	
	1 μM	10 μM
 E1	17%	91%
A10	22%	99%
D5	22%	99%

Example B2

Protein Degradation Assay

[00580] H358 cells are grown in RPMI 1640 media supplemented with 10% fetal bovine serum, streptomycin, and penicillin. The cells are plated in 10 cm plates in the growth media. The next day, the cells are rinsed in 1 x PBS with the media replaced by RPMI1640 supplemented with 2.5% fetal bovine serum, streptomycin, and penicillin. The cells are then treated with a compound (1 μM) for 24 h. Whole cell extracts are prepared using an immunoprecipitation (IP) lysis buffer. Briefly, the cells are washed once in PBS, and the cell pellets are resuspended in the IP lysis buffer and incubated for 15 min on ice. Cell debris is removed by centrifugation and the cleared whole cell lysates are transferred to new tubes for further analysis.

[00581] For a western blot analysis, the whole cell protein extracts are separated on 12% SDS-polyacrylamide gels, transferred to nitrocellulose, and probed with primary antibodies. Membranes are subsequently washed and probed with IRDYE[®] secondary antibodies. The signals are detected using an ODYSSEY[®] Imaging System. The antibodies used in the assay

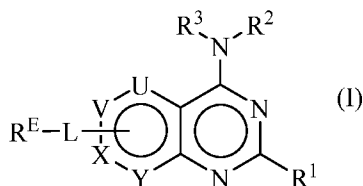
include anti-SOS1; anti-KRAS; β -actin mouse monoclonal antibody; IRDYE[®] 680RD goat anti-rabbit antibody; and IRDYE[®] 800CW goat anti-mouse antibody.

* * * * *

[00582] 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:

one of U, V, X, and Y is $-C=$ or $-N-$; and the remaining three of U, V, X, and Y are each independently $-C(R^4)=$ or $-N=$;

L is a linker;

R^E is an E3 ubiquitin ligase binding moiety;

R^1 and R^3 are each independently hydrogen, deuterium, 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;

R^2 is 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, heteroaryl- C_{1-6} alkylene, or heterocyclyl;

each R^4 is independently (i) hydrogen, deuterium, cyano, halo, nitro, or oxo; (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) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and

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, or heterocyclyl;

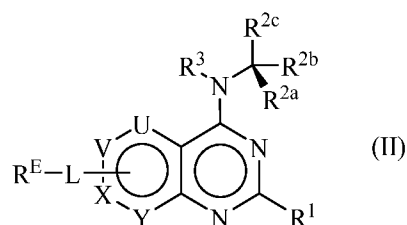
wherein each alkyl, alkylene, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more, in one

embodiment, one, two, three, or four, substituents Q, wherein each Q is independently selected from: (a) deuterium, cyano, halo, imino, 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, -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)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, imino, 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)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.

2. The compound of claim 1, wherein R² is C₁₋₆ alkyl, C₇₋₁₅ aralkyl, or heteroaryl-C₁₋₆ alkylene, each of which is optionally substituted with one or more substituents Q.

3. The compound of claim 1 or 2, wherein R^2 is C_{1-6} alkyl, optionally substituted with one or more substituents Q.
4. The compound of any one of claims 1 to 3, wherein R^2 is heteroaryl- C_{1-6} alkylene, and wherein the alkylene and heteroaryl are each optionally substituted with one or more substituents Q^a .
5. The compound of any one of claims 1 to 4, wherein R^2 is monocyclic heteroaryl- C_{1-6} alkylene, and wherein the alkylene and heteroaryl are each optionally substituted with one or more substituents Q^a .
6. The compound of any one of claims 1 to 5, wherein R^2 is 5-membered heteroaryl- C_{1-6} alkylene, and wherein the alkylene and heteroaryl are each optionally substituted with one or more substituents Q^a .
7. The compound of claim 1 or 2, wherein R^2 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q.
8. The compound of claim 1, wherein the compound is a compound of Formula (II):



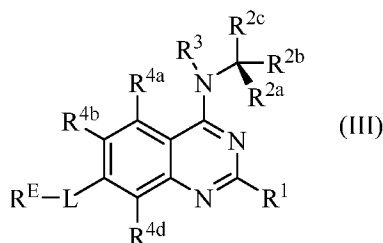
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

R^{2a} and R^{2b} are each independently hydrogen, deuterium, halo, 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; and

R^{2c} is C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl;

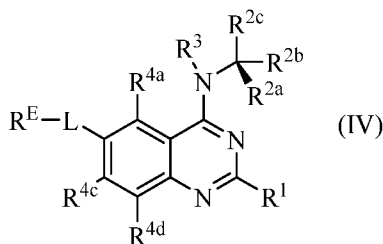
wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl and heterocyclyl is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

9. The compound of claim 8, wherein the compound 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^{4a} , R^{4b} , and R^{4d} are each independently (i) hydrogen, 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, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$.

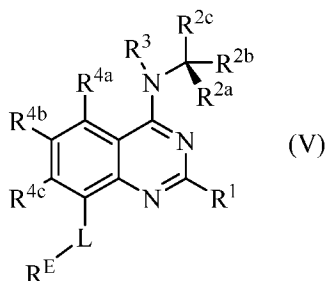
10. The compound of claim 8, wherein the compound is a compound of Formula (IV):



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^{4a} , R^{4c} , and R^{4d} are each independently (i) hydrogen, 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

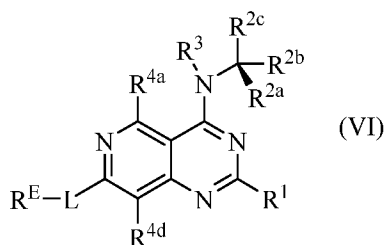
heterocyclyl, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; or (iii) $-\text{C}(\text{O})\text{R}^{1a}$, $-\text{C}(\text{O})\text{OR}^{1a}$, $-\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{C}(\text{O})\text{SR}^{1a}$, $-\text{C}(\text{NR}^{1a})\text{NR}^{1b}\text{R}^{1c}$, $-\text{C}(\text{S})\text{R}^{1a}$, $-\text{C}(\text{S})\text{OR}^{1a}$, $-\text{C}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OR}^{1a}$, $-\text{OC}(\text{O})\text{R}^{1a}$, $-\text{OC}(\text{O})\text{OR}^{1a}$, $-\text{OC}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OC}(\text{O})\text{SR}^{1a}$, $-\text{OC}(\text{NR}^{1a})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OC}(\text{S})\text{R}^{1a}$, $-\text{OC}(\text{S})\text{OR}^{1a}$, $-\text{OC}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS}(\text{O})\text{R}^{1a}$, $-\text{OS}(\text{O})_2\text{R}^{1a}$, $-\text{OS}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{SR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{NR}^{1d})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{R}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{SR}^{1a}$, $-\text{S}(\text{O})\text{R}^{1a}$, $-\text{S}(\text{O})_2\text{R}^{1a}$, $-\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, or $-\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$.

11. The compound of claim 8, wherein the compound 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^{4a} , R^{4b} , and R^{4c} are each independently (i) hydrogen, 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, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; or (iii) $-\text{C}(\text{O})\text{R}^{1a}$, $-\text{C}(\text{O})\text{OR}^{1a}$, $-\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{C}(\text{O})\text{SR}^{1a}$, $-\text{C}(\text{NR}^{1a})\text{NR}^{1b}\text{R}^{1c}$, $-\text{C}(\text{S})\text{R}^{1a}$, $-\text{C}(\text{S})\text{OR}^{1a}$, $-\text{C}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OR}^{1a}$, $-\text{OC}(\text{O})\text{R}^{1a}$, $-\text{OC}(\text{O})\text{OR}^{1a}$, $-\text{OC}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OC}(\text{O})\text{SR}^{1a}$, $-\text{OC}(\text{NR}^{1a})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OC}(\text{S})\text{R}^{1a}$, $-\text{OC}(\text{S})\text{OR}^{1a}$, $-\text{OC}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS}(\text{O})\text{R}^{1a}$, $-\text{OS}(\text{O})_2\text{R}^{1a}$, $-\text{OS}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{SR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{NR}^{1d})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{R}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{SR}^{1a}$, $-\text{S}(\text{O})\text{R}^{1a}$, $-\text{S}(\text{O})_2\text{R}^{1a}$, $-\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, or $-\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$.

12. The compound of claim 8, wherein the compound 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^{4a} and R^{4d} are each independently (i) hydrogen, deuterium, cyano, halo, nitro, or oxo; (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; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$.

13. The compound of any one of claims 8 to 12, wherein R^{2c} is C_{6-14} aryl or heteroaryl, each of which is optionally substituted with one, two, or three substituents Q.

14. The compound of any one of claims 8 to 13, wherein R^{2c} is C_{6-14} aryl, optionally substituted with one, two, or three substituents Q.

15. The compound of any one of claims 8 to 14, wherein R^{2c} is phenyl, optionally substituted with one, two, or three substituents, each of which is independently fluoro, chloro, bromo, iodo, nitro, methyl, difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, 1-hydroxyethyl, 1-hydroxy-1-methylethyl, 2-hydroxy-1,1-difluoroethyl, 3-hydroxyoxetan-3-yl, pyrazol-4-yl, or amino.

16. The compound of any one of claims 8 to 14, wherein R^{2c} is bicyclic C_{9-14} aryl, optionally substituted with one, two, or three substituents Q.

17. The compound of any one of claims 8 to 13, wherein R^{2c} is heteroaryl, optionally substituted with one, two, or three substituents Q.

18. The compound of any one of claims 8 to 13 and 17, wherein R^{2c} is monocyclic heteroaryl, optionally substituted with one, two, or three substituents Q.

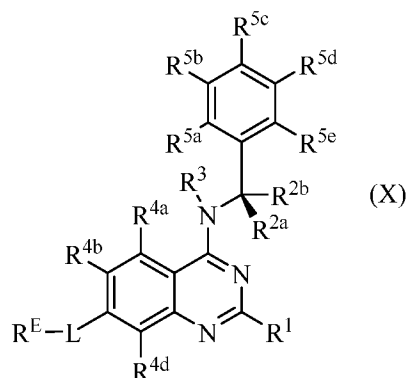
19. The compound of any one of claims 8 to 13, 17, and 18, wherein R^{2c} is 5- or 6-membered heteroaryl, each optionally substituted with one, two, or three substituents Q.

20. The compound of any one of claims 8 to 13 and 17 to 19, wherein R^{2c} is thienyl, optionally substituted with one, two, or three substituents Q.

21. The compound of any one of claims 8 to 13 and 17 to 20, wherein R^{2c} is thien-2-yl or thien-3-yl, each optionally substituted with one, two, or three substituents Q.

22. The compound of any one of claims 8 to 13, wherein R^{2c} is phenyl, 3-bromophenyl, 3-methylphenyl, 3-difluoromethylphenyl, 3-trifluoromethylphenyl, 3-(2,2,2-trifluoroethyl)phenyl, 3-(1-hydroxyethyl)phenyl, 3-(1-hydroxy-1-methylethyl)phenyl, 3-(2-hydroxy-1,1-difluoroethyl)phenyl, 3-(3-hydroxyoxetan-3-yl)phenyl, 3-(1*H*-pyrazol-4-yl)phenyl, 2-fluoro-3-methylphenyl, 2-fluoro-3-difluoromethylphenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-3-(1,1-difluoroethyl)phenyl, 2-methyl-3-difluoromethylphenyl, 2-methyl-3-trifluoromethylphenyl, 3-trifluoromethyl-5-aminophenyl, 2-fluoro-3-trifluoromethyl-5-aminophenyl, 2-methyl-3-trifluoromethyl-5-aminophenyl, 3,3-difluoro-2,3-dihydro-1*H*-inden-5-yl, naphth-1-yl, thien-2-yl, 5-(2-hydroxymethylphenyl)thien-2-yl, 5-(2-aminomethylphenyl)thien-2-yl, 4-(2-methylaminomethylphenyl)thien-2-yl, 5-(2-(2-aminoethyl)phenyl)thien-2-yl, 5-(6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl)thien-2-yl, or 3,3-difluoro-2,3-dihydrobenzofuran-5-yl.

23. The compound of claim 9, wherein the compound is a compound of Formula (X):

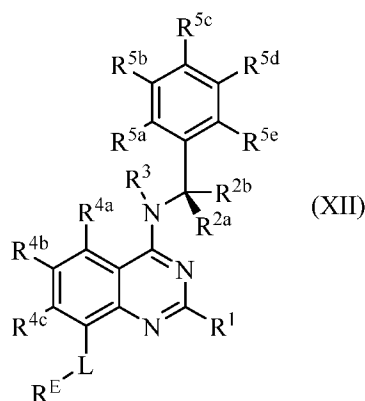


or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

R^{5a} , R^{5b} , R^{5c} , R^{5d} , and R^{5e} are each independently (i) hydrogen, deuterium, cyano, halo, nitro, or oxo; (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, or three, substituents Q; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; or

R^{5a} and R^{5b} or R^{5b} and R^{5c} together with the carbon atoms to which they are attached form C_{5-10} 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, or three, substituents Q.

24. The compound of claim 11, wherein the compound 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^{5a}, R^{5b}, R^{5c}, R^{5d}, and R^{5e} are each independently (i) hydrogen, deuterium, cyano, halo, nitro, or oxo; (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, or three, substituents Q; 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)NR^{1b}R^{1c}, or -S(O)₂NR^{1b}R^{1c}; or

R^{5a} and R^{5b} or R^{5b} and R^{5c} together with the carbon atoms to which they are attached form C₅₋₁₀ 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, or three, substituents Q.

25. The compound of claim 23 or 24, wherein R^{5a} is hydrogen, halo, or C₁₋₆ alkyl, optionally substituted with one, two, or three substituents Q.

26. The compound of any one of claims 23 to 25, wherein R^{5a} is hydrogen, fluoro, or methyl.

27. The compound of any one of claims 23 to 26, wherein R^{5b} is hydrogen or C₁₋₆

alkyl, optionally substituted with one, two, or three substituents Q.

28. The compound of any one of claims 23 to 27, wherein R^{5b} is hydrogen, methyl, difluoromethyl, trifluoromethyl, or 1,1-difluoro-2-hydroxyethyl.

29. The compound of any one of claims 23 to 28, wherein R^{5b} is trifluoromethyl or 1,1-difluoro-2-hydroxyethyl.

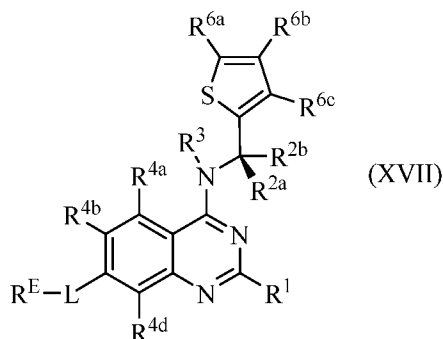
30. The compound of any one of claims 23 to 29, wherein R^{5c} is hydrogen.

31. The compound of any one of claims 23 to 30, wherein R^{5d} is hydrogen, nitro, or amino.

32. The compound of any one of claims 23 to 31, wherein R^{5d} is amino.

33. The compound of any one of claims 23 to 32, wherein R^{5e} is hydrogen.

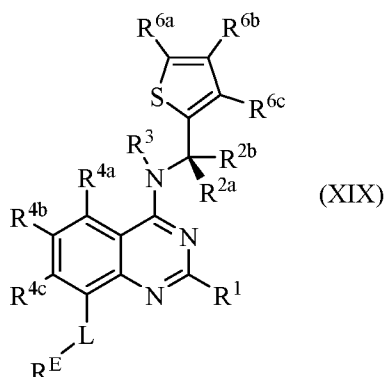
34. The compound of claim 9, wherein the compound is a compound of Formula (XVII):



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^{6a} , R^{6b} , and R^{6c} are each independently (i) hydrogen, deuterium, cyano, halo, nitro, or oxo; (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, each of which is optionally substituted with one or more, in one embodiment, one, two, or three, substituents Q; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$,

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

35. The compound of claim 11, wherein the compound 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^{6a} , R^{6b} , and R^{6c} are each independently (i) hydrogen, deuterium, cyano, halo, nitro, or oxo; (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, each of which is optionally substituted with one or more, in one embodiment, one, two, or three, substituents Q; or (iii) $-\text{C}(\text{O})\text{R}^{1a}$, $-\text{C}(\text{O})\text{OR}^{1a}$, $-\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{C}(\text{O})\text{SR}^{1a}$, $-\text{C}(\text{NR}^{1a})\text{NR}^{1b}\text{R}^{1c}$, $-\text{C}(\text{S})\text{R}^{1a}$, $-\text{C}(\text{S})\text{OR}^{1a}$, $-\text{C}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OR}^{1a}$, $-\text{OC}(\text{O})\text{R}^{1a}$, $-\text{OC}(\text{O})\text{OR}^{1a}$, $-\text{OC}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OC}(\text{O})\text{SR}^{1a}$, $-\text{OC}(\text{NR}^{1a})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OC}(\text{S})\text{R}^{1a}$, $-\text{OC}(\text{S})\text{OR}^{1a}$, $-\text{OC}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS}(\text{O})\text{R}^{1a}$, $-\text{OS}(\text{O})_2\text{R}^{1a}$, $-\text{OS}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{SR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{NR}^{1d})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{R}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{S})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{SR}^{1a}$, $-\text{S}(\text{O})\text{R}^{1a}$, $-\text{S}(\text{O})_2\text{R}^{1a}$, $-\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, or $-\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$.

36. The compound of claim 34 or 35, wherein R^{6a} is (i) hydrogen or halo; or (ii) C_{6-14} aryl or heteroaryl, each optionally substituted with one, two, or three substituents Q.

37. The compound of any one of claims 34 to 36, wherein R^{6a} is (i) hydrogen or halo; or (ii) phenyl or bicyclic heteroaryl, each optionally substituted with one, two, or three substituents Q.

38. The compound of any one of claims 34 to 37, wherein R^{6a} is hydrogen, bromo, 2-(hydroxymethyl)phenyl, 2-(aminomethyl)phenyl, 2-(methylaminomethyl)phenyl, 2-(2-aminoethyl)phenyl, or 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl.

39. The compound of any one of claims 34 to 38, wherein R^{6b} is (i) hydrogen; or (ii) C_{6-14} aryl or heteroaryl, each optionally substituted with one, two, or three substituents Q.

40. The compound of any one of claims 34 to 39, wherein R^{6b} is (i) hydrogen; or (ii) phenyl or bicyclic heteroaryl, each optionally substituted with one, two, or three substituents Q.

41. The compound of any one of claims 34 to 40, wherein R^{6b} is hydrogen, 2-(hydroxymethyl)phenyl, 2-(aminomethyl)phenyl, 2-(methylaminomethyl)phenyl, 2-(2-aminoethyl)phenyl, or 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl.

42. The compound of any one of claims 34 to 41, wherein R^{6c} is hydrogen.

43. The compound of any one of claims 1 to 42, wherein R^1 is hydrogen or C_{1-6} alkyl optionally substituted with one, two, or three substituents Q.

44. The compound of any one of claims 1 to 43, wherein R^1 is hydrogen, methyl, trifluoromethyl, or dimethylamino.

45. The compound of any one of claims 1 to 44, wherein R^1 is methyl.

46. The compound of any one of claims 1 to 45, wherein R^3 is hydrogen.

47. The compound of any one of claims 8 to 46, wherein R^{2a} is hydrogen or C_{1-6} alkyl optionally substituted with one, two, or three substituents Q.

48. The compound of any one of claims 8 to 47, wherein R^{2a} is hydrogen, methyl, or ethyl.

49. The compound of any one of claims 8 to 48, wherein R^{2b} is hydrogen or C_{1-6} alkyl optionally substituted with one, two, or three substituents Q.

50. The compound of any one of claims 8 to 49, wherein R^{2b} is hydrogen, methyl, or ethyl.

51. The compound of any one of claims 9 to 50, wherein R^{4a} is hydrogen.

52. The compound of any one of claims 9, 11, and 13 to 51, wherein R^{4b} is (i) C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more, in one embodiment, one, two, or three, substituents Q; or (ii) $-OR^{1a}$.

53. The compound of any one of claims 9, 11, and 13 to 52, wherein R^{4b} is C_{3-10} cycloalkyl, optionally substituted with one, two, or three substituents Q.

54. The compound of any one of claims 9, 11, and 13 to 53, wherein R^{4b} is monocyclic C_{3-10} cycloalkyl, optionally substituted with one, two, or three substituents Q.

55. The compound of any one of claims 9, 11, and 13 to 53, wherein R^{4b} is bicyclic C_{4-10} cycloalkyl, optionally substituted with one, two, or three substituents Q.

56. The compound of any one of claims 9, 11, and 13 to 53, wherein R^{4b} is cyclopropyl, cyclobutyl, cyclohexyl, cyclohexenyl, bicyclo[1.1.1]pentanyl, or bicyclo[2.2.2]octanyl, each of which is optionally substituted with one, two, or three substituents, where each substituent is independently fluoro, methyl, difluoromethyl, 3-cyanoazetidin-1-ylcarbonyl, 3-fluoroazetidin-1-ylcarbonyl, 3-methoxyazetidin-1-ylcarbonyl, 3-hydroxypyrrolidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-(2-methoxyethyl)piperazin-1-ylcarbonyl, hydroxycarbonyl, ethoxycarbonyl, dimethylcarbamoyl, (methyl)(ethyl)carbamoyl, (2-hydroxyethyl)(methyl)carbamoyl, (2-hydroxypropyl)(methyl)carbamoyl, (2-hydroxy-2-methylpropyl)(methyl)carbamoyl, (2,3-dihydroxypropyl)(methyl)carbamoyl, (2-methoxyethyl)-(methyl)carbamoyl, (methyl)(oxetan-3-yl)carbamoyl, (methyl)(tetrahydrofuran-3-yl)carbamoyl, hydroxyl, or acetoxy.

57. The compound of any one of claims 9, 11, 13 to 53, and 56, wherein R^{4b} is 1-

methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, 4-hydroxycyclohexyl, 4-hydroxycarbonylcyclohexyl, 4-ethoxycarbonylcyclohexyl, 4-(3-cyanoazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-fluoroazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-methoxyazetidin-1-ylcarbonyl)cyclohexyl, 4-(3-hydroxypyrrolidin-1-yl)carbonylcyclohexyl, 4-morpholin-4-ylcarbonylcyclohexyl, 4-(4-methylpiperazin-1-yl)carbonylcyclohexyl, 4-(4-(2-methoxyethyl)piperazin-1-yl)carbonylcyclohexyl, 4-dimethylcarbamoylcyclohexyl, 4-(methyl)(ethyl)carbamoylcyclohexyl, 4-(2-hydroxyethyl)(methyl)carbamoylcyclohexyl, 4-(2-hydroxypropyl)(methyl)carbamoylcyclohexyl, 4-(2-hydroxy-2-methylpropyl)(methyl)carbamoylcyclohexyl, 4-(2,3-dihydroxypropyl)(methyl)carbamoylcyclohexyl, 4-(2-methoxyethyl)(methyl)carbamoylcyclohexyl, 4-(methyl)(oxetan-3-yl)carbamoylcyclohexyl, 4-(methyl)(tetrahydrofuran-3-yl)carbamoylcyclohexyl, 4-acetoxy-1-hydroxycyclohexyl, 1,4-dihydroxycyclohexyl, 4-hydroxycarbonyl-1-hydroxycyclohexyl, 4-ethoxycarbonyl-1-hydroxycyclohexyl, 4-dimethylcarbamoyl-1-hydroxycyclohexyl, 4-(2-hydroxyethyl)(methyl)carbamoyl-1-hydroxycyclohexyl, 4-(2-hydroxypropyl)(methyl)carbamoyl-1-hydroxycyclohexyl, bicyclo[1.1.1]pentan-1-yl, or 4-fluorobicyclo[2.2.2]octan-1-yl.

58. The compound of any one of claims 9, 11, and 13 to 52, wherein R^{4b} is heterocyclyl, optionally substituted with one, two, or three substituents Q.

59. The compound of any one of claims 9, 11, 13 to 52, and 58, wherein R^{4b} is monocyclic heterocyclyl, optionally substituted with one, two, or three substituents Q.

60. The compound of any one of claims 9, 11, 13 to 52, and 58, wherein R^{4b} is bicyclic heterocyclyl, optionally substituted with one, two, or three substituents Q.

61. The compound of any one of claims 9, 11, 13 to 52, and 58, wherein R^{4b} is tetrahydrofuryl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydropyridinyl, dihydropyranyl, dihydrothiopyranyl, azaspiro[3.3]heptanyl, or 7-azaspiro[3.5]nonanyl, each of which is optionally substituted with one, two, or three substituents, where each substituent is independently oxo, imino, isopropyl, hydroxycarbonylmethyl, dimethylcarbamoylmethyl, tetrahydrofuran-3-yl, acetyl, 2-methoxyacetyl, 2-dimethylaminoacetyl, *tert*-butoxycarbonyl, or hydroxyl.

62. The compound of any one of claims 9, 11, 13 to 52, 58, and 61, wherein R^{4b} is 3-methyltetrahydrofuran-3-yl, piperidin-4-yl, 1-isopropylpiperidin-4-yl, 1-(hydroxycarbonylmethyl)piperidin-4-yl, 1-(dimethylcarbamoylmethyl)piperidin-4-yl, 1-tetrahydrofuran-3-ylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-(2-methoxyacetyl)piperidin-4-yl, 1-(2-dimethylaminoacetyl)piperidin-4-yl, 1-*tert*-butoxycarbonylpiperidin-4-yl, 4-hydroxypiperidin-4-yl, 1-acetyl-4-hydroxypiperidin-4-yl, 1-(2-methoxyacetyl)-4-hydroxypiperidin-4-yl, 4-hydroxy-1-*tert*-butoxycarbonylpiperidin-4-yl, 1-dimethylcarbamoyl-4-hydroxypiperidin-4-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, 1-oxotetrahydrothiopyran-4-yl, 1,1-dioxotetrahydrothiopyran-4-yl, 1-oxo-1-iminotetrahydrothiopyran-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, 3,6-dihydropyran-4-yl, 3,6-dihydrothiopyran-4-yl, 1-oxo-3,6-dihydrothiopyran-4-yl, 1,1-dioxo-3,6-dihydrothiopyran-4-yl, 1-oxo-1-imino-3,6-dihydrothiopyran-4-yl, 6-hydroxy-2-azaspiro[3.3]heptan-6-yl, or 2-hydroxy-7-azaspiro[3.5]nonan-2-yl.

63. The compound of any one of claims 9, 11, and 13 to 52, wherein R^{4b} is $-OR^{1a}$.

64. The compound of any one of claims 9, 11, 13 to 52, and 63, wherein R^{4b} is $-O-C_{1-6}$ alkyl, optionally substituted with one, two, or three substituents Q.

65. The compound of any one of claims 9, 11, 13 to 52, and 63, wherein R^{4b} is $-O$ -heterocyclyl, optionally substituted with one, two, or three substituents Q.

66. The compound of any one of claims 9, 11, 13 to 52, 63, and 65, wherein R^{4b} is $-O$ -(monocyclic heterocyclyl), optionally substituted with one, two, or three substituents Q.

67. The compound of any one of claims 9, 11, 13 to 52, and 63, wherein R^{4b} is methoxy, tetrahydrofuryloxy, or pyrrolidinylloxy, each of which is optionally substituted with acetyl, propionyl, cyclopropylcarbonyl, or *tert*-butoxycarbonyl.

68. The compound of any one of claims 9, 11, 13 to 52, and 63, wherein R^{4b} is methoxy, tetrahydrofuran-3-yloxy, (*R*)-tetrahydrofuran-3-yloxy, (*S*)-tetrahydrofuran-3-yloxy, pyrrolidin-3-yloxy, 1-acetylpyrrolidin-3-yloxy, 1-propionylpyrrolidin-3-yloxy, 1-cyclopropylcarbonylpyrrolidin-3-yloxy, or 1-*tert*-butoxycarbonylpyrrolidin-3-yloxy.

69. The compound of any one of claims 9, 11, 13 to 52, 63, and 64, wherein R^{4b} is

methoxy.

70. The compound of any one of claims 9, 11, 13 to 52, and 65 to 68, wherein R^{4b} is (*R*)-tetrahydrofuran-3-yloxy or (*S*)-tetrahydrofuran-3-yloxy.

71. The compound of any one of claims 10, 11, 13 to 22, 24 to 33, and 35 to 70, wherein R^{4c} is hydrogen or $-OR^{1a}$.

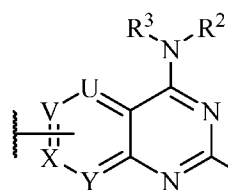
72. The compound of any one of claims 10, 11, 13 to 22, 24 to 33, and 35 to 71, wherein R^{4c} is $-OR^{1a}$.

73. The compound of any one of claims 10, 11, 13 to 22, 24 to 33, and 35 to 71, wherein R^{4c} is hydrogen, hydroxyl, or methoxy.

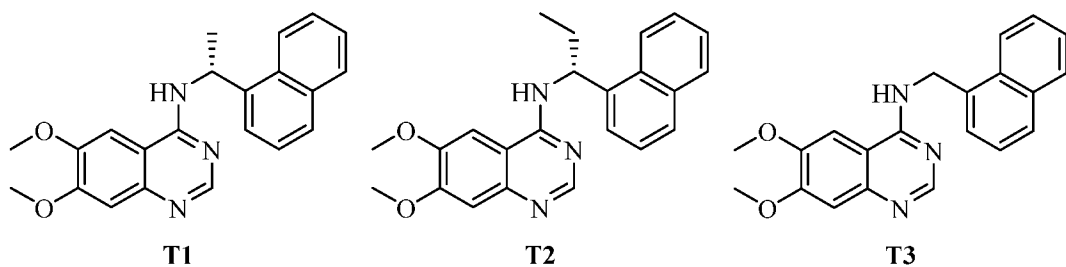
74. The compound of any one of claims 9, 10, 12 to 23, 25 to 34, and 36 to 73, wherein R^{4d} is hydrogen, halo, or C_{1-6} alkyl optionally substituted with one, two, or three substituents Q.

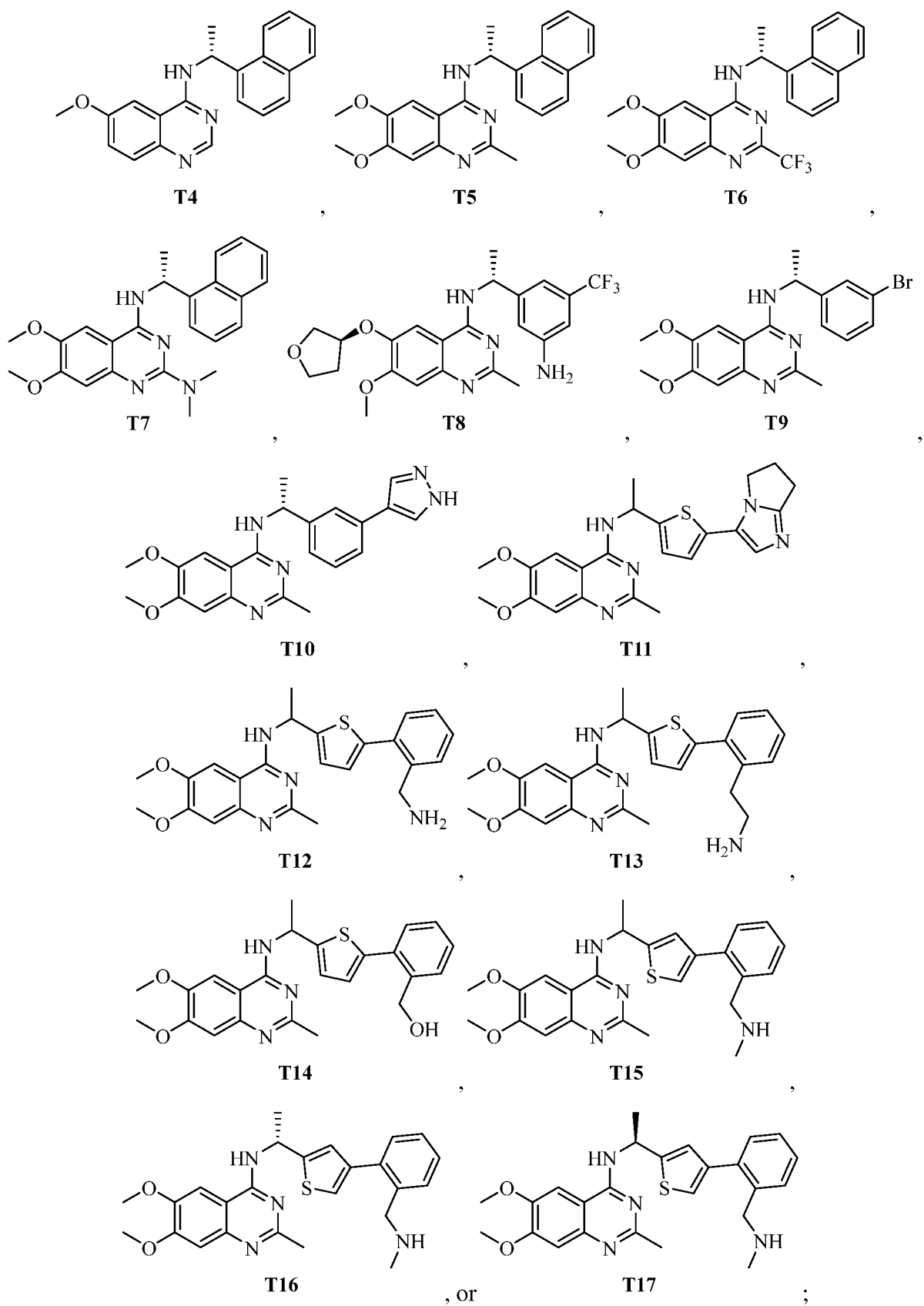
75. The compound of any one of claims 9, 10, 12 to 23, 25 to 34, and 36 to 74, wherein R^{4d} is hydrogen, fluoro, or methyl.

76. The compound of claim 1, wherein the moiety of the structure of



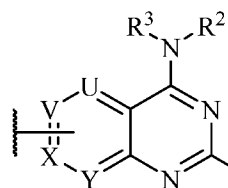
is a moiety of a compound having the structure of:



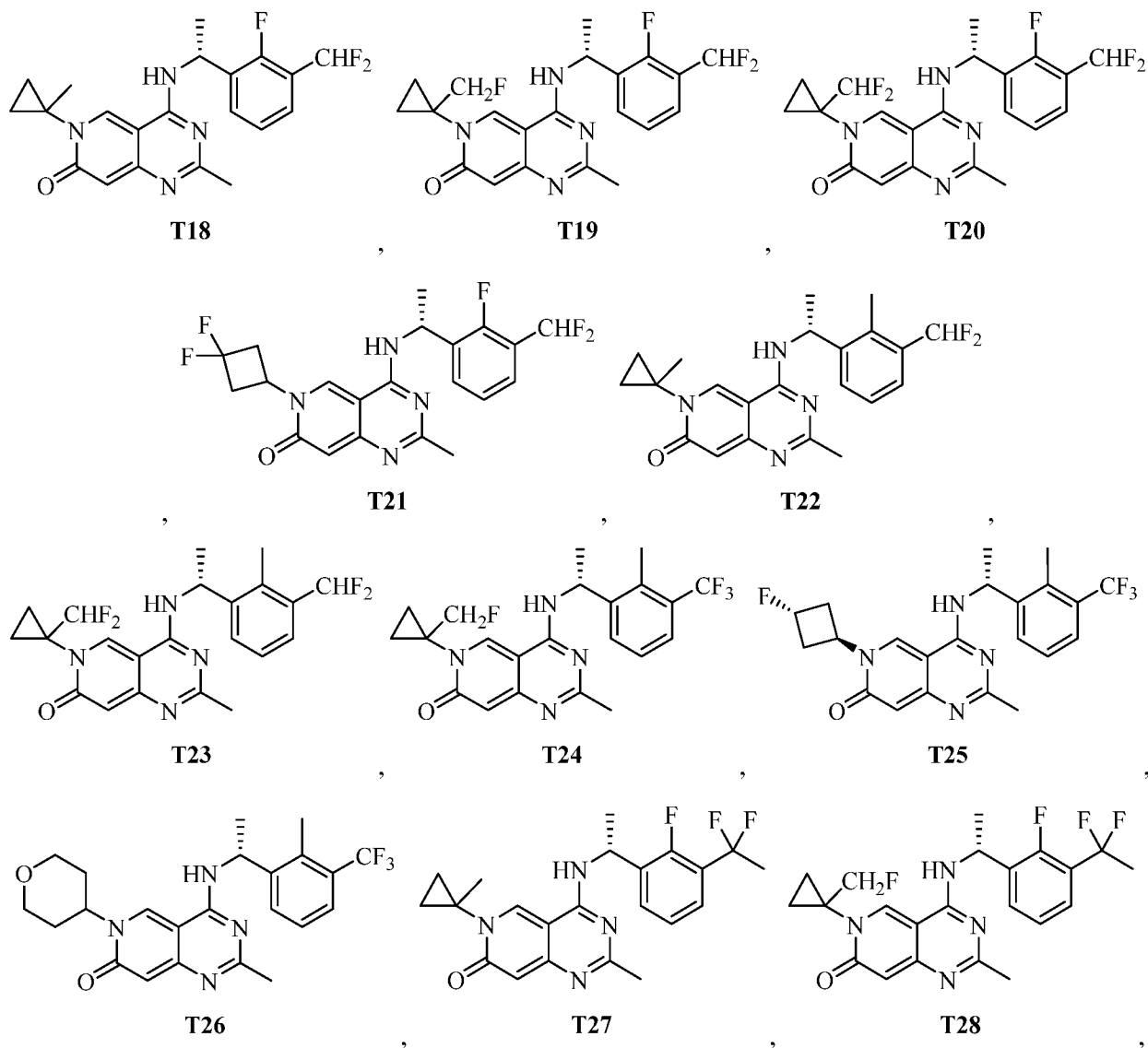


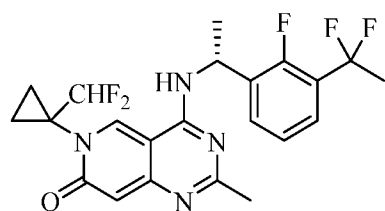
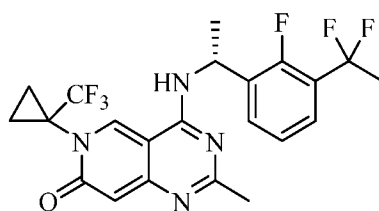
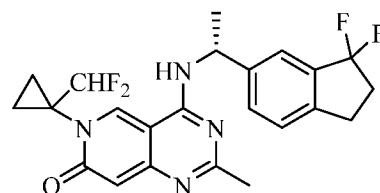
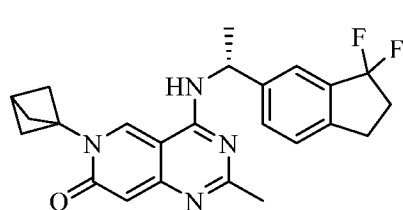
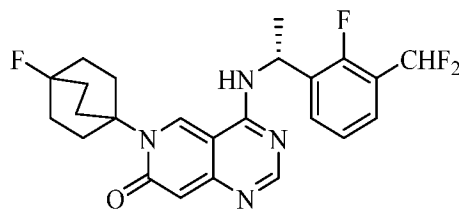
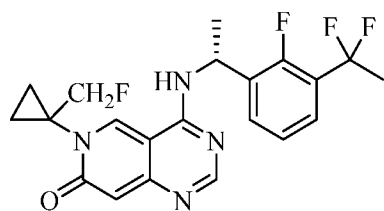
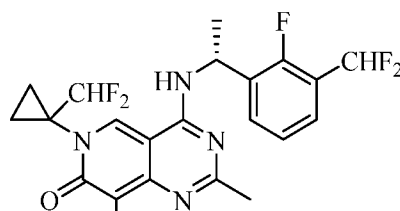
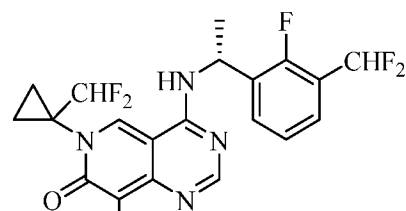
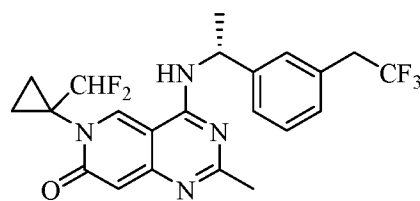
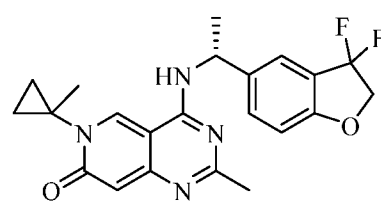
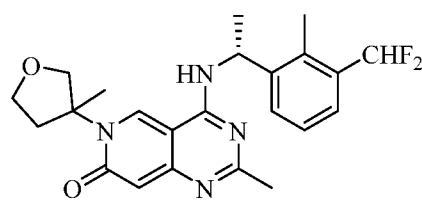
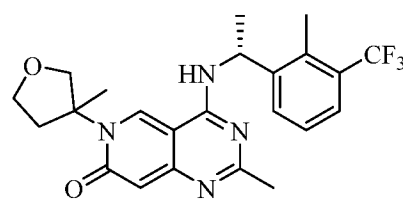
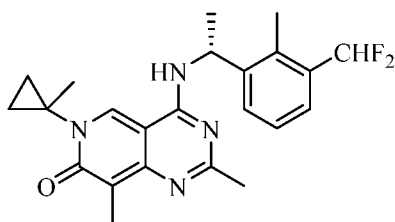
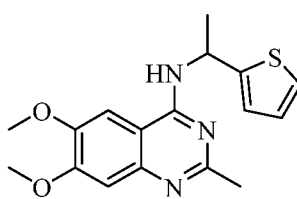
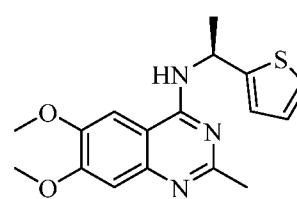
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

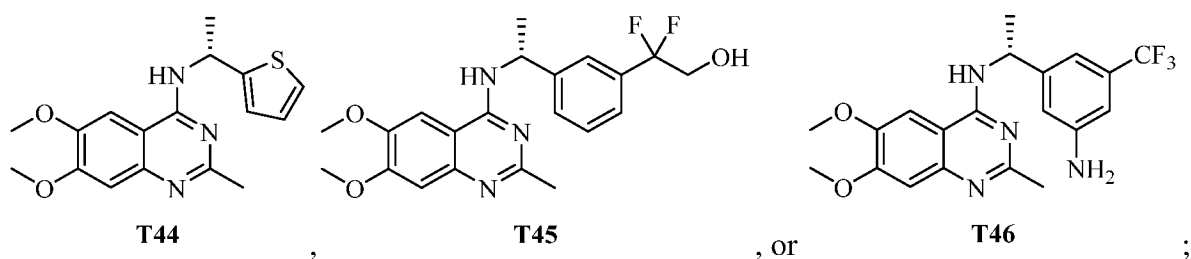
77. The compound of claim 1, wherein the moiety of the structure of



is a moiety of a compound having the structure of:

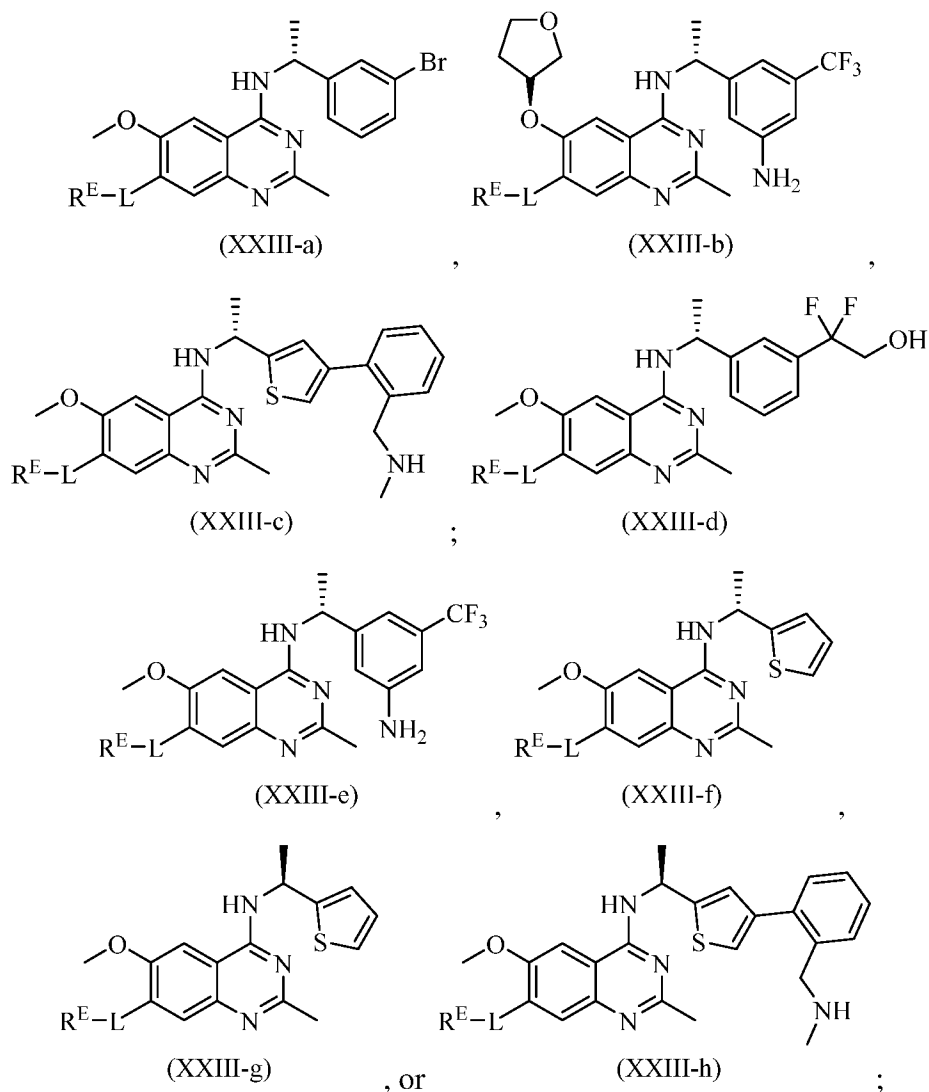


**T29****T30****T31****T32****T33****T34****T35****T36****T37****T38****T39****T40****T41****T42****T43**



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.

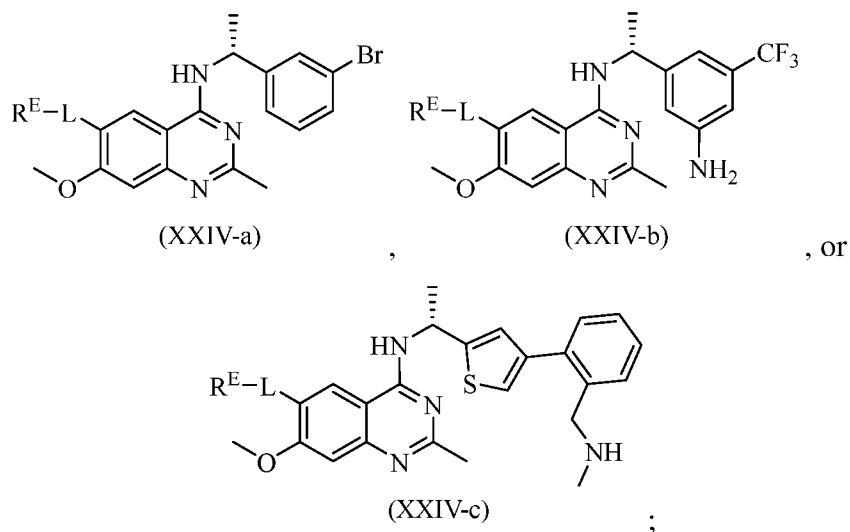
78. The compound of any one of claims 1, 8, and 9, wherein the compound is a compound of the structure of:



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

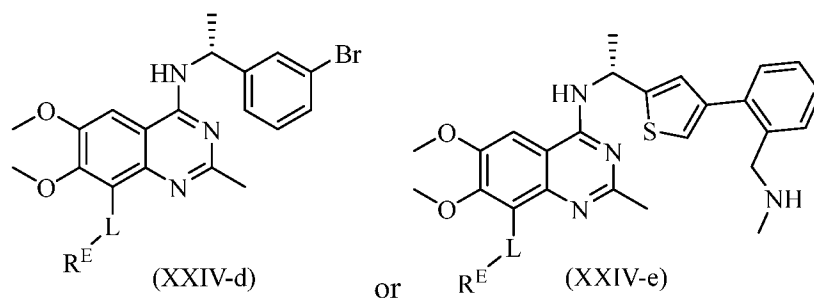
a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

79. The compound of claim 1, 8, or 10, wherein the compound is a compound of the structure of:



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.

80. The compound of claim 1, 8, or 11, wherein the compound is a compound of the structure of:

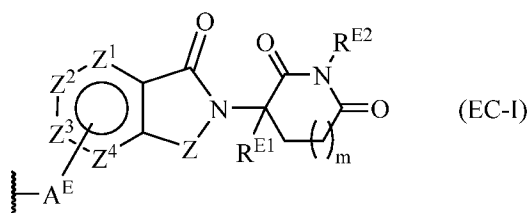


or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

81. The compound of any one of claims 1 to 80, wherein R^E is a moiety of a cereblon (CRBN) E3 ligand, an inhibitors-of-apoptosis protein (IAP) E3 ligand, a mouse double minute 2 homolog (MDM2) E3 ligand, or a von Hippel-Lindau (VHL) E3 ligand.

82. The compound of any one of claims 1 to 81, wherein R^E is a moiety of a cereblon (CRBN) E3 ligand.

83. The compound of any one of claims 1 to 82, wherein R^E is a moiety having the structure of Formula (EC-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; wherein:

A^E is a bond, $-O-$, $-N(R^{1b})-$, $-S-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} heteroalkenylene, C_{2-6} alkynylene, C_{2-6} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, C_{7-15} aralkylene, heteroarylene, heterocyclylene, C_{1-6} heteroalkylene- C_{6-14} arylene, or C_{2-6} alkynylene-heterocyclylene;

Z is $-CH_2-$ or $-C(O)-$;

one of Z^1 , Z^2 , Z^3 , and Z^4 is $-C=$ and the remaining three of Z^1 , Z^2 , Z^3 , and Z^4 are each independently $-C(R^{E5})=$; or Z^1 is a bond; one of Z^2 , Z^3 , and Z^4 is $-C=$, and the remaining two of Z^2 , Z^3 , and Z^4 are each independently $-C(R^{E5})=$ or $-S-$;

m is an integer of 0, 1, or 2;

R^{E1} is hydrogen, deuterium, halo, or C_{1-6} alkyl;

R^{E2} is hydrogen or C_{1-6} alkyl;

each R^{E4} 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) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$,

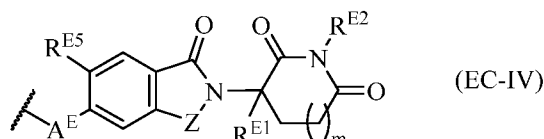
$-\text{SR}^{1a}$, $-\text{S(O)}\text{R}^{1a}$, $-\text{S(O)}_2\text{R}^{1a}$, $-\text{S(O)}\text{NR}^{1b}\text{R}^{1c}$, or $-\text{S(O)}_2\text{NR}^{1b}\text{R}^{1c}$;

each $\text{R}^{\text{E}5}$ is independently hydrogen or $\text{R}^{\text{E}4}$; and

R^{1a} , R^{1b} , R^{1c} , and R^{1d} are each as defined herein;

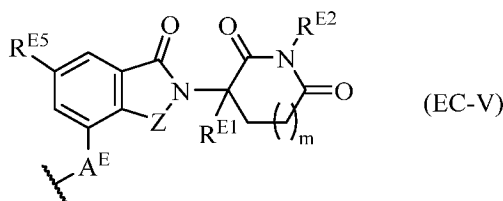
wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, alkynylene, heteroalkynylene, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, aralkylene, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

84. The compound of claim 83, wherein R^{E} is a moiety having the structure of Formula (EC-IV):



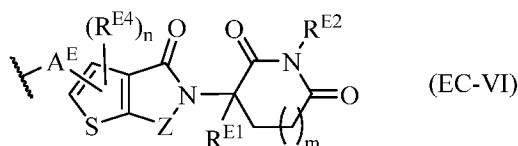
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

85. The compound of claim 83, wherein R^{E} is a moiety having the structure of Formula (EC-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.

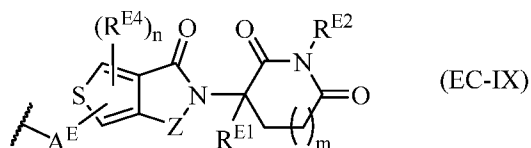
86. The compound of claim 83, wherein R^{E} is a moiety having the structure of Formula (EC-VI):



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

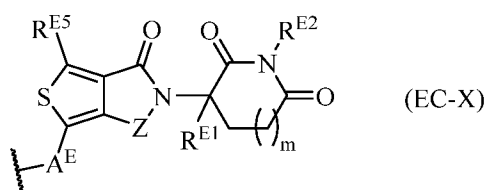
diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein n is an integer of 0 or 1.

87. The compound of claim 83, wherein R^E is a moiety having the structure of Formula (EC-IX):



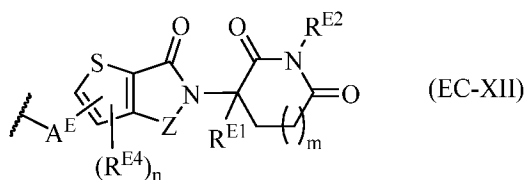
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein n is an integer of 0 or 1.

88. The compound of claim 83 or 87, wherein R^E is a moiety having the structure of Formula (EC-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.

89. The compound of claim 83, wherein R^E is a moiety having the structure of Formula (EC-XII):



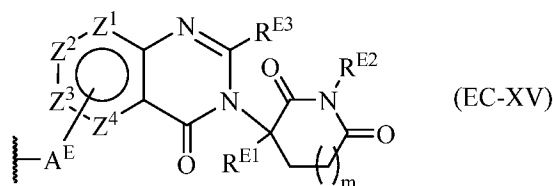
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein n is an integer of 0 or 1.

90. The compound of any one of claims 83 to 89, wherein Z is $-\text{CH}_2-$.

91. The compound of any one of claims 83 to 89, wherein Z is $-\text{C}(\text{O})-$.

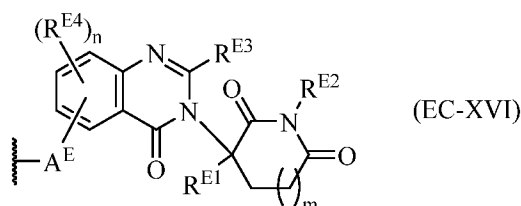
92. The compound of any one of claims 83 to 85, 88, 90, and 91, wherein R^{E5} is hydrogen or fluoro.

93. The compound of claim 81, wherein R^E is a moiety having the structure of Formula (EC-XV):



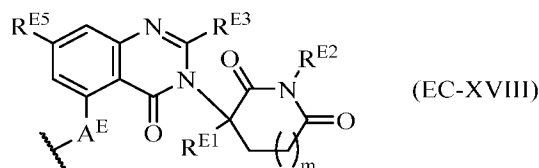
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein R^{E3} is hydrogen, deuterium, halo, or C_{1-6} alkyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

94. The compound of claim 81 or 93, wherein R^E is a moiety having the structure of Formula (EC-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; wherein R^{E3} is hydrogen, deuterium, halo, or C_{1-6} alkyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

95. The compound of claim 81, 93, or 94, wherein R^E is a moiety having the structure of Formula (EC-XVIII):



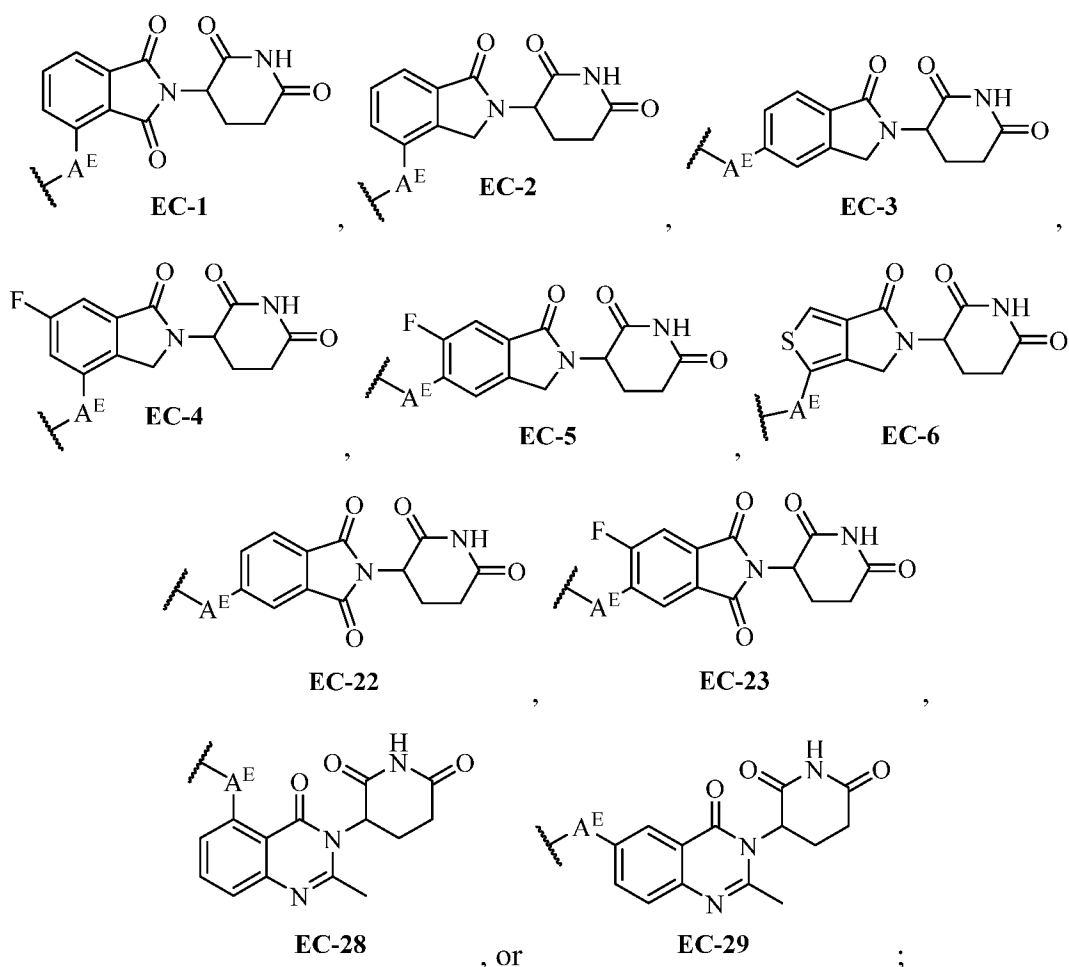
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof;

wherein R^{E3} is hydrogen, deuterium, halo, or C_{1-6} alkyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

96. The compound of any one of claims 83 to 95, wherein R^{E1} is hydrogen.

97. The compound of any one of claims 83 to 96, wherein R^{E2} is hydrogen.

98. The compound of any one of claims 1 to 83, wherein R^E is a moiety having the structure of:



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; wherein A^E is a bond, $-O-$, $-N(R^{1b})-$, $-S-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} heteroalkenylene, C_{2-6} alkynylene, C_{2-6} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, C_{7-15} aralkylene, heteroarylene, heterocyclylene, C_{1-6} heteroalkylene- C_{6-14} arylene, or C_{2-6}

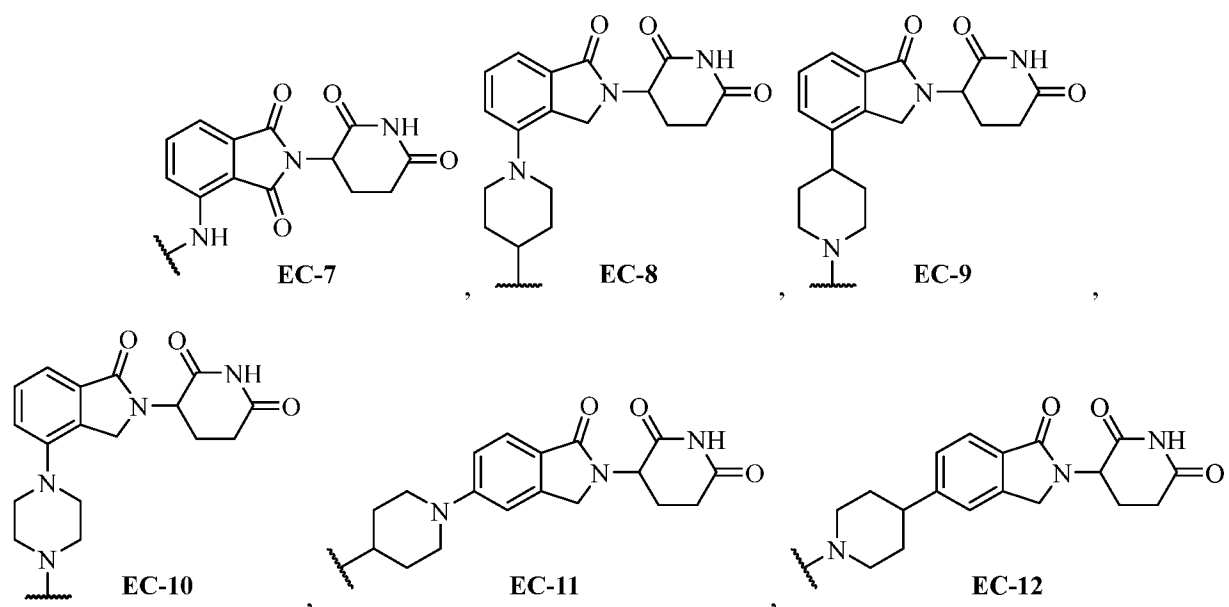
alkynylene-heterocyclylene; and wherein each alkylene, heteroalkylene, alkenylene, heteroalkenylene, alkynylene, heteroalkynylene, cycloalkylene, arylene, aralkylene, heteroarylene, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

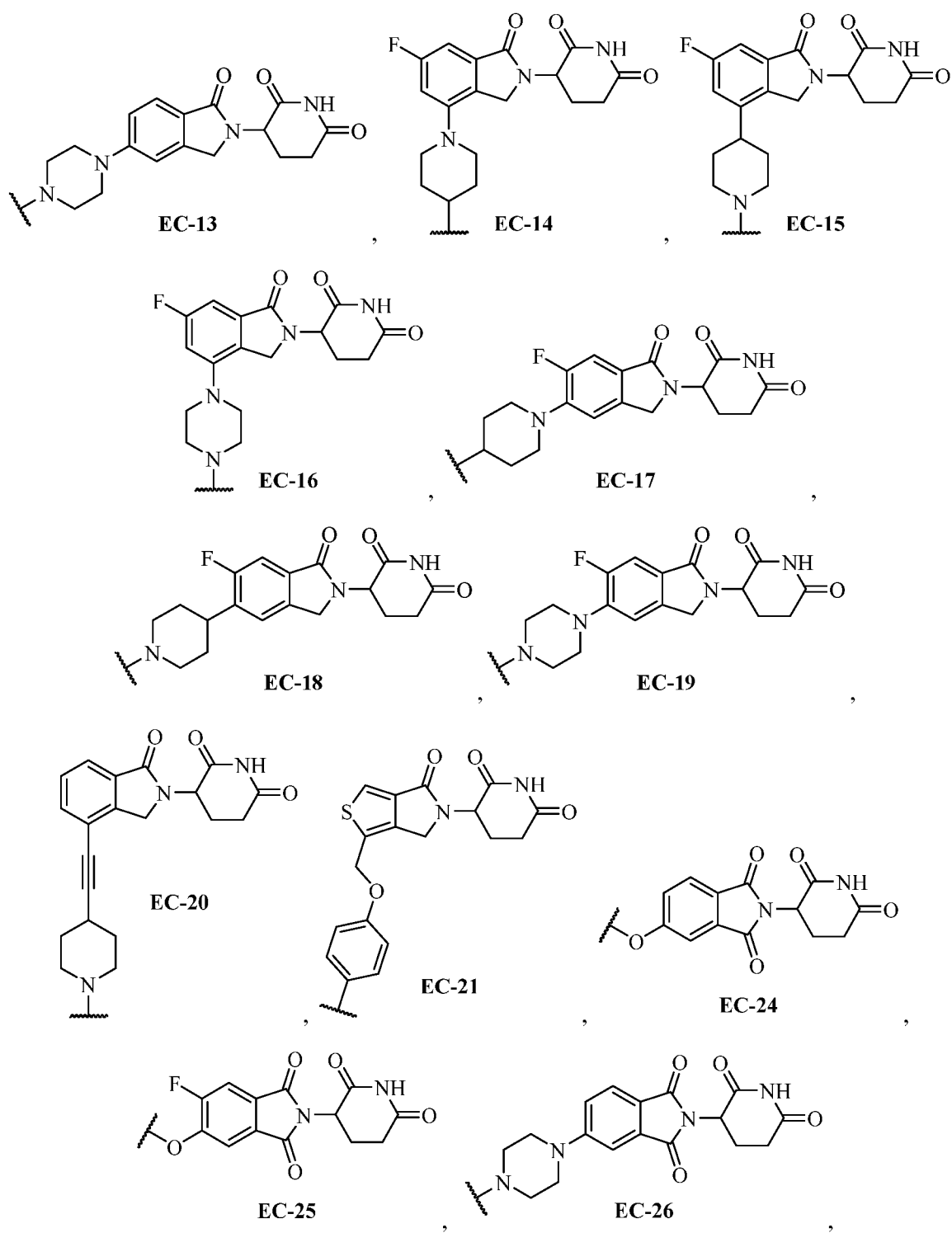
99. The compound of any one of claims 83 to 98, wherein A^E is a bond, $-O-$, $-N(R^{1b})-$, C_{2-6} alkynylene, heterocyclylene, C_{1-6} heteroalkylene- C_{6-14} arylene, or C_{2-6} alkynylene-heterocyclylene, where each heteroalkylene, alkynylene, arylene, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q;

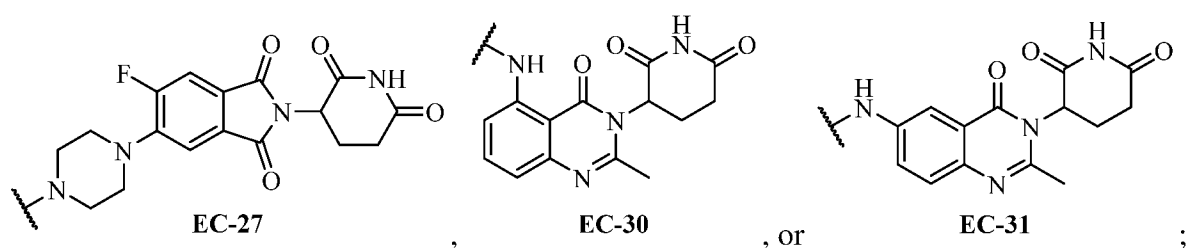
100. The compound of any one of claims 83 to 99, wherein A^E is a bond, $-O-$, $-NH-$, ethynediyl, piperidindiyl, piperazindiyl, (phendiyl)oxymethanediyl, or (piperidindiyl)ethynediyl.

101. The compound of any one of claims 83 to 100, wherein A^E is a bond, $-NH-$, piperidin-1,4-diyl, piperaz-1,4-diyl, (phen-1,4-diyl)oxymethanediyl, or (piperidin-1,4-diyl)ethynediyl.

102. The compound of any one of claims 1 to 82, wherein R^E is a moiety having the structure of:

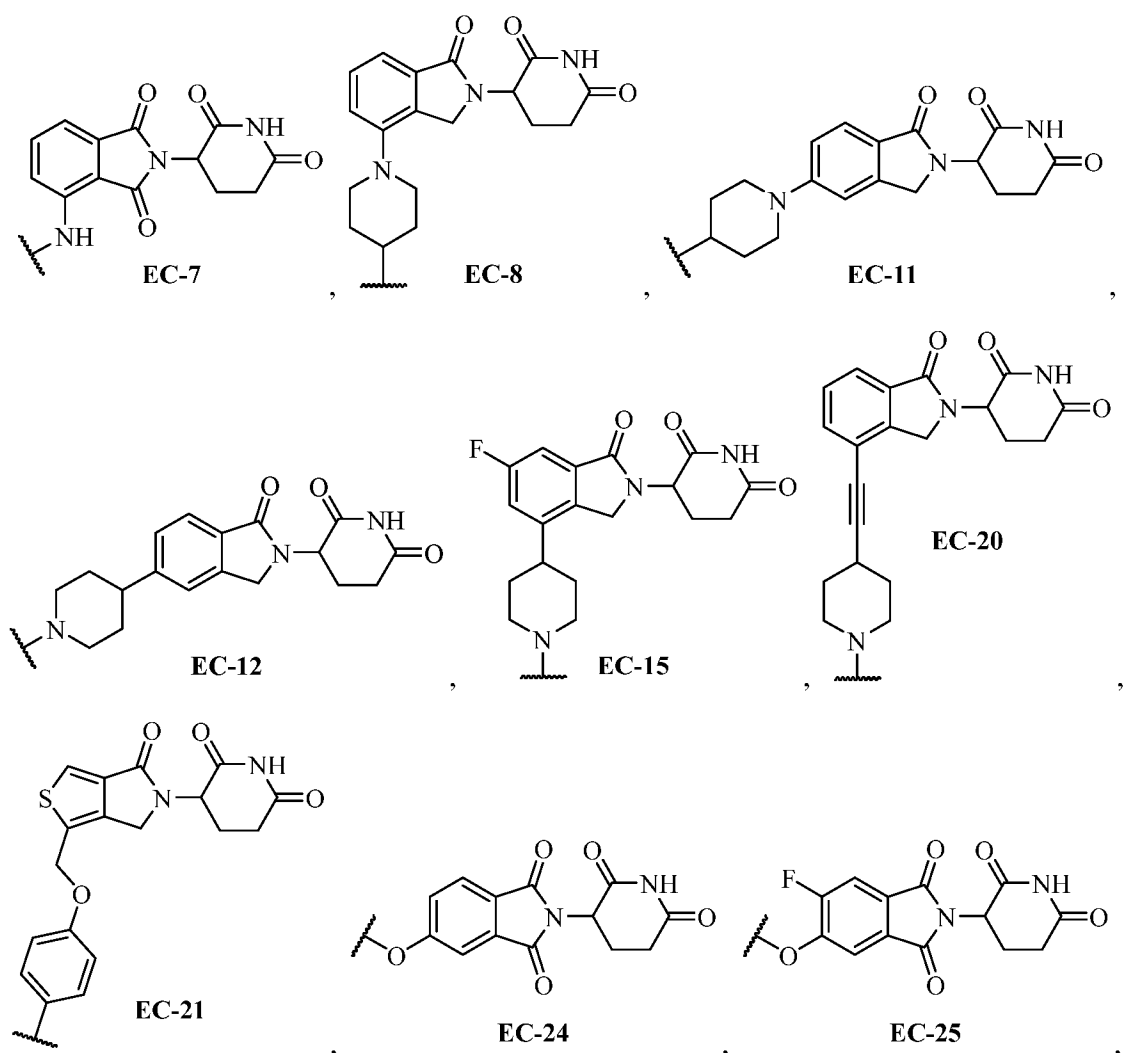


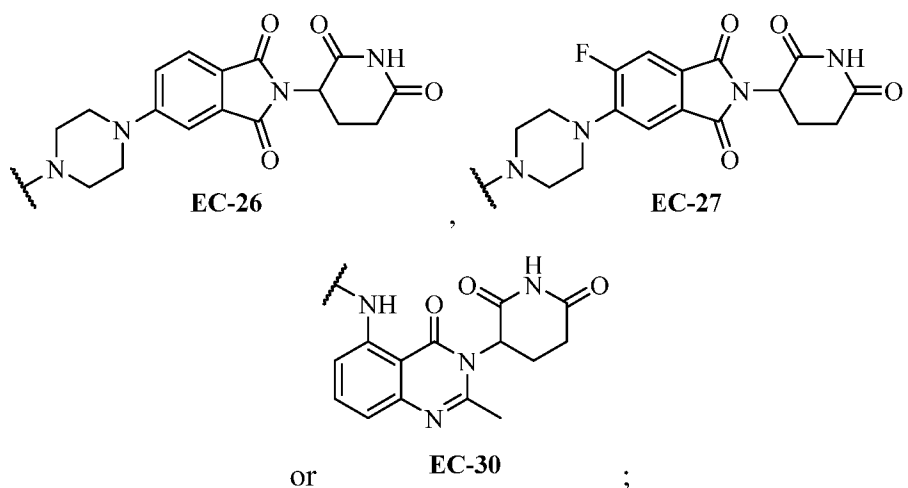




or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

103. The compound of any one of claims 1 to 82 and 102, wherein R^E is a moiety having the structure of:

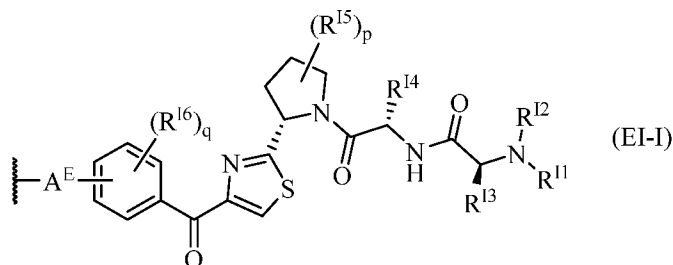




or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

104. The compound of any one of claims 1 to 81, wherein R^E is a moiety of an IAP E3 ligand.

105. The compound of any one of claims 1 to 81 and 104, wherein R^E is a moiety having the structure of Formula (EI-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; wherein:

R^{11} and R^{12} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl;

R^{13} and R^{14} are each independently C_{1-6} alkyl, C_{3-10} cycloalkyl, or heterocyclyl;

each R^{15} and R^{16} is independently (i) deuterium, cyano, halo, nitro, or oxo; (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) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$,

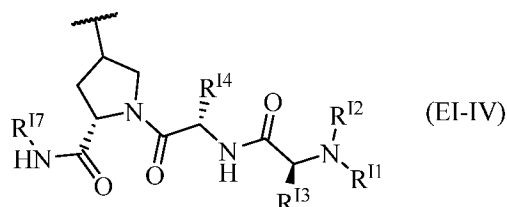
$-\text{OS(O)}\text{R}^{1a}$, $-\text{OS(O)}_2\text{R}^{1a}$, $-\text{OS(O)}\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS(O)}_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C(O)}\text{R}^{1d}$,
 $-\text{NR}^{1a}\text{C(O)}\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C(O)}\text{NR}^{1b}\text{R}^{1c}$,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

p is an integer of 0, 1, 2, 4, or 5; and

q is an integer of 0, 1, 2, or 4;

wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q.

106. The compound of any one of claims 1 to 81 and 104, wherein R^E is a moiety having the structure of Formula (EI-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; wherein:

R^{11} and R^{12} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl;

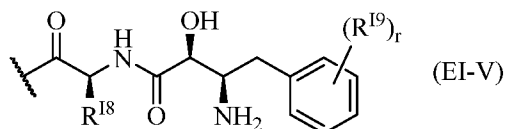
R^{13} and R^{14} are each independently C_{1-6} alkyl, C_{3-10} cycloalkyl, or heterocyclyl;

and

R^{17} is C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl;

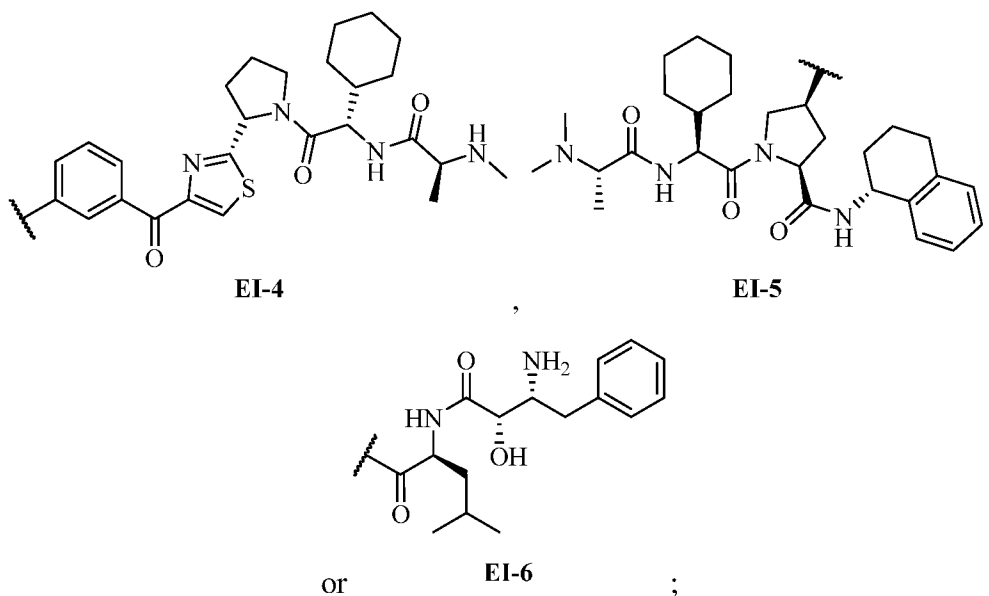
wherein each alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q.

107. The compound of any one of claims 1 to 81 and 104, wherein R^E is a moiety having the structure of Formula (EI-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;

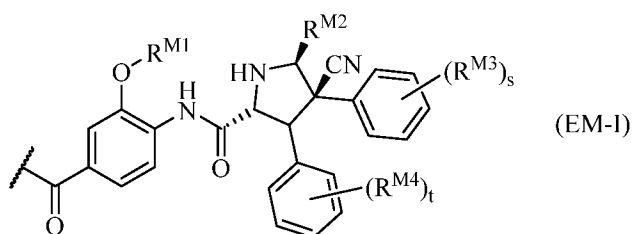
109. The compound of any one of claims 1 to 81, 104, and 108, wherein R^E is a moiety having the structure of:



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

110. The compound of any one of claims 1 to 81, wherein R^E is a moiety of an MDM2 E3 ligand.

111. The compound of any one of claims 1 to 81 and 110, wherein R^E is a moiety of an MDM2 E3 ligand having the structure of Formula (EM-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; wherein:

R^{M1} and R^{M2} are each independently C_{1-6} alkyl or C_{3-10} cycloalkyl;

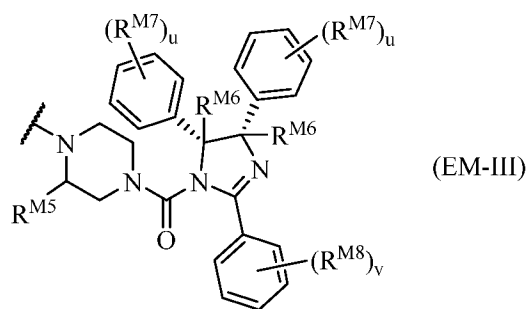
each R^{M3} and R^{M4} is independently (i) deuterium, cyano, halo, nitro, or oxo; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl,

heteroaryl, or heterocyclyl; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and

s and t are each independently an integer of 0, 1, 2, 3, 4, or 5;

wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q.

112. The compound of any one of claims 1 to 81 and 110, wherein R^E is a moiety of an MDM2 E3 ligand having the structure of Formula (EM-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; wherein:

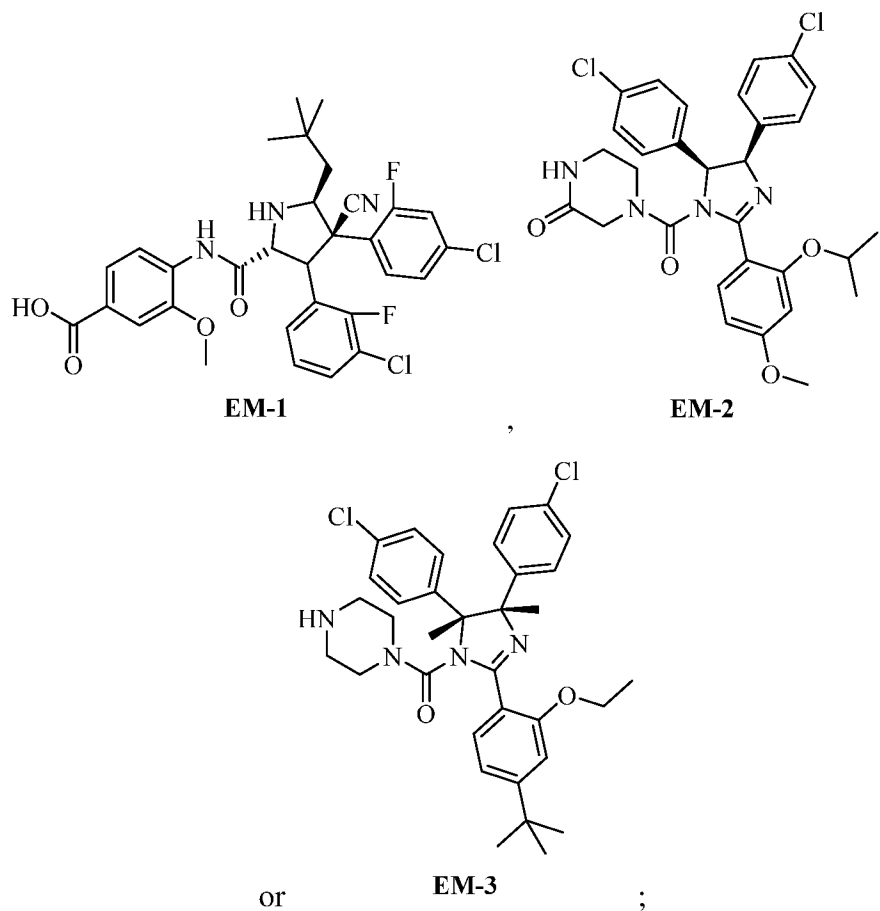
R^{M5} is hydrogen or oxo;

each R^{M6} is independently hydrogen, deuterium, or C_{1-6} alkyl; and

each R^{M7} and R^{M8} is independently (i) deuterium, cyano, halo, nitro, or oxo; (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) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$,

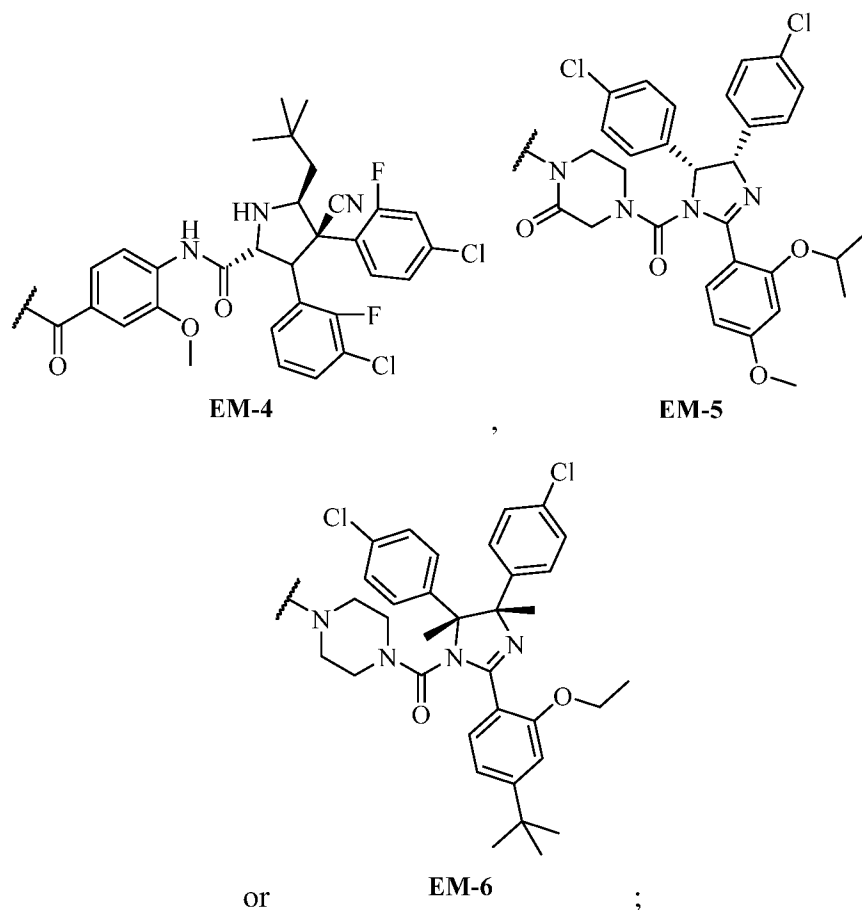
$-\text{NR}^{1a}\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{SR}^{1a}$, $-\text{S}(\text{O})\text{R}^{1a}$, $-\text{S}(\text{O})_2\text{R}^{1a}$, $-\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, or $-\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$; and
 each u and v is independently an integer of 0, 1, 2, 3, 4, or 5;
 wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q .

113. The compound of any one of claims 1 to 81 and 110, wherein R^E is a moiety of an MDM2 E3 ligand having the structure of:



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

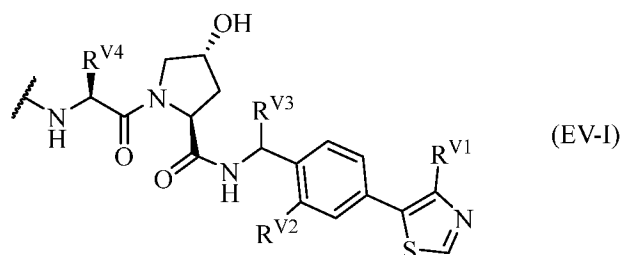
114. The compound of any one of claims 1 to 81, 110, and 113, wherein R^E is a moiety having the structure of:



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

115. The compound of any one of claims 1 to 81, wherein R^E is a moiety of a VHL E3 ligand.

116. The compound of any one of claims 1 to 81 and 115, wherein R^E has the structure of Formula (EV-I):



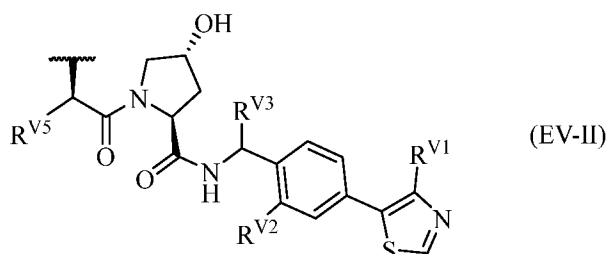
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein:

R^{V1} , R^{V3} , and R^{V4} are each independently hydrogen, deuterium, C_{1-6} alkyl, or C_{3-10} cycloalkyl; and

R^{V2} is hydrogen, deuterium, halo, hydroxyl, $-OC_{1-6}$ alkyl, or $-OC_{3-10}$ cycloalkyl;

wherein each alkyl and cycloalkyl is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

117. The compound of any one of claims 1 to 81 and 115, wherein R^E has the structure of Formula (EV-II):



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

R^{V1} and R^{V3} are each independently hydrogen, deuterium, C_{1-6} alkyl, or C_{3-10} cycloalkyl;

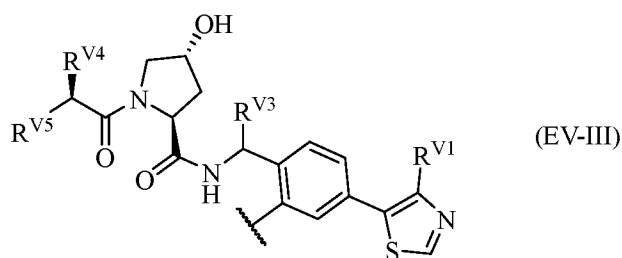
R^{V2} is hydrogen, deuterium, halo, hydroxyl, $-OC_{1-6}$ alkyl, or $-OC_{3-10}$ cycloalkyl;

and

R^{V5} is $-NHC(O)C_{1-6}$ alkyl, $-NHC(O)C_{3-10}$ cycloalkyl, or heterocyclyl;

wherein each alkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

118. The compound of any one of claims 1 to 81 and 115, wherein R^E has the structure of Formula (EV-III):



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

R^{V1}, R^{V3}, and R^{V4} are each independently hydrogen, deuterium, C₁₋₆ alkyl, or C₃₋₁₀ cycloalkyl; and

R^{V5} is -NHC(O)C₁₋₆ alkyl, -NHC(O)C₃₋₁₀ cycloalkyl, or heterocyclcyl;

wherein each alkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

119. The compound of any one of claims 116 to 118, wherein R^{V1} is methyl.

120. The compound of claim 116, 117, or 119, wherein R^{V2} is hydrogen.

121. The compound of any one of claims 116 to 120, wherein R^{V3} is hydrogen.

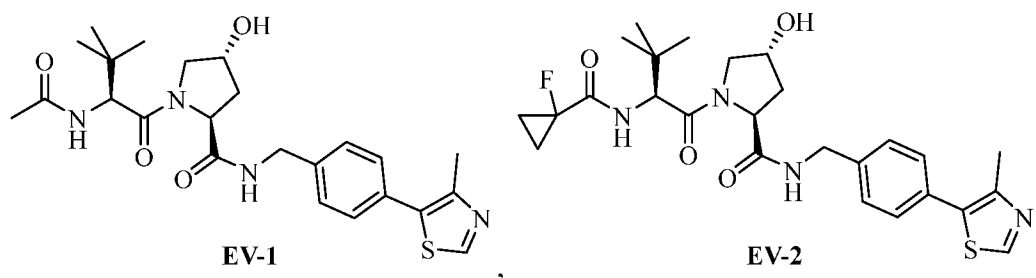
122. The compound of any one of claims 116 and 118 to 121, wherein R^{V4} is propyl, butyl, or cyclopropyl, each of which is optionally substituted with cyano, fluoro, or trifluoromethyl.

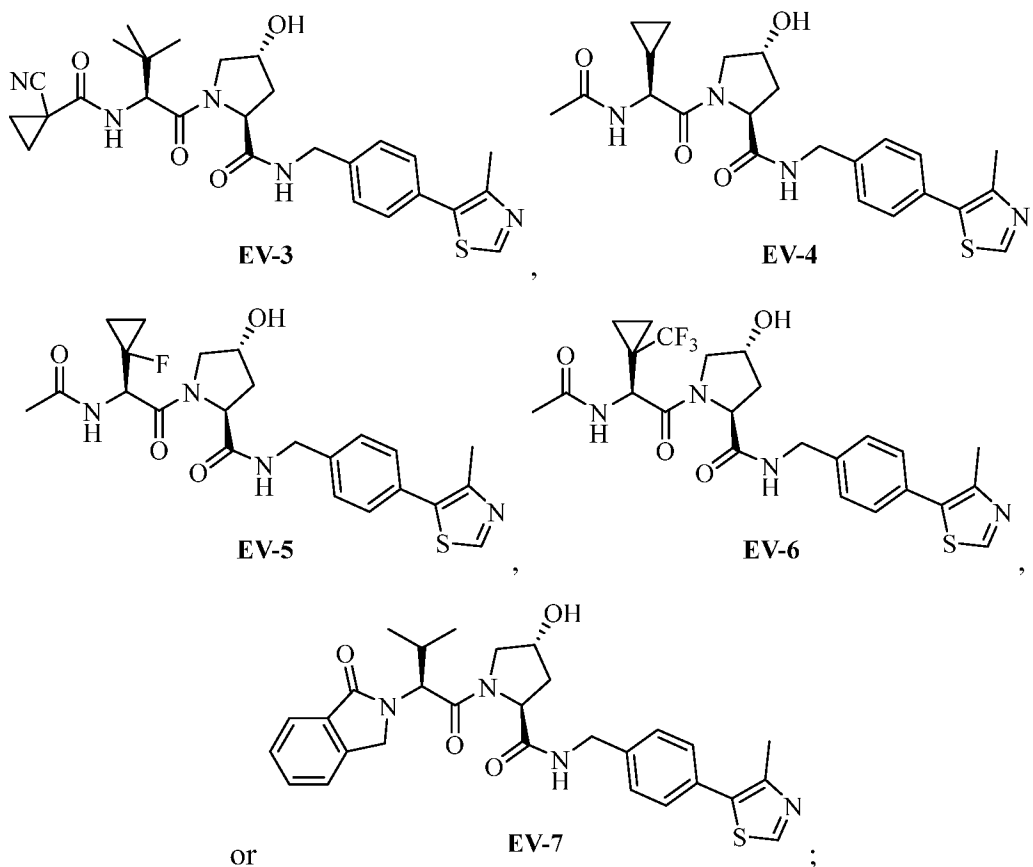
123. The compound of any one of claims 116 and 118 to 122, wherein R^{V4} is isopropyl, *tert*-butyl, cyclopropyl, 1-fluorocyclopropyl, or 1-trifluoromethylcyclopropyl.

124. The compound of any one of claims 117 to 123, wherein R^{V5} is acetamido, cyclopropamido, or isoindolinyl, each of which is optionally substituted with cyano, fluoro, or trifluoromethyl.

125. The compound of any one of claims 117 to 124, wherein R^{V5} is acetamido, cyclopropamido, 1-cyanocyclopropamido, 1-fluorocyclopropamido, or 1-oxoisindolin-2-yl.

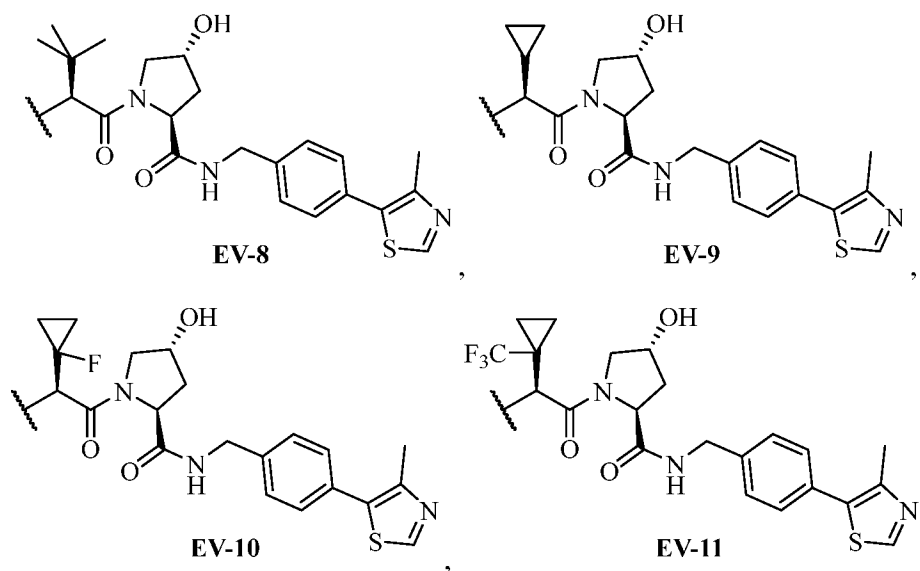
126. The compound of any one of claims 1 to 81 and 115, wherein R^E is a moiety of a VHL E3 ligand having the structure of:

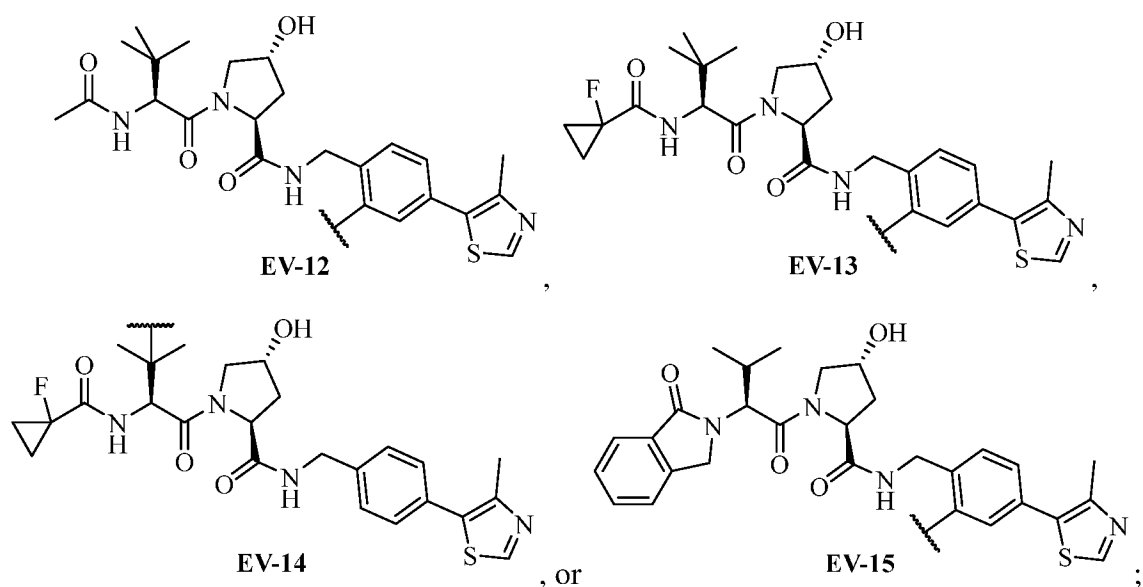




or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

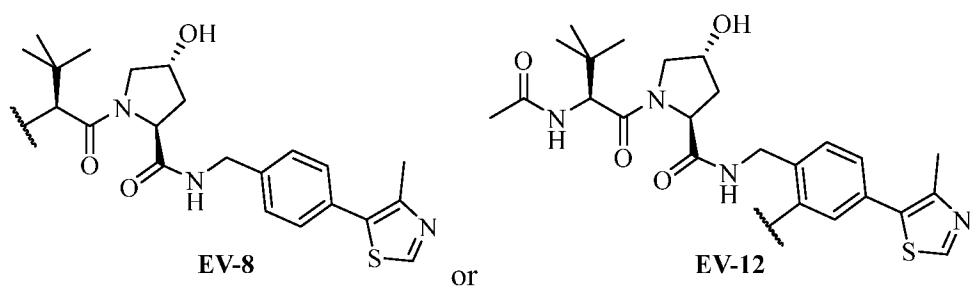
127. The compound of any one of claims 1 to 81, 115, and 126, wherein R^E is a moiety having the structure of:





or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

128. The compound of any one of claims 1 to 81, 115, 126, and 127, wherein R^E is a moiety having the structure of:



or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

129. The compound of any one of claims 1 to 128, wherein L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20} alkenylene, C_{2-20} heteroalkenylene, C_{2-20} alkynylene, C_{2-20} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene, each of which is optionally substituted with one or more substituents Q.

130. The compound of any one of claims 1 to 128, wherein L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20} alkenylene, C_{2-20} heteroalkenylene, C_{2-20} alkynylene, or C_{2-20} heteroalkynylene, each of which is optionally substituted with one or more substituents Q.

131. The compound of any one of claims 1 to 130, wherein L is C₁₋₂₀ alkylene, optionally substituted with one or more substituents Q.

132. The compound of any one of claims 1 to 131, wherein L is -(CH₂)_x-, optionally substituted with one or two oxo; and wherein x is an integer of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

133. The compound of any one of claims 1 to 130, wherein L is C₁₋₂₀ heteroalkylene, optionally substituted with one or more substituents Q.

134. The compound of any one of claims 1 to 128, wherein L is C₁₋₂₀ alkylene, C₁₋₂₀ heteroalkylene, C₂₋₂₀ alkenylene, C₂₋₂₀ heteroalkenylene, C₂₋₂₀ alkynylene, or C₂₋₂₀ heteroalkynylene, where one or more methylene groups are replaced by a divalent group, and each divalent group is independently C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, heteroalkylene, alkenylene, heteroalkenylene, alkynylene, heteroalkynylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents Q.

135. The compound of claim 134, wherein L is C₁₋₂₀ alkylene, where one or more methylene groups are replaced by a divalent group, and each divalent group is independently C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents Q.

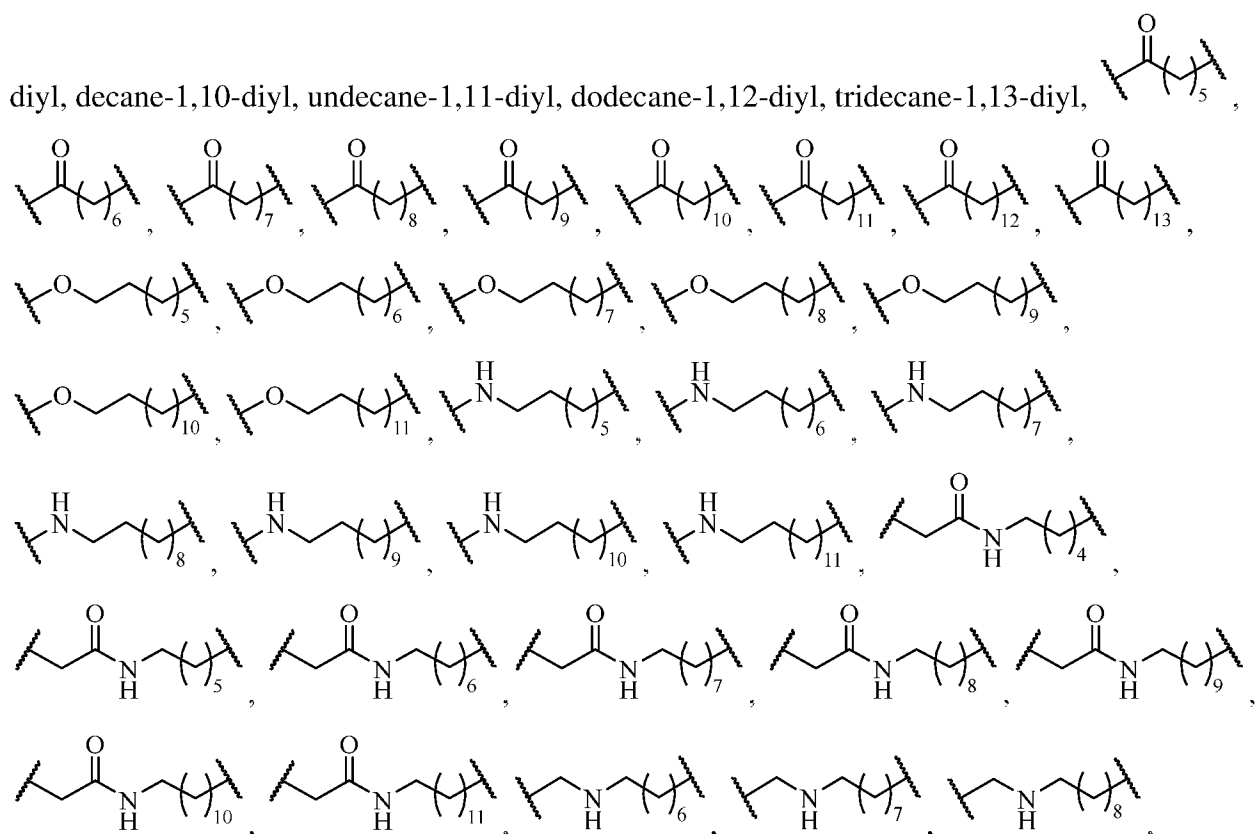
136. The compound of claim 134, wherein L is C₁₋₂₀ heteroalkylene, where one or more methylene groups are replaced by a divalent group, and each divalent group is independently C₃₋₁₀ cycloalkylene, C₆₋₁₄ arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents Q.

137. The compound of any one of claims 1 to 128, wherein L is C₁₋₁₅ alkylene-C₃₋₁₀ cycloalkylene, C₁₋₁₅ heteroalkylene-C₃₋₁₀ cycloalkylene, C₁₋₁₅ alkylene-C₆₋₁₄ arylene, C₁₋₁₅ heteroalkylene-C₆₋₁₄ arylene, C₁₋₁₅ alkylene-heteroarylene, C₁₋₁₅ heteroalkylene-heteroarylene, C₁₋₁₅ alkylene-heterocyclylene, C₁₋₁₅ heteroalkylene-heterocyclylene, or heteroarylene-

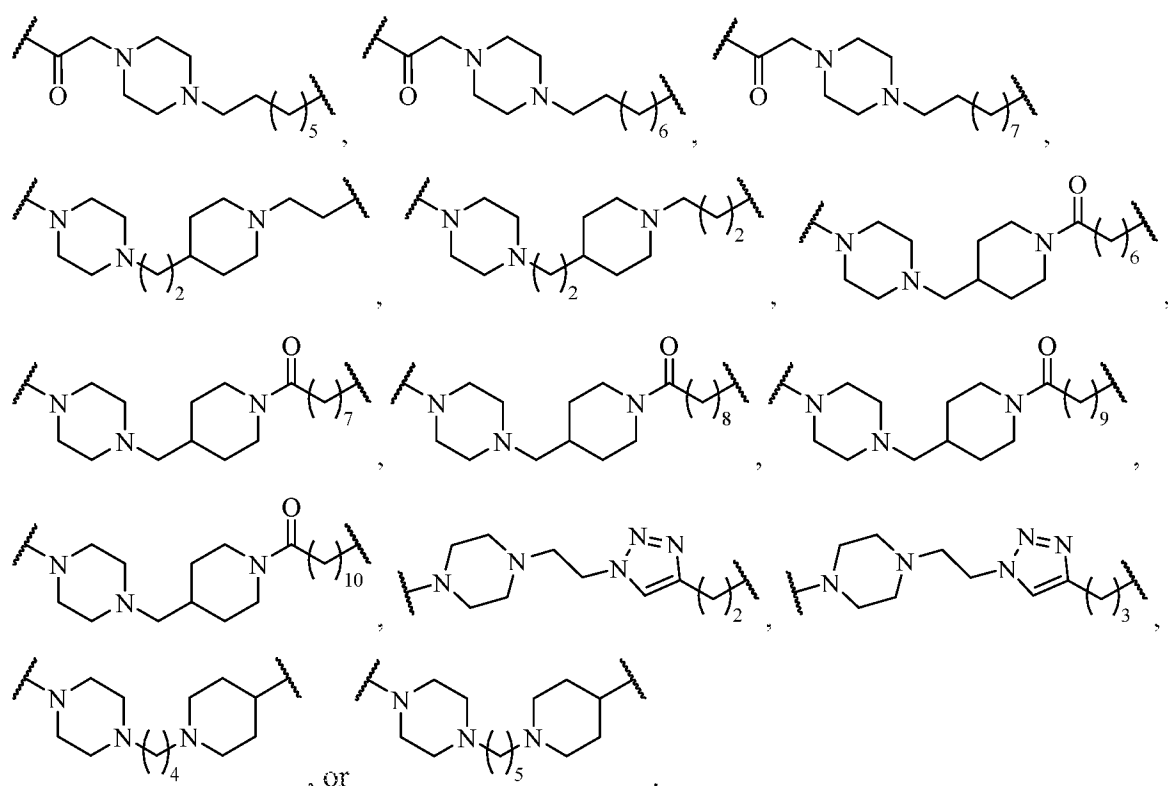
heterocyclylene, where each alkylene, heteroalkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene is optionally substituted with one or more substituents Q.

138. The compound of any one of claims 1 to 128, wherein L is C₁₋₁₀ alkylene-C₃₋₁₀ cycloalkylene-C₁₋₁₀ alkylene, C₁₋₁₀ alkylene-C₃₋₁₀ cycloalkylene-C₁₋₁₀ heteroalkylene, C₁₋₁₀ heteroalkylene-C₃₋₁₀ cycloalkylene-C₁₋₁₀ heteroalkylene, C₁₋₁₀ alkylene-C₆₋₁₄ arylene-C₁₋₁₀ alkylene, C₁₋₁₀ alkylene-C₆₋₁₄ arylene-C₁₋₁₀ heteroalkylene, C₁₋₁₀ heteroalkylene-C₆₋₁₄ arylene-C₁₋₁₀ heteroalkylene, C₁₋₁₀ alkylene-heteroarylene-C₁₋₁₀ alkylene, C₁₋₁₀ alkylene-heteroarylene-C₁₋₁₀ heteroalkylene, C₁₋₁₀ heteroalkylene-heteroarylene-C₁₋₁₀ heteroalkylene, C₁₋₁₀ alkylene-heterocyclylene-C₁₋₁₀ alkylene, C₁₋₁₀ alkylene-heterocyclylene-C₁₋₁₀ heteroalkylene, or C₁₋₁₀ heteroalkylene-heterocyclylene-C₁₋₁₀ heteroalkylene, where each alkylene, heteroalkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene is optionally substituted with one or more substituents Q.

139. The compound of any one of claims 1 to 128, wherein L is propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl, hexane-1,6-diyl, heptane-1,7-diyl, octane-1,8-diyl, nonan-1,9-diyl, decane-1,10-diyl, undecane-1,11-diyl, dodecane-1,12-diyl, tridecane-1,13-diyl,







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

3-(4-(1-(7-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A1**;

3-(4-(1-(7-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A2**;

3-(4-(1-(7-(((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)-piperidine-2,6-dione **A3**;

4-((2-(2-(2-(2-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione **A4**;

2-(2,6-dioxopiperidin-3-yl)-4-((2-(2-(2-(2-(((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)ethoxy)ethoxy)-ethoxy)ethyl)amino)isoindoline-1,3-dione **A5**;

9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-

oxy)-*N*-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)methyl)nonanamide **A6**;

8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-oxy)-*N*-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)methyl)octanamide **A7**;

8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-oxy)-*N*-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)octanamide **A8**;

9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)-oxy)-*N*-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)nonanamide **A9**;

3-(4-(1-(3-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)propyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A10**;

3-(4-(1-(5-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A11**;

3-(4-(1-(9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A12**;

3-(4-(2-(4-(4-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A13**;

3-(4-(2-(4-(5-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A14**;

3-(6-fluoro-4-(1-(7-((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A15**;

3-(6-fluoro-4-(1-(7-((6-methoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A16**;

3-(4-(1-(5-(4-(4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)piperidin-1-yl)pentyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A17**;

3-(4-(1-(4-(4-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)piperidin-1-yl)butyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A18**;

3-(4-(1-(7-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-7-methoxy-2-methylquinazolin-6-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A19**;

3-(4-(1-(7-(4-(((R)-1-(3-bromophenyl)ethyl)amino)-6,7-dimethoxy-2-methylquinazolin-8-yl)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A20**;

3-(5-(1-(5-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A21**;

3-(5-(1-(7-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A22**;

3-(5-(1-(9-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A23**;

3-(5-(1-(11-((4-(((R)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A24**;

3-(6-fluoro-5-(1-(7-((6-methoxy-2-methyl-4-(((R)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A25**;

3-(6-fluoro-5-(1-(7-((6-methoxy-2-methyl-4-(((S)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione **A26**;

3-(5-(1-(7-((4-(((R)-1-(3-(1,1-difluoro-2-hydroxyethyl)phenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A27**;

3-(5-(1-(7-((4-(((R)-1-(3-amino-5-(trifluoromethyl)phenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)-

piperidine-2,6-dione **A28**;

3-(5-(2-(4-(4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A29**;

3-(5-((2-(4-(4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A30**;

3-(5-(2-(4-(5-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethoxy)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A31**;

3-(5-((2-(4-(5-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisindolin-2-yl)-piperidine-2,6-dione **A32**;

5-(4-((1-(7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisindoline-1,3-dione **A33**;

5-(4-((1-(9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisindoline-1,3-dione **A34**;

5-(4-((1-(11-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecanoyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisindoline-1,3-dione **A35**;

4-((2-(2-(2-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isindoline-1,3-dione **A36**;

6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methyl)-hexanamide **A37**;

8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methyl)-octanamide **A38**;

10-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methyl)-decanamide **A39**;

12-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methyl)-dodecanamide **A40**;

3-(1-((4-(((7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)amino)methyl)phenoxy)methyl)-4-oxo-4*H*-thieno[3,4-*c*]pyrrol-5(6*H*)-yl)piperidine-2,6-dione **A41**;

3-(5-(3-(4-(6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)piperazin-1-yl)propyl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A42**;

3-(5-(3-(4-(6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)piperazin-1-yl)prop-1-yn-1-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A43**;

3-(5-(9-(3-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)propyl)-3,9-diazaspiro[5.5]undecan-3-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A44**;

3-(5-((9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonyl)amino)-2-methyl-4-oxoquinazolin-3(4*H*)-yl)piperidine-2,6-dione **A45**;

3-(5-((11-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecyl)amino)-2-methyl-4-oxoquinazolin-3(4*H*)-yl)piperidine-2,6-dione **A46**;

3-(5-((7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)amino)-2-methyl-4-oxoquinazolin-3(4*H*)-yl)piperidine-2,6-dione **A47**;

3-(5-(1-(7-((4-(((*S*)-1-(3-(1,1-difluoro-2-hydroxyethyl)phenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione **A48**;

16-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-

yl)oxy)-*N*-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methyl)-hexadecanamide **A49**;

3-(5-(1-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)piperidin-4-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A50**;

3-(4-(1-(10-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)piperidin-4-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A51**;

3-(6-fluoro-4-(1-(7-((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)-1-methylpiperidine-2,6-dione **A52**;

3-(6-fluoro-4-(1-(7-((6-methoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)-methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)heptyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)-1-methylpiperidine-2,6-dione **A53**;

3-(4-(1-(7-(6,7-dimethoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-8-yl)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A54**;

3-(4-((2-(4-(5-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)pentyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A55**;

3-(4-(1-(7-(6,7-dimethoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-8-yl)heptyl)piperidin-4-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A56**;

3-(4-((2-(4-(4-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)butyl)piperazin-1-yl)-2-oxoethyl)amino)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A57**;

3-(4-(1-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)piperidin-4-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione **A58**;

(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-

cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B1**;

(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B2**;

(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((10-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B3**;

(*S*)-*N*-((*S*)-2-((*S*)-2-(4-(3-((12-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)dodecyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)-2-(methylamino)propanamide **B4**;

(2*S*,4*S*)-4-(7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanamido)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)-acetyl)-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide **B5**;

(*S*)-2-((2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanamido)-*N*-(6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)-4-methylpentanamide **B6**;

(*S*)-2-((2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanamido)-*N*-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)-4-methylpentanamide **B7**;

(*S*)-2-((2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanamido)-*N*-(10-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)-4-methylpentanamide **B8**;

(*S*)-2-((2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanamido)-*N*-(12-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)dodecyl)-4-methylpentanamide **B9**;

(2*S*,4*S*)-4-(13-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)tridecanamido)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)-acetyl)-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide **B10**;

(2*S*,4*S*)-4-(11-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecanamido)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)-acetyl)-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide **B11**;

2-(4-(((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)-2-oxopiperazin-1-yl)-*N*-(6-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)hexyl)acetamide **C1**;

2-(4-(((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)-2-oxopiperazin-1-yl)-*N*-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)acetamide **C2**;

2-(4-(((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)-2-oxopiperazin-1-yl)-*N*-(10-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)acetamide **C3**;

2-(4-(((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-*N*-(8-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)octyl)acetamide **C4**;

2-(4-(((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-*N*-(10-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)decyl)acetamide **C5**;

2-(4-(((4*S*,5*R*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-*N*-(12-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)dodecyl)acetamide **C6**;

(2*S*,4*R*)-1-((*S*)-2-(7-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D1**;

(2*S*,4*R*)-1-((*S*)-2-(9-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D2**;

(2*S*,4*R*)-1-((*S*)-2-(11-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D3**;

(2*S*,4*R*)-1-((*S*)-2-(13-((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)tridecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D4**;

(2*S*,4*R*)-4-hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*R*)-1-(thiophen-2-yl)-

ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D5**;

(2*S*,4*R*)-4-hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*S*)-1-(thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D6**;

(2*S*,4*R*)-1-((*S*)-2-(9-((4-(((*R*)-1-(4-bromothiophen-2-yl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D7**;

(2*S*,4*R*)-1-((*S*)-2-(9-((4-(((*S*)-1-(4-bromothiophen-2-yl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D8**;

(2*S*,4*R*)-4-hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*R*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D9**;

(2*S*,4*R*)-4-hydroxy-1-((*S*)-2-(9-((6-methoxy-2-methyl-4-(((*S*)-1-(4-(2-((methylamino)methyl)phenyl)thiophen-2-yl)ethyl)amino)quinazolin-7-yl)oxy)nonanamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **D10**;

(2*S*,4*R*)-1-((*S*)-2-acetamido-3,3-dimethylbutanoyl)-*N*-(2-(((7-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)heptyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D11**;

(2*S*,4*R*)-1-((*S*)-2-acetamido-3,3-dimethylbutanoyl)-*N*-(2-(((9-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)nonyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D12**;

(2*S*,4*R*)-1-((*S*)-2-acetamido-3,3-dimethylbutanoyl)-*N*-(2-(((11-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)undecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D13**; or

(2*S*,4*R*)-1-((*S*)-2-acetamido-3,3-dimethylbutanoyl)-*N*-(2-(((13-(((4-(((*R*)-1-(3-bromophenyl)ethyl)amino)-6-methoxy-2-methylquinazolin-7-yl)oxy)tridecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxypyrrolidine-2-carboxamide **D14**;

or 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.

141. A pharmaceutical composition comprising the compound of any one of claims 1 to 140, 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.

142. The pharmaceutical composition of claim 141, wherein the composition is in single dosage form.

143. The pharmaceutical composition of claim 141 or 142, wherein the composition is in an oral, parenteral, or intravenous dosage form.

144. The pharmaceutical composition of claim 143, wherein the composition is formulated in an oral dosage form.

145. The pharmaceutical composition of claim 144, wherein the oral dosage form is a tablet or capsule.

146. A method of treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition mediated by a son of sevenless homolog 1 (SOS1) in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of a compound of any one of claims 1 to 140 or a pharmaceutical composition of any one of claims 141 to 145.

147. The method of claim 146, wherein the disorder, disease, or condition mediated by the SOS1 is a proliferative disease.

148. A method of treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition mediated by a Ras 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 140 or a pharmaceutical composition of any one of claims 141 to 145.

149. The method of claim 148, wherein the disorder, disease, or condition mediated by

the Ras is a proliferative disease.

150. A method of 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 140 or a pharmaceutical composition of any one of claims 141 to 145.

151. The method of claim 147, 149, or 150, wherein the proliferative disease is cancer.

152. The method of claim 151, wherein the cancer is colon cancer, colorectal cancer, lung cancer, or pancreatic cancer.

153. The method of claim 151 or 152, wherein the cancer is relapsed or refractory.

154. The method of any one of claims 151 to 153, wherein the cancer is metastatic.

155. The method of any one of claims 151 to 154, wherein the cancer is drug-resistant.

156. The method of any one of claims 146 to 155, wherein the subject is a human.

157. 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 140 or a pharmaceutical composition of any one of claims 141 to 145.

158. The method of claim 157, wherein the cell is a cancerous cell.

159. A method of inducing degradation of an SOS1, comprising contacting the SOS1 with an effective amount of a compound of any one of claims 1 to 140 or a pharmaceutical composition of any one of claims 141 to 145.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/071475

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	C07D239/94 C07D401/14 C07D403/12 C07D403/14 C07D409/14 C07D417/14 C07D471/10 C07D495/04	
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/140380 A1 (KYMERA THERAPEUTICS INC [US]) 18 July 2019 (2019-07-18) claim 1 page 398, line 6 -----	1-159
X	WO 2017/201069 A1 (BIOTHERYX INC [US]) 23 November 2017 (2017-11-23) claims 1, 90 page 135; compound 59 ----- -/-	1,46,81, 106,109, 134-139, 141-151, 157-159
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 8 November 2021		Date of mailing of the international search report 19/11/2021
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Gutke, Hans-Jürgen

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2021/071475

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	----- WO 2018/115380 A1 (BOEHRINGER INGELHEIM INT [DE]) 28 June 2018 (2018-06-28) claims 12, 28, 30	1-159
A	----- WO 2020/180770 A1 (REVOLUTION MEDICINES INC [US]) 10 September 2020 (2020-09-10) claim 1	1-159
X,P	----- CN 112 608 302 A (FIRST AFFILIATED HOSPITAL ZHENGZHOU UNIV) 6 April 2021 (2021-04-06) claim 1	1
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A,P	----- WO 2021/051034 A1 (BIOTHERYX INC [US]) 18 March 2021 (2021-03-18) claim 1	1
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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	SCHAPIRA MATTHIEU ET AL: "Targeted protein degradation: expanding the toolbox", NATURE REVIEWS DRUG DISCOVERY, NATURE PUBLISHING GROUP, GB, vol. 18, no. 12, 30 October 2019 (2019-10-30), pages 949-963, XP036929738, ISSN: 1474-1776, DOI: 10.1038/S41573-019-0047-Y [retrieved on 2019-10-30] table 1 figures 3a, 3c -----	1-159

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Information on patent family members

International application No

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